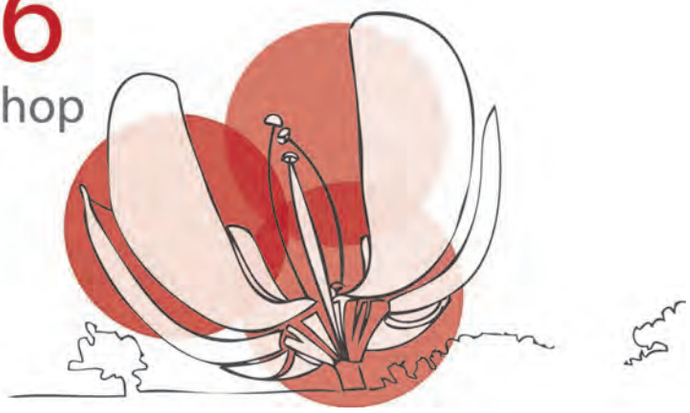
ISSVA 2016

21st International Workshop on Vascular Anomalies

BUENOS AIRES ARGENTINA



About The International Society for the Study of Vascular Anomalies - ISSVA

The International Society for the Study of Vascular Anomalies was founded in 1992 during the International Workshop on Vascular Anomalies held in 1990 in Amsterdam. The Society represents the formalization of prior biennial international workshops, which were started in 1976 by Drs. John Mulliken and Anthony Young. This basic concept of workshops was maintained, fostering the time proven personal contacts and informal exchange of scientific knowledge concerning vascular anomalies that has been a feature of this organization.

The term anomalies encompasses hemangiomas and vascular malformations. The purpose of the Society is to promote, on a national and international level, clinical and scientific research in all fields that will lead to advances in knowledge concerning all aspects of vascular anomalies. The Society encourages the transmission of data through a free flow of information between its members and interested groups, through workshop meetings, teaching programs and by the publication of pertinent scientific data.

The Society organizes biennial workshops. The official language of the Society is English. The Society is governed by the law of the United States of America.
www.issva.org

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ISSVA 2016 - 21st International Workshop on Vascular Anomalies

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Welcome Letter

Dear ISSVA members and guests,

On behalf of the International Society for the Study of Vascular Anomalies I am very proud to be able to welcome you to our 21st International Workshop in the beautiful Buenos Aires.

An interesting scientific program paired up with typically Argentinean social activities that will guarantee not only an exchange of knowledge but of culture.

Since the first ISSVA meeting the society has been the leading society in vascular anomalies .The workshop organized every other year is very special due to the fact that we are making progress in our research, and we therefore can spread the knowledge in different countries and treat patients all over the world in a better way. And that is our goal.

We are very excited and proud to have Dr. Leslie Biesecker, he will share with us his vast knowledge on segmental overgrowth disorders .

We have organized the meeting so as to start with the basic course on Tuesday 26th, as we consider it extremely important to agree on a consistent terminology so as to be understood when we further develop the subject on the following days.

With warm regards,

Ana Giachetti

Under the Official Auspices of:

Sociedad Argentina de Dermatologia
Sociedad Argentina de Flebología y Linfología
Sociedad Argentina de Pediatría
Asociación Civil Argentina de Cirugía Pediátrica
Sociedad Argentina de Radiología

General Information

Registration Opening Hours

Tuesday 26	*07:30-18:00h*
Wednesday 27	*07:30-15:00h*
Thursday 28	*07:30-17:30h*
Friday 29	*07:30-16:00h*

Exhibiton Opening Hours

Tuesday 26	*09:00-18:00h*
Wednesday 27	*08:00-15:00h*
Thursday 28	*08:00-17:00h*
Friday 29	*08:00-16:00h*

Disclaimer

The Organizing Committee and Ana Juan Congresos cannot accept liability for injuries or losses of whatever nature incurred by participants and/or accompanying persons, nor for loss or damage to their luggage and/or personal belongings. Delegates participate in all tours and events at their own risk.

Participants are advised to take out insurance against loss, accidents or damage that could incur during the Congress

General Information

Wi-Fi
Internet Access will be provided during the Congress.
It will be free, unlimited, and no password is required.
Network: Invitados
Please bear with us if you have trouble connecting to the Wi-Fi, as this may be due to the volume of people and number of devices being used.

Mobile Phones
Use of mobile phones is strictly prohibited within the scientific session rooms.
Please ensure you have your mobile phone switched off when attending the sessions.

Official language
All sessions will be in English. Simultneous translation will be available only during the Basic Course.

Smoking Policy
This is a non-smoking event. Smoking is not allowed in meeting rooms, exhibition, poster areas, registration area, restrooms, and halls. Please help keep the conference premises a non-smoking environment.

Badges
Each participant will receive a name badge upon check-in at the Registration Desk. The badge will be the official meeting document and should be worn at all times in order to gain entry to the meeting rooms. Please note that access to any of the Congress areas will not be possible without an official badge.

Speakers' Pre-View Room
There is a Speakers' Pre-View Room situated in room 134, first floor.
Speakers are requested to arrive at Speaker's Preview Room at least 2 hours prior to session in order to test and edit the presentation before sending it to the corresponding room. There will be a trained operator to test and solve any inconvenient or change it may arise in any presentation.

Opening Hours

Tuesday 26	*07:15-18:00h*
Wednesday 27	*07:15-15:00h*
Thursday 28	*07:15-17:30h*
Friday 29	*07:15-16:00h*

Certificate of Attendance
Registrants who require a Certificate of Attendance can download them online after the Workshop. Use your registration number provided at your badge so to accede to the online diploma.

Abstracts Certificates
Authors can download them after the Workshop, together with the Certificate of Attendance.

Coffee breaks and lunches
Lunches & coffee breaks are included in the registration fee and will be provided as scheduled.

Posters
Mounting:
April, Tuesday 26 – *14:00 to 17:00 h*

Dismantling:
April, Friday 29 – *11:00 to 13:00 h*
The poster exhibition staff will remove posters that are not taken down. Conference organizers assume no responsibility for any material left behind.
Posters will be displayed for 2 days during the Meeting (April 27 & 28) from 09.00 to 18:00 h.

Travel Desk
A desk for hotel and tour bookings will be located in the first floor.

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Social Activities

Welcome Reception
Included in the registration fee
Tuesday 26, 19:00-21:00 h
Juan Pablo II Room

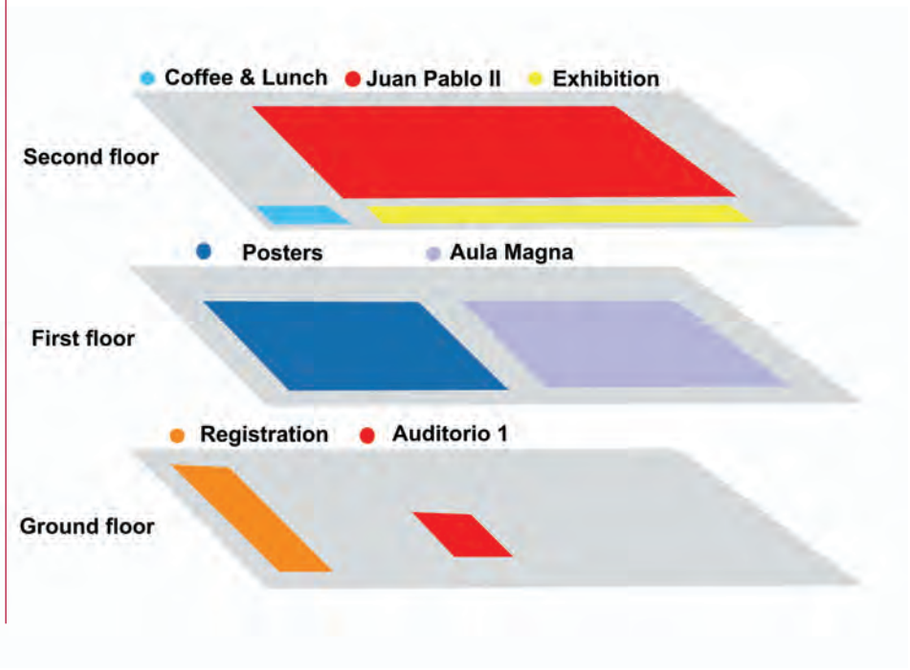
City tour
Included in the registration fee
Wednesday 27, 16.00-19:00 h

Departure from Madero Hotel
Dique 2, Rosario Vera Penaloza 360, Puerto Madero
Delegates wishing to participate must register previously at the Registration Desk (Ground Floor).
Deadline: Wednesday 27, 12:00 h
Limited capacity

Gala Dinner
Not included in the registration fee
Thursday 28, 20:00 h

Madero Tango
Alicia Moreau de Justo & Brasil Streets
Dique 1, Puerto Madero
Transportation will not be provided
Limited capacity

VENUE



VENUE, HOTELS & GALA DINNER LOCATION

ISSVA 2016

21st International Workshop on Vascular Anomalies

BASIC COURSE PROGRAM

APRIL 26th-29th, 2016
BUENOS AIRES-ARGENTINA

ISSVA

BASIC COURSE PROGRAM

Tuesday April 26, 2016

Juan Pablo II

08:00-12:40	**Basic Course**
12:40-13:40	**Lunch**
13:40-17:25	**Basic Course**
18:00-19:00	**Opening Ceremony**
19:00 -21:00	**Welcome Reception**

08:00 - 10:15 Session 1

Chairs: *PICCONE, Zulema - GRECO, M. Fernanda* ***Co-Chairs:*** *CARBAJOSA, Ana - ABAD, María Eugenia*

08:00	**Welcome**
08:05	**Vascular Anomalies Classification** *GIACHETTI, Ana*
08:20	**Infantile Hemangiomas: Clinical features and Diagnosis** *BASELGA, Eulalia*
08:35	**Hemangiomas and associated structural anomalies** *DROLET, Beth*
08:50	**Which Infantile hemangiomas to treat and when** *FRIEDEN, Ilona J.*
09:05	**Infantile Hemangiomas Treatment** *CASTRO, Carla*
09:20	**Differential Diagnosis on Vascular Tumors** *POWELL, Julie*
09:35	**Case Presentations**
09:35	**Case 1: Verrucous Hemangioma** *DELLA GIOVANNA, Patricia*
09:45	**Case 2: PHACES Syndrome** *SOJO, M. Magdalena*
09:55	**Case 3: Segmental facial hemangioma and Hipopituitarism** *MACCARIO, María Fernanda*
10:05	**Questions**
10:15 - 10:45	**Coffee Break**

10:45 - 12:40 Session 2

Chair: BOENTE, María Del Carmen ***Co-Chairs:*** KRAMER, Daniela - ALTUNA, Diana

10:45	**Basic Knowledge regarding genetics in Vascular Anomalies** *VIKKULA, Miikka*
11:00	**Congenital Hemangiomas** *LARRALDE, Margarita*
11:15	**Kaposiform Hemangioendothelioma. Kasabach Merritt Phenomenom** *BRANDAO, Leonardo*
11:30	**Capillary Vascular Malformations** *CORDISCO, María Rosa*

11:45	**Laser treatment for Vascular Anomalies** *LANOEL, Agustina*
12:00	**Case Presentations**
12:00	**Case 1: Challenging Case** *MCCUAIG, Catherine*
12:10	**Case 2: Angiokeratoma: Combined use of Lasers and Topical Rapamycin** *VILA-ECHAGÜE, Agustina*
12:20	**Case 3: Diffuse capillary malformation with overgrowth** *BOGGIO, Paula*
12:30	**Questions**
12:40 - 13:40	**Lunch**

13:40 - 15:30 Session 3

Chairs: *GIACHETTI, Ana - LIPSICH, José* ***Co-Chair:*** *GALIMBERTI, Daniel*

13:40	**Vascular Malformations Classification Clinical features** *GRECO, M. Fernanda*
13:55	**Imaging Characteristics of Vascular Anomalies** *DUBOIS, Josee*
14:20	**Venous and Lymphatic Vascular Malformations Treatment** *GARCÍA MÓNACO, Ricardo*
14:40	**Case presentations**
14:40	**Case 1: CLOVES Syndrome** *KREINDEL, Tamara*
14:50	**Case 2: Angiomatous eccrine hamartoma. Why isn't it considered in the ISSVA classification?** *LUNA, Paula*
15:00	**Questions**
15:30 - 16:00	**Coffee Break**

16:00 - 17:25 Session 4

Chair: *GREES, Susana* ***Co-Chairs:*** *Moreno, Silvia - UDAQUIOLA, Julia*

16:00	**Arteriovenous Vascular Malformations Treatment** *GARCÍA MÓNACO, Ricardo*
16:15	**Surgery for Vascular Malformations** *GOLDENBERG, Dov*
16:30	**Vascular Syndromes KT, Proteus Cloves** *LOPEZ-GUTIERREZ, Juan Carlos*
16:45	**Case presentations**
16:45	**Case 1: Hereditary Hemorrhagic Telangiectasia: multisystemic vascular disorder. Management of a complex case** *SERRA, Marcelo*
16:55	**Case 2: Mafucci Sydrome** *GONTIJO, Bernardo*
17:05	**Case 3: Capillary malformation-arteriovenous malformation (CM-AVM)** *ROSITTO, Alicia*
17:15	**Questions**
17:25	**Close**

PROGRAM

Wednesday April 27, 2016

Juan Pablo II

08:00-08:15	**Welcome Speech**
08:15-09:55	**Session 1: Hemangioma Diagnosis and Research**
10:10-10:30	**Difficult Case Presentations I**
10:30-11:00	**Coffee Break**
11:00-12:00	**Keynote** Segmental overgrowth disorders and the future of therapeutics Speaker: **Leslie Biesecker, MD**
12:00-13:00	**PIERRE FABRE** Sponsored Symposium
13:00-14:00	**Lunch**
14:00-15:00	**ISSVA General Assembly** (Members only)
	Free Afternoon. Social Activity

08:00– 08:15	Welcome Speech	Juan Pablo II Room

08:15– 09:55	SE1 - Session 1: Hemangioma Diagnosis and Research	Juan Pablo II Room

Chairs: Ana Giachetti, Eulalia Baselga

08:15-08:25 234 ***PHACE syndrome: A reconsideration of diagnostic criteria and recommendations for health surveillance***

Maria Garzon1, Peter Frommelt2, Francine Blei3, Robert Chun4, Sarah Chamlin5, Leon Epstein4, Christopher Hess6, Geoffrey Heyer7, Shawna Joachim4, Sean Lew4, Marilyn Liang8, Mohit Maheshwari4, Denise Metry9, Priya Monrad4, Darren Orbach8, Elena Pope10, Julie Powell11, Wendy Schumacher-Kim4, Tor Shwayder12, Dawn Siegel4, Megha Tollefson13, Sudhakar Vadivelu14, Patricia Burrows2, Ilona Frieden6, BETH DROLET15

1,2 Children's Hospital of Wisconsin, 3 North Shore LIJ Healthcare System, 4Medical College of Wisconsin, 5Northwestern University, IL, 6University of California, San Francisco, 7The Ohio State University, 8Harvard Medical School, 9Baylor College of Medicine, 10Hospital for Sick Children, 11CHU Sainte-Justine, U of Montreal, 12Henry Ford Hospital, 13Mayo Clinic College of Medicine, 14Cincinnati Children's Hospital, 15MCW

Purpose: PHACE Syndrome is characterized by large infantile hemangiomas (IH) of the face, neck, and scalp associated with developmental defects. This acronym was first used in 1996 and associated features are still emerging. There are over 250 case reports/case series detailing the various multisystem features of PHACE syndrome, but no established guidelines of care. The most visible feature of PHACE syndrome is infantile hemangioma; however, abnormalities of the brain, aorta, medium-sized arteries of the chest, neck and head are common and have the greatest potential to cause long-term morbidity. As patients with PHACE mature many new comorbidities have emerged. Evidenced-based data on screening and ongoing monitoring of these potentially progressive morbidities is lacking. There is also significant divergence of opinions regarding which infants are at risk for PHACE, screening evaluation before diagnosis, and ongoing surveillance for those with diagnosed with PHACE.
Methods: A multi-institutional and multi-specialty PHACE workshop was held in Milwaukee, Wisconsin in June of 2014 bringing together expertise in many pediatric specialties (e.g. neuroradiology, neurosurgery, neurology, cardiology, cardiothoracic surgery, dermatology, otolaryngology, and plastic surgery) to address clinically relevant questions. Twenty-eight physicians attended from 14 unique institutions representing 8 pediatric specialties. In addition, patient families and members of the PHACE syndrome advocacy group attended to insure a focus on patient-important outcomes. The multidisciplinary groups reviewed existing data and all published reports on the associated anomalies of PHACE syndrome. Data was presented and small groups developed content. These were presented at the meeting and discussed. Comments were recorded and content was revised accordingly. Protocols were circulated and finalized via conference calls and via electronic communication.
Results: Formal diagnostic criteria for PHACE syndrome were first published in 2009, but after 6 years' experience using the criteria in both clinical practice and research, participants recognized the

importance of reassessing clinical applicability and incorporating new knowledge. There was overall agreement regarding the general reliability of established diagnostic criteria, but also a consensus to modify this criteria to include segmental IH of not just the face but all of the head/neck OR chest/upper arm as allowing a diagnosis of definite PHACE. PHACE- specific major criteria arterial anomalies were expanded to include all persistent carotid-vertebrobasilar anastomosis (proatlantal segmental, hypoglossal, otic and/or trigeminal arteries). Systemic venous anomalies were added to the minor criteria. Risk-adjusted health surveillance guidelines were developed for in on-going monitoring of aortic arch, brachiocephalic, cervical and cerebral arterial anomalies. There was recognition of the need to monitor for other organ system involvement including hearing deficits, dental enamel defects, and endocrine (thyroid and pituitary) abnormalities. The psychological impact of PHACE was also emphasized.

Conclusion: The work of this multidisciplinary group proposes both updates to previous diagnostic criteria and guidelines of care to direct both screening of at-risk infants and risk-adjusted ongoing health surveillance of those diagnosed with PHACE.

08:25-08:33 252 ***Rapamycin (Sirolimus) Inhibits Proliferation and Increases Vascular Maturation of GLUT1-positive Endothelial Cells from Infantile Hemangioma***

LAN HUANG1, John Mulliken2, Joyce Bischoff3

1Boston Children's Hospital, 2Departments of Plastic and Oral Surgery, Vascular Anomalies Center, Boston Children's Hospital, 3Departments of Surgery, Vascular Biology Program, Boston Children's Hospital

Background: Infantile hemangioma (IH) appears within 1-2 weeks after birth, grows rapidly during the first several months of life, and begins a slow but spontaneous involution process after approximately one year. A hallmark of IH is the expression of glucose transporter-1 (GLUT1) along the endothelium of many but not all of the blood vessels in the tumor. We showed there is a significant decrease in GLUT1-positive endothelial cells (ECs) in IH specimens removed from children over one year of age and that GLUT1-positive ECs harbor stem cell properties. The presence of GLUT1-positive and GLUT1-negative ECs in proliferating phase IH suggests there may be two types of ECs within the tumor, each of which may have differing susceptibilities to drug treatments.

Methods: GLUT1-positive and GLUT1-negative ECs were isolated from proliferating phase IH (n=5) using anti-GLUT1-coated magnetic beads followed by anti-CD31-coated magnetic beads. Cellular phenotypes were assessed by quantitative PCR (qPCR) for GLUT1, CD31, VE-cadherin, VEGFR2, JAGGED1, PlexinD1 and PDGFRβ. The cells were expanded in vitro in endothelial growth medium, treated with/without rapamycin (Sirolimus) (22nM), added every 48 hours or treated with/without propranolol (10uM), added every 12 hours. After 4 days, drugs were washed out and (1) cellular proliferation was measured in "drug-free" endothelial growth medium or (2) the cells were lysed for RNA isolation and qPCR analysis of endothelial and pericyte markers.

Results: Rapamycin pre-treatment significantly reduced proliferation of both GLUT1-selected cells and the GLUT1-negative ECs; propranolol pre-treatment had no effect. Since the previous work showed rapamycin induced differentiation of hemangioma-derived stem cells (HemSCs)1, we examined expression of both endothelial and pericyte markers in the rapamycin-treated GLUT1-selected cells (n=3). Rapamycin increased expression of VEGFR1, JAGGED1, and PlexinD1 (endothelial markers) and calponin, NG2 and PDGFRβ (pericyte markers).

Conclusion: A short 4 day exposure to rapamycin inhibits proliferation of hemangioma-derived GLUT1-positive and GLUT1-negative ECs, similar to its inhibition of HemSCs. Rapamycin increased vascular maturation of GLUT1-selected cells, as shown by increased expression of endothelial and pericytic markers. Importantly, rapamycin increased VEGFR1, a VEGF receptor that is only weakly expressed in IH, a deficit that has been implicated in the pathogenesis of IH2, 3. We speculate that besides its anti-proliferative effects, rapamycin may increase VEGFR1 levels in IH and thereby attenuate excess VEGF signaling that may contribute to the pathogenesis of IH.

1. Greenberger S, Yuan S, Walsh LA, Boscolo E, Kang KT, Matthews B, Mulliken JB, Bischoff J. Rapamycin suppresses self-renewal and vasculogenic potential of stem cells isolated from infantile hemangioma. The Journal of investigative dermatology. 2011;131:2467-2476

2. Picard A, Boscolo E, Khan ZA, Bartch TC, Mulliken JB, Vazquez MP, Bischoff J. Igf-2 and flt-1/vegf-r1 mrna levels reveal distinctions and similarities between congenital and common infantile hemangioma. Pediatr. Res. 2008;63:263-267

3. Jinnin M, Medici D, Park L, Limaye N, Liu Y, Boscolo E, Bischoff J, Vikkula M, Boye E, Olsen BR. Suppressed nfat-dependent vegfr1 expression and constitutive vegfr2 signaling in infantile hemangioma. Nat. Med. 2008;14:1236-1246

08:33-08:41 143 ***Neurodevelopmental Effects from the Use of propranolol: Retrospective Oversight (NEURO) of children with infantile hemangiomas***

Khor Jia Ker1, Joy Wan2, Charles Bailey3, Albert Yan4

1National Skin Centre, Singapore, 2Department of Dermatology, Hospital of the University of Pennsylvania, USA, 3Divisions of Hematology and Oncology, Children's Hospital of Philadelphia, USA, 4Section of Dermatology, Children's Hospital of Philadelphia, USA

Purpose: Propranolol has been widely used for the treatment of infantile hemangioma (IH) worldwide with a satisfactory safety record profile to date. However, intermediate and long-term neurological effects of propranolol in infants and children remain incompletely characterized.[1] In the pediatric population, gross motor abnormalities of delayed walking have been reported in infants and children with IH treated with propranolol.[2] As such, there is concern that propranolol may exert effects on the CNS during the crucial developmental period of infancy and childhood. The primary objective is to determine if use of propranolol for treatment of IH has any adverse impact on neurodevelopment in the pediatric population.
Methods: This retrospective cohort study was conducted at the Children's Hospital of Philadelphia pediatric dermatology clinic. Electronic medical records of patients with IH treated with propranolol from January 1 2008 to December 31 2012 were reviewed. Follow-up information through December 31 2014 was obtained.
Results: Records of 291 patients were identified, and 26 (8.9%) had new-onset developmental delay during the study period, with combined motor and speech delay being the most common Four patients had autism or autism spectrum disorder. Among patients with developmental delay, 31% had persistent delays during the study period, 15% had resolution of their delays while on propranolol, and 31% had resolution after propranolol was stopped. Developmental delay was significantly associated with extremely low birth weight of less than 1.0 kg (OR 19.5, 95% CI 1.99-191.4) in adjusted analyses. While the odds of developmental delay decreased as the age at propranolol initiation increased (OR 0.77, 95% CI 0.58-1.01), this did not reach statistical significance. However, gender, race, duration of propranolol use and cumulative dose of propranolol were not significantly associated with developmental delay on multivariable analysis.
Conclusion: Patients with IH on propranolol who have extremely low birth weights are at greatest risk for developmental delay. Although age of propranolol initiation, duration and cumulative dose of propranolol were not found to be significantly associated with developmental delay, the small sample size in this study may be a limiting factor.

08:41-8:49 146 ***A Multicenter Cohort Study of Infantile Hemangiomas Treated with Topical Timolol***

Kate Puttgen1, Denise Adams2, Elena Pope3, Catherine McCuaig4, Dana Feigenbaum5, Yulia Savva6, Eulalia Baselga7, Kristen Holland8, Beth Drolet8, Dawn Siegel8, Kimberly Morel9, Maria Garzon9, Erin Mathes5, Christine Lauren9, Amy Nopper10, Kimberly Horii10, Brandon Newell10, Ilona Frieden5

1Johns Hopkins University School of Medicine, 2Cincinnati Children's Hospital, Cincinnati, Ohio, 3Hospital for Sick Children, Toronto, Canada, 4Sainte-Justine Hospital, Montreal, Quebec, 5University of California, San Francisco, San Francisco, California, 6Johns Hopkins University, Baltimore, Maryland, 7Hospital de la Santa Creu i Sant Pau, Barcelona, Spain, 8Medical College of Wisconsin, Milwaukee, Wisconsin, 9Columbia University, New York, New York, 10University of Missouri, Kansas City School of Medicine, Kansas City, Missouri

Purpose: There has been a dramatic increase in off-label use of the ophthalmic formulation of timolol, as the topical counterpart to propranolol, for treatment of infantile hemangiomas (IH). Its safety and efficacy in a pediatric population with IH have not been evaluated in a large cohort. Our goal was to assess timolol's effectiveness, discern characteristics associated with response and to document adverse events.
Methods: A multicenter retrospective cohort study of 731 patients treated with timolol was completed at 9 pediatric dermatology and vascular anomalies centers in 2014. Descriptive statistics and univariate and multivariate logistic regression analysis were performed. Primary outcome measures were treatment response judged by Visual Analog Scales for size and color.
Results: The most common subtypes of IH in the cohort were superficial (405 [55.3%]) and localized (572 [80.1%]). Risk of disfigurement was the most common indication for therapy (544 [74.3%]). Duration of therapy ($p<0.0001$), initial thickness ($p=0.008$) and morphologic subtype ($p=0.031$) were significant predictors of response. Best response occurred in superficial IH <1 mm thick. In this pre-selected cohort, 53 (7.3%) required a switch of oral propranolol or nadolol due to insufficient response. Adverse events were rare and generally mild, occurring in 25 (3.4%) patients. No cardiovascular side effects, symptomatic or asymptomatic, were noted.
Conclusion: With appropriate patient selection, timolol is a well tolerated, safe treatment option with moderate to good effectiveness, demonstrating best response in thin IH with a superficial component regardless of pre-treatment size based on data from this large cohort. Timolol can be recommended as a safe alternative to systemic beta-blockers and watchful waiting for many patients.

08:49-08:57 64 ***Adverse Events in Young and Preterm Infants Receiving Topical Timolol for Infantile Hemangioma***

Peter Frommelt1, Anna Juern1, Dawn Siegel1, Kristen Holland1, Marcia Seefeldt1, JiaDe Yu1, Michael Uhing1, Kelly Wade1, Beth Drolet2

1Medical College of Wisconsin, 2MCW

Purpose: The success of oral propranolol for infantile hemangioma (IH) treatment has led practitioners to use topical beta-blockers for IH. In preterm infants, clinicians frequently turn to topical timolol with the presumption that topical application will result in less systemic absorption. We have employed Holter monitoring to assess for drug-induced bradycardia in high risk infants.
Methods: We retrospectively reviewed charts of 22 at risk infants who received a Holter monitor to assess for association between timolol administration and development of significant bradycardia.
Results: 4/22 infants had episodic bradycardia detected by Holter monitoring. Two of these infants were term, weighed >3000 g, and had asymptomatic rare brief episodes unrelated to the timing of the timolol application. The other two infants were symptomatic from the timolol-induced bradycardia and represented the only two babies with weights <2500g at initiation of therapy. Both were young age (postmenstrual age (PMA) 34 and 37 weeks) at initiation, and had a timolol dose above the average exposure for the cohort.
Conclusion: In this cohort of at risk infants, topical timolol appeared to provide safe treatment for IH in term infants receiving a dose <0.2 mg/kg/day. However, infants with PMA of <44 weeks and weight at treatment initiation of <2500g may be at increased risk of adverse events including bradycardia, hypotension, apnea, and hypothermia. We recommend close monitoring of temperature, blood pressure and heart rate in premature and low birth weight infants IH at initiation, and during therapy with topical timolol.

08:57-09:05 78 ***Lymphatic Vessels in Congenital Hemangioma. Description and Use in Differential Diagnosis***

Sophie El Zein1, Michel Wassef2, Véronique Soupre3, Olivia Boccara3, Annouk Bisdorff4, Aurore Coulomb5, Sylvie Fraitag1

1Dept of pathology, Necker Hosp. Paris, France, 2Dept of pathology, Lariboisiere hospital, 3Vascular anomalies clinic, Necker Hosp. Paris, France, 4Vascular anomalies clinic, Lariboisiere Hosp. Paris, France, 5Dept of pathology, Trousseau Hosp. Paris, France

Purpose: Congenital hemangioma (CH) (NICH, RICH and PICH) are made of capillary lobules surrounded by a fibrous dermis containing distorted arteries and veins, and thin-walled slit like vessels resembling lymphatic vessels. The lymphatic nature of these vessels was only occasionally confirmed by immunohistochemistry. The aim of this study is to systematically describe the lymphatic component of CH, using immunohistochemistry, and to investigate the role of this component in the differential diagnosis of infant and children vascular tumors.
Methods: CH specimens were retrospectively retrieved from the pathology department files of three vascular anomalies centres (n=38). Pathological and clinical data were reviewed. The expression of the lymphatic marker Podoplanin was detected using D2-40 antibody. The morphology of Podoplanin-expressing vessels was recorded and their number was counted in three hotspots (x20 objective, x10 eyepiece). These CH were compared to a series of kaposiform hemangioendothelioma / tufted angioma (KHE/TA, n=20) and pyogenic granuloma (PG, n=20), especially deep ("dermal") PG.
Results: All CH contained thin-walled vessels expressing Podoplanin, consistent with lymphatic vessels. These vessels were situated in the fibrous tissue around the capillary lobules. They were often large and distorted, with slit-like or open lumen. The number of lymphatic vessels in the hotspots was high (mean 13.05 per square mm). Unlike kaposiform hemangioendothelioma / tufted angioma, the expression of podoplanin in CH was restricted to the extralobular vessels, except in three cases. PG contained rare lymphatic vessels, also situated in the extralobular fibrosis, probably representing persisting normal dermal lymphatics. These vessels were smaller than those of CH and lacked large open lumen.
Conclusion: Our study confirms that CH contain a high number of vessels with a lymphatic phenotype. Except in three cases, no podoplanin expression was found in the CH capillary lobules. The morphology and number of lymphatic vessels is different in CH, KHE/TA and PG and could help in the differential diagnosis of infant and children vascular tumors.

09:05-09:13 49 ***Infantile Hemangiomas Are Often Present at Birth***

Lorelei Grunwaldt2 , Chelsey Johnson1, Jessica Lee1, Megan Natali2, Amy Davis2, Noel Jabbour2, Sabri Yilmaz2, James Park2, Chido Vera2, Andrew McCormick2

1University of Pittsburgh Medical Center, 2Children's Hospital of Pittsburgh of University of Pittsburgh Medical Center

Purpose: Infantile hemangiomas (IH) are the most common birthmark of infancy and are classified by depth of soft tissue involvement: superficial, deep, or mixed. While widely accepted that IH are not present at birth, this has not been consistent with our observations.
Methods: A retrospective chart review was done of all patients with IH at a multidisciplinary vascular anomalies center from 2009-2015. Data collected included type of hemangioma (superficial, mixed, or deep) and time at which it was first noted.
Results: 473 of 500 patients identified with IH had complete data and were included. 51% of IH were superficial, 27% mixed, and 22% deep. Time at which the IH was first noted was skewed right in superficial and mixed IH, with a median appearance at 3 days of life (interquartile range of 0-14 days) in superficial IH and 7 days (0-30) in mixed IH, compared to 47 days (15-65) in deep IH. There was a statistically significant difference between the deep IH compared to the superficial ($p<0.0001$) and mixed IH ($p<0.0001$). Timing of the appearance of IH is noted cumulatively as follows. On day of life 0 (DOL0), 46% of superficial, 42% of mixed, and 12% of deep IH had been noted. By DOL7, 69% of superficial, 52% of mixed, and 19% of deep IH had been noted. By DOL30, 93% of superficial, 84% of mixed, and 38% of deep IH had been noted. Combining all three types of IH, 37% were noted by DOL0, 53% by DOL7, and 79% by DOL30.
Conclusion: Greater than one third of all IH were noted at birth, and over half were present by one week. Lesions with only deep involvement were noted later likely due to their "buried" location. This large retrospective review challenges the accepted literature stating that IH are not present at birth.

09:13-09:21 251 ***Beta blockers for infantile hemangiomas in the young, the small, and the pre-term***

Wendy Kim1, Smita Aggarwal1, Eulalia Baselga2, Leslie Castelo-Soccio3, Carol Cheng4, Ilona Frieden5, Maria Garzon6, Sharon Glick7, Kristen Holland8, Marilyn Liang9, Kari Martin10, Erin Mathes11, Kimberly Morel12, Jennifer Reeve9, Marianne Rosen7, Sonal Shah5, Dawn Siegel8, Shanna Spring5, Megha Tollefson13, Lily Uihlein1, Albert Yan3, Beth Drolet14

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Purpose: Since the initial report of oral propranolol use for the treatment of infantile hemangioma (IH) in 2008, there has been a number of case series describing both topical and oral beta-blocker efficacy. Young and preterm infants are considered to be at higher risk of adverse events from beta blockers. Recent publications using oral propranolol for treatment of retinopathy of prematurity substantiated these concerns, demonstrated 20% serious event rate in very preterm infants. This is an important consideration as low birth weight and preterm infants are at higher risk for infantile hemangiomas. This is a multisite retrospective cohort review of adverse events observed in young and preterm infants who were treated with oral propranolol or topical timolol for infantile hemangioma.
Methods: IRB was obtained at 10 sites and a total of 391 babies less than 8 weeks corrected gestational age at the time of drug initiation were identified. A RedCap database was developed to capture data on adverse events, patient demographics, dose and route of drug administration (topical vs oral), age and weight at both drug initiation and at time of adverse event.
Results: Of the 391 patients enrolled 379 were eligible for analysis. 246 were treated with oral propranolol and 179 were treated with topical timolol. Some patients were treated with topical timolol first and then oral propranolol or both drugs simultaneously, so participants may be included in both categories. Median age at drug initiation was 4.16 weeks corrected gestational age (range: -9 to 8 weeks) for oral propranolol, and 3.90 weeks corrected gestational age (range: -11 to 8 weeks) for topical timolol. There were a total of 113 adverse events observed in 90/246 (37%) patients on oral propranolol. There were 41 events observed in 32/179 (18%) patients treated with topical timolol. There were 11 serious adverse events in 11/246 patients (4.8%) treated with oral propranolol (3 bradycardia, 1 hypotension, 5 bronchospasm, 2 hypoglycemia) and 3 events in 2/179 patients (1.1%) treated with topical timolol (1 bradycardia, 1 hypotension, 1 hypothermia). All of the cardiovascular serious adverse events occurred at a young age (all less than 5 weeks corrected gestational age) while bronchospasm and hypoglycemia did not seem to be age related.
Conclusion: This retrospective chart review demonstrates the frequent use of off-label oral and topical beta blockers in young and preterm infants for the treatment of IH. The rate of serious adverse events was lower in topical vs oral administration. Cardiovascular adverse events preferentially affected younger infants. The overall serious adverse event was low occurring 4.8 % of participants on oral propranolol and 1.1 % on topical timolol, however, it is higher than what has been previously reported in hemangioma trials. The rate of serious adverse events was significantly lower than what has been observed in trials using oral propranolol for the treatment of retinopathy of prematurity. Additional prospective studies are needed to determine optimal dosing, ideal route of administration, and risk factors for adverse events in the young and preterm infants receiving beta blockers for IH.

09:21-09:29 289 ***Atenolol for the treatment of infantile hemangiomas***

D.V. Romanov

Purpose: Propranolol therapy has been effective in infants with infantile hemangioma (IH). However, this treatment is not risk-free and many patients are excluded because of respiratory comorbidities, sleep disturbances etc. Atenolol is a cardioselective beta-blocker that may have fewer adverse effects. The aim of this study was to evaluate the efficacy and safety of oral atenolol.
Methods: From 2014 and 2015 the children with IH were treated with oral atenolol 0,5-1mg/kg per day. All patients underwent a comprehensive check-up before treatment: photographing hemangiomas, cardiac evaluation (ECG, echocardiography, Holter monitoring, measurement of blood pressure), determination of the glucose level in the blood, ultrasound with Doppler. 193 patients with IH at the age from 1 week to 2 years were treated. The boys were 51 (26.4%), the girls - 142 (73.5%). IHs were located: on the face and head in 124 patients (64%); on the body - 34 (17.6%); in the limbs - 14 (15.4%); IH multiple areas in 22 (11.4%), haemangiomatosis - 10 (5.1%), 3 (1.5%) patients had hepatic hemangiomas.
Results: Treatment with oral atenolol was conducted in two stages. The starting dosage was 0.5 mg/kg body weight per day, according to the results of a cardiac examination the dosage was increased to 1 mg/kg body weight per day. This dose was divided into two equal fractions, every 12 hours. Cardiac changes were following: arrhythmia 42 (21.7%), tachycardia, 30 (15.5%), mild bradycardia -28 (14.5%). The norm of ECG during treatment was observed in 90 (46.6%) patients. There were no cardiac indications for discontinuation of atenolol treatment. Respiratory changes were not revealed. All patients had no sleep disturbances (94%). Reduction of blood glucose in patients was not observed. The heart ultrasound examination had minor anomalies (patent foramen oval etc) in 98% of patients, the hemodynamic instability was not observed during therapy. The dosage of Atenolol of 0.5 mg/kg per day was given to the patients with the light bradycardia and heart rate levels at the lower limit of the norm - 59 (30.6%). Atenolol dosage of 1 mg/kg per day was given to 134 patients (69.4%). The good results of treatment were achieved after 4-6 months of therapy with atenolol.
Conclusion: Atenolol therapy is a safe and effective alternative propranolol therapy. Application of atenolol prevents respiratory complications and does not lead to sleep disturbances in patients. The use of atenolol reduces duration of drug therapy of children with IH.

09:20-09:37 210 ***Adjuvant therapy improves outcomes in patients undergoing propranolol therapy***

Milton Waner1, Eric Cerrati2, David Binetter1, Teresa O1

1Vascular Birthmark Institute of New York, AVM Center, at Lenox Hill and Manhattan Eye, Ear, and Throat Hospitals., 2Department of Otolaryngology, New York University Medical Center

Purpose: Focal and segmental infantile hemangiomas(IH) differ in many ways. Their response to propranolol as well as their need for adjuvant therapy has never been compared. Since it is difficult to compare and especially to quantify the response of a diffuse, segmental IH to a focal lesion, we studied the need for adjuvant treatment as well as the type of treatment, surgery or laser, needed to complete treatment amongst the two groups.
Methods: A retrospective chart review of all children with diagnosis of IH treated with propranolol (2-3mg per kg per day) between 2008-2012 with complete records(including photos) were studied. Demographic information and the need for adjuvant treatment as well as the type of adjuvant therapy was noted.
Results: A total of 84 patients were studied; 60 had focal lesions and 24 segmental. The age range and the age at commencement of treatment for the two groups was similar. The duration of treatment for patients with segmental IH was longer(average=9.54mo) compared with the focal group (average=5.85mo) (p=0.0089). Overall, the number that required adjuvant therapy was similar(27% for the focal and 33% for the segmental groups). More patients with focal IH(58%) required adjuvant surgery compared with the segmental group (33%)(P=0.39). More patients with segmental IH(83%) required adjuvant pulsed dye laser treatment than the focal group (48%) (p=0.0005).
Conclusion: Patients with segmental IH required longer treatment with propranolol but required less surgery than patients with focal IH. If adjuvant therapy was necessary for this group it was most likely to be laser treatment.

09:37-09:45 239 ***Aggressive Metastatic Vascular Tumors Arising from Hepatic Infantile Hemangioma in Childhood***

Lonela Lacobas

Baylor College of Medicine, Houston, TX

Purpose: Hepatic infantile hemangioma (HIH) is classified as a benign vascular tumor with a classic natural course of proliferation, stabilization and involution. There are no guidelines for long term monitoring. We describe two cases of HIH that progressed to metastatic vascular tumors.
Methods: Both patients were three years of age, unrelated presenting with abdominal distension, constipation and the history of small, untreated, cutaneous IH in infancy that were in the involution stage.
Results: Case 1: Previously healthy girl had multiple, diffuse hepatic hemangiomas; therefore, she underwent liver transplantation. Pathological evaluation of the explant showed typical GLUT-1 positive HIH and hypercellular islands with cytologic atypia and high mitotic activity. One year after the transplant, surveillance imaging detected pulmonary nodules. Two of them were resected and histology showed identical atypical highly proliferative pattern again. She remains in complete remission 6 months after completing 6 cycles of ifosfamide/doxorubicin. Case 2: Previously healthy boy presented with a large hepatic mass, secondary goiter and multiple pulmonary nodules. The hepatic tumor was resected with negative margins and pathologic evaluation showed typical GLUT-1 positive HIH and islands of classic angiosarcoma. His goiter resolved after hepatic tumor removal. His disease progressed on sorafenib. After an initial partial response, the angiosarcoma progressed also on ifosfamide and doxorubicin, and he had progressive disease on bevacizumab/gemcitabine/docetaxel therapy. Interestingly, two separate biopsies of recurrent liver nodules showed GLUT-1 positive HIH without evidence of angiosarcoma. He died 1 year after diagnosis due to tumor progression.
Conclusion: Hepatic infantile hemangioma may be a risk factor for developing metastatic vascular tumors at a very young age. A study is on-going to collect additional cases and review therapeutic measures and outcomes. Systemic therapy with greater activity is needed for unresectable/metastatic patients to improve outcomes.

10:10-10:30	DC 1 - Difficult Case Presentations I	Juan Pablo II Room

Chairs: Anne Dompmartin, Tony Penington

10:10-10.20 39 ***Congenital intra-muscular hemangioma and "CM-AVM like"capillary malformations, a variant of CM-AVM syndrome or a novel entity***

Olivia Boccara1, Jean Philippe Arnault2, Valérie Li Thiao Te2, Christine Léauté-Labrèze3, Michel Wassef4, Sylvie Fraitag1, Veronique Soupre1, miika Vikkula5, Stéphanie Pannier1, Francis Brunelle1

1Necker Hospital, 2CHU Amiens, 3CHU Bordeaux, 4Lariboisière Hospital, 5UCLouvain

Purpose: Purpose: To describe the clinical, radiological and histological features of a peculiar paediatric case of a high flow vascular anomaly associated with multiple progressive "CM-AVM like" capillary malformations (CM), without RASA-1 mutation, and to discuss its multidisciplinary management.
Results: Observation: A healthy female infant presented at birth with a huge tumor located to the right shoulder. Clinical examination revealed numerous CM of various size, pale pink, surrounded by a pale halo. The tumor was warm, pulsating, without thrill. US Doppler indicated the presence of fast-flow vessels, with a right axillar artery flow 10 times above the left side. MRI showed a well delimitated mass infiltrating the underlying muscles, with high signal intensity in T1 and T2 weighted images, and gadolinium enhancement. The histological analysis showed a GLUT-1 negative capillary proliferation dissecting between muscle cell fascicles with variable arteries, veins, fibrosis and fat tissue. The diagnosis of intra-muscular hemangioma was proposed. RASA-1 gene was completely sequenced, with no mutation found. Propranolol, high dose corticosteroids associated with vincristine, and rapamycin, successively failed to reduce the tumor's size. At the age of 3 years, cardiac high output occurred, in an otherwise thriving child, with increasing CM number. Embolization was performed, the tumor became less pulsating but did not shrink. Surgical debulking is then considered.
Conclusion: The association of a fast flow lesion histologically close to AVM, with multiple "CM-AVM like" CM but without RASA-1 mutations rises the hypothesis of a syndrome close to CM-AVM syndrome, possibly due to a mutation in the RAS signalling pathway. In our experience, neither embolization nor medical treatments commonly used in vascular anomalies, were efficient in reducing the intramuscular hemangioma size, for which surgical debulking should be considered.

10:20-10:30 371 ***Proximal ileal arteriovenous malformation causing recurrent, occult gastrointestinal bleeding in a 14-year-old boy***

Anna Lillis, Andrew Murphy, Victor Fox, Harry Kozakewich, Heung Bae Kim, Ahmad Alomari
Boston Children's Hospital

Purpose: To describe a successful multi-disciplinary approach to a case of recurrent occult gastrointestinal bleeding in a child
Methods: We present the case of a 14-year-old boy, who experienced chronic gastrointestinal bleeding over a period of one year. He initially presented with severe dizziness, abdominal discomfort, melena and hemoglobin of 5.6 g/dL, requiring blood transfusions every two weeks. Extensive non-invasive workup followed by laparotomy and enteroscopy performed elsewhere failed to localize the source of bleeding. Video small bowel capsule endoscopy at our center revealed blood in the ileum without identification of a discrete source. CT angiogram identified a 6-mm focal area of enhancement in the ileum communicating with a distal branch of the superior mesenteric artery. Visceral angiogram with super-selective arteriography identified a fast-flow vascular malformation supplied by terminal branches of the ileal artery. Inability to super-selectively catheterize individual feeding arteries precluded safe embolization of the lesion. Diagnostic laparoscopy revealed multiple intra-abdominal adhesions and no clear vascular malformation. Initial careful visual and manual examination of the bowel after conversion to laparotomy failed to identify the lesion.
Results: On-table colonoscopy and enteroscopy demonstrated a punctate, pulsatile lesion without ulceration or adherent clot in the small bowel mucosa of the proximal ileum. With the assistance of transillumination from the endoscope, a cluster of serpiginous vessels could be seen visually coursing within the wall of the small bowel. Intraoperative ultrasound with probe placed directly onto the lesion confirmed high-flow. Inflow and outflow vessels were ligated with suture and lesion resected with a TA stapler. Histologic sections of the resected specimen demonstrated small intestine with enlarged arteries and enlarged veins in the submucosa, some with wall-thickening, consistent with an arteriovenous malformation. The patient was discharged from the hospital tolerating a regular diet after one week and is without gastrointestinal bleeding 9 months later.
Conclusion: Arteriovenous malformation is a rare cause of occult, chronic gastrointestinal bleeding in the pediatric population. A multidisciplinary approach optimizes the likelihood of therapeutic success.

10:30-11.00	Coffee Break

11.00-12:00	KN - Keynote: Segmental overgrowth disorders and the future of therapeutics	Juan Pablo II Room

Speaker: Leslie Biesecker, MD

Chief & Senior Investigator of Genetic Disease Research Branch, National Human Genome Research Institute

Chairs: Steven Fishman, Francine Blei

12:00-13:00	SS - PIERRE FABRE Sponsored Symposium	Juan Pablo II Room

Chair: Ana Giachetti

12:00-12:15 ***Mechanism of action of propranolol in infantile hemangioma: true and false***
Francois Moisan

12.15-12:30 ***Cardiac safety of beta-blockers in pediatric cardiology and for the treatment of infantile hemangioma***
Damien Bonnet

12:30-12.45 ***Oral propranolol in infantile hemangioma: resolved and unresolved problems***
Christine Leaute-Labreze

12.45-13:00 *Alain Delarue*

13:00-14:00	LUNCH

14:00-15:00	ISSVA General Assembly *(Members only)*	Juan Pablo II Room

Free afternoon

Thursday April 28, 2016

Juan Pablo II

08:00-09:30	**Session 2: Genetics**
09:45-10:15	**Coffee Break**
10:15-11:45	**Session 3: Basic Science**
11:45-12:15	**Difficult Case Presentations II**
12:15-13:30	**Lunch**
13:30-14:45	**Session 4: Sirolimus for Vascular Anomalies**
14:45-15:05	**Difficult Case Presentations III**
15:05-15:30	**Coffee Break**
15.30-15:45	**Poster Pearls**
15:45-16:50	**Session 5: Lymphatic Malformations and Syndromic Vascular Malformations**
16:50-17:20	**Difficult Case Presentations IV**

08:00– 09:30 | **SE 2 - Session 2: Genetics** | **Juan Pablo II Room**

Chairs: Miikka Vikkula, Douglas Marchuk

08:00-08:10 272 ***GNAQ p.R183Q Mutation Disrupts Endothelial Behavior in Capillary Malformation***

LAN HUANG1, Javier Couto2, John Mulliken2, Arin Greene2, Joyce Bischoff3

1Boston Children's Hospital, 2Departments of Plastic and Oral Surgery, Vascular Anomalies Center, Boston Children's Hospital and Harvard Medical School, 3Departments of Surgery, Vascular Biology Program, Boston Children's Hospital and Harvard Medical School

Background: Capillary malformation (CM) is a common congenital vascular malformation. It is comprised of enlarged endothelial-lined channels surrounded by disorganized perivascular cells located in the papillary dermis. CM can be sporadic and also be associated with other abnormalities such as Sturge-Weber syndrome (SWS). SWS is a neurocutaneous disorder consisting of facial CM and malformed vessels in the ipsilateral leptomeninges. A somatic mosaic mutation in GNAQ (c.548G A, p.Arg183Gln (R183Q)), encoding the G-protein subunit Gαq, was found in both sporadic CMs and SWS. Our laboratory has recently shown the GNAQ p.R183Q mutation is enriched in endothelial cells (EC) in CM. The current study aims to determine how the GNAQ p.R183Q mutation disrupts normal endothelial phenotype and function thus causing CM.
Methods: Lentiviral expression constructs encoding wild-type (WT) GNAQ or p.R183Q mutant GNAQ were introduced into human endothelial colony forming cells (ECFCs). EC-WT and EC-R183Q were assayed in in vitro angiogenesis assays to understand how GNAQ mutation affects basal and VEGF-stimulated endothelial behaviors. MAP-kinase, AKT and mTOR signaling pathways were assessed by immuno-blot. Indirect and direct co-culture assays were performed to test for potential alterations in the crosstalk between GNAQ p.R183Q ECs and normal perivascular cells. For example, we examined EC-R183Q for their ability to induce human bone marrow-derived mesenchymal progenitor cells (MPCs) to differentiate into pericytic/smooth muscle cells.
Results: EC-R183Q displayed decreased migratory ability compared to EC-WT. In contrast, proliferation in response to basic FGF or VEGF-A stimulation was similar between EC-R183Q and EC-WT. ERK1/2 phosphorylation was marginally increased in EC-R183Q compared to EC-WT upon VEGF-A stimulation but no differences were found in pAKT or mTOR targets. EC-R183Q secreted more PDGF-BB compared to EC-WT, indicating a potential for enhanced recruitment and stimulation of pericytes and smooth muscle cells. EC-R183Q were less able to stimulate MPC to differentiate into pericyte/smooth muscle cells, as seen by reduced expression of Calponin, PDGFRβ and NG2 when EC-R183Q were placed in co-culture with MPC compared to EC-WT in co-culture with MPC.
Conclusion: The GNAQ p.R183Q mutation confers specific changes in EC behavior, which may potentially alter interactions between endothelial and mural cells. This could account for the chaotic arrangement of perivascular cells surrounding CM vessels, evident in histological sections. The GNAQ mutant ECs may also have relevance to the abnormal vessels found in the leptomeninges of SWS patients, which are speculated to contribute to the neurological deficits in these patients.

08:10-08-20 22 ***Phakomatosis pigmentovascularis is caused by post-zygotic mutations in GNA11 or GNAQ***

Anna Thomas1, Zhiqiang Zheng2, JeanBaptiste Rivière3, Ryan O'Shaughnessy4, Lara AlOlabi5, Judith StOnge6, David Atherton7, Hélène Aubert8, Lorea Bagazgoitia9, Sébastien Barbarot8, Emmanuelle Bourrat10, Christine Chiaverini11, W Kling Chong12, Yannis Duffourd3, Mary Glover13, Leopold Groesser14, Smail HadjRabia15, Henning Hamm16, Rudolf Happle17, Imran Mushtaq18, JeanPhilippe Lacour11, Regula Waelchli13, Marion Wobser16, Pierre Vabres19, Elizabeth Patton2, Veronica Kinsler20

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Purpose: Phakomatosis Pigmentovascularis (PPV) is a group of syndromes defined by the simultaneous congenital presentation of both vascular and pigmentary birthmarks. Subtypes are defined by the specific birthmark classifications, the commonest being capillary malformations with dermal melanocytosis. PPV is associated with neuro-vascular, ophthalmological, overgrowth and malignant complications. We sought to investigate the genetic basis of PPV, based on the similarity of neurological abnormalities with those seen in Sturge-Weber syndrome.

Methods: Skin biopsies were taken with written consent from vascular and pigmentary birthmarks from eight patients. DNA was extracted directly from these and from a peripheral blood sample. Candidate genes sequenced were GNAQ and the highly homologous GNA11, which encode Gαsubunits of heterotrimeric G-proteins. Sequencing was performed by Sanger sequencing with restriction digest of putative normal alleles, and by a next generation sequencing targeted panel. The effects of in vitro expression of mutant GNA11R183C and GNA11Q209L in human cell lines were characterised using RT-PCR and Western blotting for downstream signaling pathway phosphorylation targets (p38 MAPK, JNK, ERK, AKT). Transgenic mosaic zebrafish models expressing mutant GNA11R183C under promoter mitfa were developed and grown to adulthood.

Results: 6/8 patients were found to have missense mutations in GNA11(n=4) or GNAQ (n=2). The mutations were detected at very low level in affected tissues but were undetectable in the blood, indicating that these conditions are post-zygotic mosaic disorders. The same mutation was found in both vascular and pigmentary birthmarks in any one patient, implying that a single mutation to a common precursor has given rise to both cutaneous lesions. No evidence was found for the now-retracted theory of twin-spotting. Mutations were characterized in vitro as activating, and the zebrafish model recapitulated the human phenotype.

Conclusion: PPV is caused by activating mutations in GNA11 or GNAQ. This is the first description of GNA11 mutations as a cause of capillary malformations, and an extension of the GNAQ mosaic phenotype. PPV is therefore a new diagnosis in the group of mosaic heterotrimeric G-protein disorders, joining McCune-Albright and Sturge-Weber syndromes. These findings will allow accurate clinical and molecular diagnosis of this subset of common birthmarks, thereby identifying infants at risk of serious complications.

08:20-08:30 151 ***Identification of a Second Gene Mutated in Capillary Malformation–Arteriovenous Malformation***

Nicole Revencu1, Mustapha Amyere2, Eleonore Pairet3, Raphael Helaers2, Eulalia Baselga4, Maria Cordisco5, Wendy Chung6, Josee Dubois7, JeanPhilippe Lacour8, Loreto Martorell9, Juliette Maze-reeuwHautier10, Reed E. Pyeritz11, John B. Mulliken12, Laurence M. Boon13, Miikka Vikkula2

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Purpose: Capillary Malformation–Arteriovenous Malformation (CM-AVM) is an autosomal dominant disorder manifesting multifocal CMs together with high risk for fast-flow vascular malformations. We have detected RASA1 heterozygous loss-of-function mutations in about 70% of screened CM-AVM families, which suggests genetic heterogeneity. Here we report the identification of a new gene involved in CM-AVM.

Methods: We performed a genome-wide linkage study in a large family with autosomal dominantly inherited CMs. We also performed whole exome sequencing (WES) on 11 blood samples of patients from 9 families with CM-AVM and no RASA1 mutation. Subsequently, a pinpointed candidate-gene was screened by targeted massively parallel sequencing for mutations in 350 families with CMs associated or not with fast-flow vascular malformations. Expression studies of some identified missense mutations were performed.

Results: We identified highly significant evidence for linkage on chromosome 7. A damaging mutation in a gene on Chr7 was identified in 5 out 9 families using WES. Targeted sequencing unravelled mutations in an additional 50 families with CMs with/without fast-flow vascular malformations. In total, 56 mutations were identified: 50% were non-sense, frame-shift, or splice site mutations, and 50% were substitutions predicted to strongly impact protein function. Expression studies demonstrated loss of protein function. Mutations were identified in a total of 103 individuals: more than 95% of them had capillary malformations, usually multifocal, and 20% an associated fast-flow vascular malformation (mainly cutaneous, subcutaneous, muscular or bony arteriovenous malformation/arteriovenous fistula located in the head and neck region or in the extremities; some were intracranial, intraspinal or a Parkes Weber syndrome).

Conclusion: Our results point to a new gene for CM-AVM and contribute to a better understanding of the pathophysiological mechanism of this disorder. This will help develop targeted therapies in the future. The clinical features can now be compared with those associated with RASA1.

08:30-08:40 43 ***SOMATIC ACTIVATING PIK3CA MUTATIONS CAUSE VENOUS MALFORMATION***

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Purpose: Somatic mutations in the endothelial cell receptor TIE2/TEK cause more than half of sporadically occurring VMs. Here we aimed to identify, what causes VMs that do not encompass a TIE2/TEK mutation. We chose PIK3CA as a candidate gene, because the TIE2/TEK mutations cause activation of the PI3K/AKT signaling pathway, and PIK3CA mutations (the gene encoding the catalytic p110α subunit of PI3K) have been identified in LMs and in capillaro-lymphatico-venous malformations.
Methods: We screened surgically excised VMs from 87 unrelated individuals with VM. Informed consent was obtained from all participants. Sensitive targeted deep-sequencing (detecting as low as 1% of mutant alleles) of all TEK and PIK3CA coding exons was carried out using an IonAmpliSeq Custom DNA Panel. Identified mutations were expressed in vein endothelial cells to study cellular effects.
Results: PIK3CA hot-spot mutations (frequent in PIK3CA-associated cancers, overgrowth syndromes and LM) were identified in VMs from 27 out of 87 individuals (31%), and TEK mutations in 37 individuals. When combined with previous data, mutations in TEK account for 80/130 VMs (61.5%), and PIK3CA mutations account for 27/130 VMs (20.8%). >92% of PIK3CA mutations were hot-spot mutations. Genotype-phenotype correlations in lesion localization and histology were observed between PIK3CA vs. TEK mutated VMs, pointing to gene-specific effects. In vein endothelial cells, PIK3CA mutations had effects similar to those seen with TIE2 mutations: activation of AKT, dysregulation of important angiogenic factors, and abnormal endothelial cell morphology. The PI3K inhibitor BYL719 restored the abnormal phenotypes, even more efficiently than rapamycin.
Conclusion: This study demonstrates that about 20% of VMs are caused by PIK3CA mutations and 60% by TIE2 mutations. Both cause activation of PI3K/AKT signaling pathway, but at different levels of the cascade. This might partially explain why some individuals with VM respond better to rapamycin than others.

08:40-08:50 155 ***PIK3CA mutations in Vascular Malformations***

Gema Gordo Trujillo1, Pablo Lapunzina1, Angela del Pozo1, Lara Rodriguez Laguna1, Kristina Ibañez1, Jair Tenorio1, Juan Carlos Silla1, Pedro Arias1, Irene Dapia Garcia1, Ruben Martin Arenas1, Victoria Eugenia Fernandez Montaño1, Inmaculada RuedaArenas1, Maria Victoria Gomez1, Elena Vallespin1, Rocio Mena de la Cruz1, Victor MartinezGlez1, Juan Carlos LopezGutierrez2

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Purpose: Vascular malformations are a subset of vascular anomalies that arise during developmental morphogenesis. The PI3K/AKT/mTOR signalling pathway is frequently dysregulated in disorders of cell growth and survival, including lymphatic malformations (LM) and capillary malformations (CM). LMs are a common component of CLOVES Syndrome (Congenital Lipomatous Overgrowth, Vascular malformations, Epidermal nevi, and Skeletal anomalies) and CMs are one of the principal features of Macrocephaly-Capillary Malformation. These two syndromes were recently included into the group PIK3CA-Related Overgrowth Spectrum (PROS), as both are caused by somatic mutations in the PIK3CA gene. To date, all described patients with PROS are sporadic (no family history) and practically all have shown mosaic distribution. As somatic mosaicism makes clinical expression variable in severity and location, the phenotypic spectrum of this group of segmental overgrowth syndromes is still to be elucidated. In the field of therapy, a variety of agents as Rapamycin have been successfully used to target PI3K/AKT/mTOR pathway in vascular malformations; however, the specific mechanism of action of these drugs and its possible use in PROS patients remains still unknown. Here we present a phenotypic and molecular characterization of more than 60 patients with PROS.
Methods: In the last decade, the Institute of Medical and Molecular Genetics (INGEMM) and the Vascular Anomalies Center at La Paz Hospital in Madrid have been established as nationwide referral services for patients with overgrowth disorders and vascular malformations. We have clinically assessed a cohort of 60 patients diagnosed with PROS, and we have developed an experimental and bioinformatic protocol for the diagnosis of these patients including blood, saliva, and tissue samples analysis by Next Generation Sequencing (NGS).
Results: Our tool allowed us to detect low mosaic genetic variants and to discriminate variants located in exons (10 to 14) of PIK3CA gene known for having more than 98% of homology with another genome region located in chromosome 22.
Conclusion: The application of bioinformatics tools to analyze massive data from NGS is able to discriminate low mosaic variants and the uniqueness of the variant in those regions with high homology to other regions of the genome. Detecting mutations in PIK3CA gene in our cohort of 60 PROS patients might serve in the near future as a biomarker for pharmacological treatment (i.e., Rapamycin).

08:50-09:00 45 ***Blue Rubber Bleb Nevus (Brbn) Syndrome Is Caused by Specific Somatic Tie2-mutations***

Julie Soblet1, Jaakko Kangas2, Marjut Nätynki2, Antonella Mendola1, Raphael Helaers1, Melanie Uebelhoer1, Mika Kaakinen2, Maria Cordisco3, Anne Dompmartin4, Odile Enjolras5, Simon Holden6, Alan D. Irvine7, Loshan Kangesu8, Christine LeauteLabreze9, Agustina Lanoel10, Zerina Lokmic11, Saskia Maas12, Maeve A. McAleer13, Anthony Penington14, Paul Rieu15, Samira Syed16, Carine van der Vleuten17, Rosemarie Watson7, Steven J. Fishman18, John B. Mulliken19, Lauri Eklund2, Nisha Limaye1, Laurence M. Boon20, Miikka Vikkula21

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Purpose: Blue rubber bleb nevus syndrome (BRBN) is a rare, sporadically occurring, severe congenital disorder, characterized by numerous cutaneous and internal VMs; GI-lesions are pathognomonic. Bleeding from lesions causes chronic iron deficiency anemia. We aimed to characterize the cause of this disorder. We hypothesized that BRBN is caused by somatic mutations in TEK, the gene encoding the endothelial cell receptor TIE2, as activating germline and somatic TIE2-mutations cause inherited cutaneomucosal venous malformation (VMCM) and 60% of VMs, respectively.
Methods: We assessed for TIE2 mutations in 17 unrelated BRBN patients. Six additional patients had multifocal VMs, but without the typical features of BRBN; instead, the phenotype was reminiscent of VMCM, but without family history. We categorized these patients under: multifocal sporadic venous malformation (MSVM). We looked for TIE2 mutations in surgically resected lesions using targeted deep sequencing with a custom AmpliSeq panel. Blood-extracted DNA was subsequently studied to see if the individual was mosaic for the tissular mutation. Mutations were expressed in vein endothelial cells to study cellular effects.
Results: We discovered somatic activating TIE2/TEK mutations in 15/17 BRBN and 5/6 MSVM patients. Both BRBN and MSVM are characterized by double cis mutations, identical in all lesions from a given patient. These mutations are somatic in BRBN, and a combination of a mosaic (R915C, detected at low levels in blood) and a somatic change (Y897C, in affected tissue only) in MSVM. BRBN-associated mutations increased survival, migration, invasion and colony-formation of vein endothelial cells.
Conclusion: BRBN is caused by somatic mutations in TIE2/TEK. The mutations and downstream effects differ from VM- and MSVM-mutations, which may explain the fact that BRBN uniquely shows evidence of ongoing dissemination of mutant cells from a niche throughout life. The data suggests that mTOR inhibitors, such as rapamycin, can also be used to treat BRBN.

09:00-09:10 44 ***Mutations in VEGFR3 Signaling Pathway Explain a Third of Familial Primary Lymphedema***

Elodie Fastre1, Matthieu Schlogel1, Antonella Mendola1, Nicole Revencu2, Isabelle Quere3, Laurence M. Boon4, Pascal Brouillard1, Miikka Vikkula5

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Purpose: Lymphedema, caused by dysfunction of lymphatic vessels, leads to disabling swelling that occurs mostly on the extremities. Lymphedema can be either primary (congenital) or secondary (acquired). Familial primary lymphedema commonly segregates in an autosomal dominant or recessive manner. It can also occur in combination with other clinical features. Altogether 19 mutated genes have been identified in different isolated or syndromic forms of lymphedema. However, the prevalence of primary lymphedema that can be explained by these genetic alterations is unknown. In this study, we investigated systematically eleven of these putative genes.
Methods: We screened 112 index patients from families with inherited primary lymphedema and 328 patients with sporadic or unknown origin primary lymphedema. A targeted next generation sequencing panel for IonTorrent (Personal Genome Machine) was designed. We included coding regions of FLT4, VEGFC, KIF11, FOXC2, SOX18, CCBE1, PTPN14, GATA2, IKBKG, GJC2 and GJA1.
Results: We discovered 44 mutations explaining 39 % of the inherited cases. In addition, 49 mutations were found in sporadic or with unknown origin patients, explaining 15 % of the cases. Moreover, we are performing co-segregation analyses and more detailed clinical phenotyping for additional patients with a possible pathogenic nucleotide change.
Conclusion: The genetic cause of primary lymphedema remains unexplained in 61 % of patients with a family history and 85 % of sporadic or with unknown origin cases. Identification of those genes is important for understanding of etiopathogenesis, stratification of treatments and generation of disease models. Interestingly, most of the proteins that are encoded by the genes mutated in primary lymphedema seem to act in a single functional pathway involving VEGFR3 signaling. This underscores the important role this pathway plays in lymphatic development and function, and suggests that the unknown genes may also have a role in the same pathway.

09:10-09:20 153 ***Somatic GNAQ c.548G→A Mutation is Specific for Sturge-Weber Syndrome (SWS) and Port-Wine Stain (PWS) and is Reliably Detected by ddPCR in Small FFPE or Frozen Biopsies***

Valerie K Salato1, Qiuhui Yang1, Jonathan Pevsner2, Anne M. Comi2, Douglas A. Marchuk3, Beth A. Drolet1, John Jensen1, Robert H. Chun1, David M. King1, Patricia E. Burrows1, Dawn H. Siegel1, Paula North1

1Medical College of Wisconsin, 2Johns Hopkins School of Medicine, 3Duke University Medical Center

Purpose: SWS and non-syndromic PWS are caused by activating somatic GNAQ mutations, predominately c.548G→A,p.Arg183Gln. This offers a novel diagnostic target by which PWS/SWS cutaneous stains could potentially be distinguished from biologically unrelated vascular anomalies (VA) associated with cutaneous discolorations resembling PWS, guiding therapeutic intervention.
Methods: Using ddPCR, we screened for c.548G→A mutation and wild-type allele using bulk-extracted DNA (FFPE/frozen) samples of affected skin/subcutis and/or brain from 133 patients with VA, including: SWS (5 brain/4 skin) and non-syndromic PWS (16 facial/1 leg/1 shoulder); other vascular malformations with cutaneous staining: KTS (12), CM (9), VM (5), CM-AVM (1), verrucous venulocapillary malformation (7), CLOVES (2), Proteus syndrome (2), AVM (4), GVM (6); deeper soft tissue/brain malformations (AVM-6, VM-7, LM-3, lobular CM of fat -4, Maffucci syndrome-2, cavernoma-6); vascular tumors/tumor-like conditions (11 IH, 9 NICH/RICH, 3 KHE, 6 PG, PTEN-associated hamartoma (1). Controls were tonsil (4), epilepsy brain resections (7), melanocytic lesions (8), normal skin (4). Percent variant allelic frequency was quantitated.
Results: Specimen rejection criteria were based on threshold amplification of wild type allele (100 amplimers), eliminating 3 specimens. Positive and negative call criteria were rigorously developed and validated for clinical diagnostic testing. GNAQ c.548G→A mutation was detected in PWS (18/18) and SWS (4/4 skin; 3/5 brain) samples. No other non-PWS/SWS VA (0/98 patients), melanocytic lesions (0/8), or control tissues (0/15) harbored the mutation. Unaffected tissue available for 3 PWS/SWS patients was also negative for the mutation. FFPE tissue was as acceptable for analysis as frozen tissue in 16 of 20 cases for which both were available.
Conclusion: The GNAQ c.548G→A somatic mutation appears, among VA, to be specific for SWS/PWS, and can reliably be detected in small frozen or FFPE samples (e.g., punch biopsies). Clinically, this would be particularly useful in distinguishing true PWS, with risk of SWS, from atypical CM.

09:20-09:30 347 ***A Somatic MAP3K3 Mutation is Associated with Verrucous Venous Malformation***

Javier Couto, Matthew Vivero, Harry Kozakewich, Amir Taghinia, John Mulliken, Matthew Warman, Arin Greene

Boston Children's Hospital, Harvard Medical School

Purpose: Verrucous venous malformation (VVM), also called "verrucous hemangioma", is a sporadically occurring, nonhereditary congenital vascular anomaly. This hyperkeratotic skin lesion typically affects extremities, bleeds, and causes a deformity. The purpose of the study was to test the hypothesis that VVM is caused by a somatic mutation.
Methods: Whole-exome sequencing (WES) was performed on VVM tissue excised from 6 individuals. The sequence findings were compared to those from population databases and from patients with other types of vascular lesions. Mutations found only in VVM samples from ≥ 3 patients were further evaluated by subcloning and by droplet digital PCR (ddPCR).
Results: Three of 6 VVMs were found by WES to have a point mutation (c.1323C→G; p.I441M) in MAP3K3, that encodes mitogen-activated protein kinase kinase kinase 3. The MAP3K3 mutation was detected in 3 of 4 additional VVM specimens by ddPCR. Between 11.8% - 38.6% of cells in the affected tissues contained this mutation, which was not present in control databases or in other vascular anomalies (Figure).
Conclusion: A somatic mutation in MAP3K3 was found in 6/10 VVMs. MAP3K3 is involved in vascular development, and thus a somatic missense mutation in this gene likely is responsible for VVM. Further investigation is required to determine if other MAP3K3 mutations are present in VVMs, and whether MAP3K3 mutations are sufficient to cause VVM.

09:45-10:15 Coffee Break

10:15-11:45 SE 3 - Session 3: Basic Science Juan Pablo II Room

Chairs: Joyce Bischoff, Paula North

10:15-10:25 270 ***Role of hemangioma stem cell NOTCH3 in infantile hemangioma blood vessel development***

Andrew Edwards, June Wu, Carrie Shawber, Jan Kitajewski, Justin Kung, Alison Kitajewski

Columbia University Medical Center

Purpose: Infantile hemangiomas (IHs) are vascular tumors of infancy that occur within the first five years, and proceed through a phase of rapid proliferation followed by involution. IHs are thought to originate from CD133+ hemangioma stem cells (HemSCs). HemSCs are localized in perivascular cells of the IH vasculature and express NOTCH3, a protein required for proper mural cell differentiation and maturation. We hypothesize that NOTCH3 functions in HemSCs to promote perivascular cell differentiation.
Methods: HemSCs were infected with lentiviruses encoding a NOTCH3 shRNA (N3KD) or scrambled control (SCR). To evaluate NOTCH3 function in HemSC differentiation in vitro, HemSCs were cultured with cord blood endothelial progenitor cells (cbEPCs), which express high levels of the NOTCH ligand, JAGGED1. To assess the role of NOTCH3 in IH development in vivo, a mouse IH model was used in which HemSCs and cbEPCs were suspended in Matrigel and engrafted in immunodeficient mice. After 14 days the IH matrigel implants were harvested for immunohistological analyses.
Results: In vitro, control HemSCs differentiated into α-SMA+ cells when co-cultured with cbEPCs. In N3KD HemSCs, α-SMA expression was reduced when compared to control HemSCs (Figure 1). In vivo, control HemSC implants developed vascular structures with blood flow, measurable by Doppler ultrasound, and flow was reduced in N3KD HemSCs implants. Histological analysis of control implants revealed vessels with typical IH morphology covered by α-SMA+ perivascular cells. In contrast, IH matrigel implants with N3KD HemSCs had decreased α-SMA+ perivascular cell coverage and poor vessel integrity (Figure 2).
Conclusions: In IHs, NOTCH3 promotes HemSC differentiation into α-SMA+ perivascular cells that may contribute to stabilization of pathological IH vasculature, suggesting NOTCH3 is a potential therapeutic target.

10:25-10:35 53 ***Endothelial Expression and Systemic Circulation of C19MC Placental MicroRNAs are Distinguishing Features of Infantile Hemangiomas***

Graham Strub1, Andrew Kirsh1, Mark Whipple2, Mark Majesky1, Jonathan Perkins3

1Seattle Children's Hospital, 2University of Washington, 3Seattle Childrens Hospital

Purpose: Infantile hemangioma (IH) is the most common vascular tumor of infancy and uniquely regresses in response to oral propranolol, yet its origin, pathophysiology, and mechanism of propranolol response remain under investigation. We previously identified expression of the placental microRNA (miRNA) cluster C19MC in IH tissue. The current study sought to identify the C19MC miRNA expressing IH cell type, demonstrate the specificity of C19MC to IH among other vascular anomalies, determine if circulating C19MC miRNAs can serve as reliable biomarkers, and illustrate the effect of propranolol treatment on C19MC expression.
Methods: Cell type identification was accomplished by miRNA in-situ hybridization in conjunction with immunofluorescent detection CD31 and GLUT-1 and by miRNA qRT-PCR analysis of cell fractions separated by flow cytometry. Expression specificity and detection in circulation was accomplished by qRT-PCR in tissue from 27 patients and plasma from 71 patients. Propranolol effect was demonstrated by qRT-PCR of serially collected plasma samples during drug treatment.
Results: GLUT-1 expressing endothelial cells are the C19MC expressing cell type in IH. Of the 9 types of vascular anomaly tissue studied, only IH expressed C19MC miRNAs. Circulating C19MC miRNAs were detectable in plasma from IH patients at levels which correlated to tumor size and patient age, while circulating levels of C19MC miRNAs decreased with 1 and 6 months of propranolol treatment and correlated clinically with drug response.
Conclusion: The placental miRNA cluster C19MC is expressed by GLUT-1 positive IH endothelial cells, is specific to IH among vascular anomalies, is detectable in the circulation of IH patients, and decreases with propranolol treatment. These data support a placental origin hypothesis of IH and implicate a cluster of miRNAs as potential drivers of IH pathogenesis. Detection of C19MC miRNAs in the circulation of infants with IH may provide a specific and non-invasive means of diagnosing IH to identify candidates for propranolol therapy.

10:35-10:45 91 ***Expression of Wilms' Tumor Gene 1 in Vascular Malformations and Juvenile Hemangiomas***

Chunyang Fan1, Gresham Richter1, Yuemeng Dai1, James Suen2

1Univ. of Arkansas for Medical Sciences, 2Univ. of Arkansas for Medical Sciences

Purpose: Infantile hemangioma (IH) is the most common vascular tumor of infancy and uniquely regresses in response to oral propranolol, yet its origin, pathophysiology, and mechanism of propranolol response remain under investigation. We previously identified expression of the placental microRNA (miRNA) cluster C19MC in IH tissue. The current study sought to identify the C19MC miRNA expressing IH cell type, demonstrate the specificity of C19MC to IH among other vascular anomalies, determine if circulating C19MC miRNAs can serve as reliable biomarkers, and illustrate the effect of propranolol treatment on C19MC expression.
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Conclusion: The placental miRNA cluster C19MC is expressed by GLUT-1 positive IH endothelial cells, is specific to IH among vascular anomalies, is detectable in the circulation of IH patients, and decreases with propranolol treatment. These data support a placental origin hypothesis of IH and implicate a cluster of miRNAs as potential drivers of IH pathogenesis. Detection of C19MC miRNAs in the circulation of infants with IH may provide a specific and non-invasive means of diagnosing IH to identify candidates for propranolol therapy.

10:45-10:55 133 ***Effects of AKT-GSK-3β signaling pathway on Apoptosis of Mouse Hemangioendothelioma Endothelial Cells caused by Propranolol***

Xu Xianyun1, Xie Qiongjun1, Peng Wei1, Tao Chao2, Huang Haijin3, Yan Jinlong2, Xu Lu4, Ning Huiting1, Ma Liangwen1, Wen Tingyu1, He Xiaodong5, Liu Qian3

1Gannan Medical University, 2Medical College of Nanchang University, 3Pediatric surgery Department of the First Affiliated Hospital of Gannan Medical University, 4Guangdong Provincial Maternity and Child Care Center, 5Kindcare Children's Hospital Chongqing

Purpose: Propranolol has been shown to hold potent antiproliferative and apoptosis induction properties for infant hemangioma in vitro and in vivo. In this study,we observed the effect of propranolol on proliferation and Apoptosis of Mouse Hemangioendothelioma Endothelial Cells(EOMA),the expression of Akt Phospho-Akt (Ser473) GSK-3β and Phospho-GSK-3β (Ser9) in EOMA after treatment with propranolol in vitro.To investigate the potential role of Akt/GSK-3β signaling pathway on the mechanism of propranolol induced Apoptosis effects.
Methods: EOMA cells were cultured in vitro, the logarithmic growth phase EOMA cell, were randomly divided into drug group and control group, with different concentrations of propranolol and timolol effects of EOMA cells, 24h interference. Application of four methyl thiazolyl tetrazolium colorimetric assay (MTT) to detect cell viability , the apoptosis index was determined by acridine orange staining and AnnexinV/PI FCM assay, application of Western blot detection of Akt, Phospho-Akt (Ser473), GSK-3 β and Phospho-GSK-3 β (Ser9) protein expressions
Results: The results demonstrated that propranolol-inhibit cell viability in a dose-dependent manner in EOMA cells treated with propranolol (50, 100, 200,400 and 800 μmol/L) for 24 h ,significant differences of cell viability were noted ($P < 0.05$) at the concentration of 50μmol/L76%,while continuing to increase to 800μmol/L, the cell survival rate decreased sharply to close to 5% Figure 1. Propranolol was also shown to induce apoptosis in a dose-dependent manner in EOMA cells treated with propranolol (50, 100and 200μmol/L) for 24 h($P<0.05$)Figure 2 3 4 5 .The significantly decreased levels of p-AKT and p-GSK-3β expression were observed in EOMA cells after propranolol treatments in a dose-dependent manner ($P<0.05$)(Figure6,7).
Conclusion: This study shows that propranolol can effectively inhibit the proliferation and induce the EOMA cell apoptosis in vitro, the apoptosis induction in EOMA cells by propranolol may be regulated through a AKT-GSK-3β pathway. These results demonstrate a potential mechanism by which propranolol to induce apoptosis initiation in EOMA cells.

10:55-11:05 340 ***EVIDENCE FOR SOMATIC MUTATIONS THAT COMPLEMENT ACTIVATING PIK3CA ALLELES IN DETERMINING THE GROWTH AND METABOLISM OF LYMPHATIC MALFORMATION-DERIVED ENDOTHELIAL CELLS***

Belinda Dickie

CCHMC - Cincinnati Children's Hospital Medical Center

Purpose: Multiple centers have confirmed the presence of activating PIK3CA alleles in lymphatic endothelial cells (LECs) derived from patient lymphatic malformations. We sought evidence for the existence of other genetic changes involved in the etiology of disease by isolating and characterizing multiple LEC populations derived from independent patient lesions.
Methods: Endothelial cells were isolated from either the fluid or tissue from 14 independent lymphatic malformations. Inflammatory/activation phenotypes were defined by qRT-PCR with, and without, the inhibition of PI3K with GDC-0941. Other signaling kinases were investigated for their roles in a similar fashion. Growth characteristics of the various cultures were measured by Wst-1 assay. Whole exome sequencing was performed to identify putative mutations that contributed to the disease phenotype.
Results: Inflammatory genes COX-2, IL-8, HO-1 and ANGPTL4 were generally up-regulated in LM-LECs. The inflammatory phenotype persisted with PI3K inhibition. HO-1 induction was shown to be dependent on AMPK activation, consistent with a cellular response to oxidative stress. ANGPTL4 up-regulation was indicative of metabolic stress, as demonstrated with normal LECs in which metabolism was experimentally perturbed. Whole exome sequencing has been performed on 6 of the patient samples. Three candidate SNPs, ATG2A, ANK3, and MTA1, seen with LM-LECs but not control cells from the three different patients have been identified at high frequencies and high read depth (>30% read frequency).
Conclusion: These novel alleles (ATG2A, ANK3, and MTA1) are currently being evaluated for their functional relevance. In total, our results support the hypothesis that cooperative mutations are necessary to establish a metabolic balance compatible with LEC growth or differentiation. This has clear implications for the development of viable animal models.

11:05-11:15 51 ***Overexpression of VEGF-C in bone induces a Gorham-Stout disease-like phenotype***

Asitha Silva1, Jian Feng2, Paul Dechow2, Kari Alitalo3, Michael Dellinger1

1UT Southwestern Medical Center, 2Texas A&M Baylor College of Dentistry, 3University of Helsinki

Purpose: Gorham-Stout disease (GSD) is a rare disease of unknown etiology characterized by the proliferation of lymphatic vessels to bone and by the progressive destruction of bone. Unfortunately, current therapies do little for patients suffering from this this disabling, disfiguring and deadly disease. The identification of effective therapies for GSD has been hindered, in part, because there are no animal models of this disease. The objective of this project was to develop an animal model of GSD. We hypothesized that the lymphatic defects in GSD could be modeled by overexpressing vascular endothelial growth factor C (VEGF-C) in bone.
Methods: To overexpress VEGFC in bone, we bred Osterix-tTA (Osx-tTA) transgenic mice with TetO-Vegfc transgenic mice. Femurs were collected from 5-week-old Osx-tTA and Osx-tTA;TetO-Vegfc mice and used for immunohistochemical and micoCT analysis.
Results: Lymphatic vessels were not present in femurs from Osx-tTA mice. In contrast, femurs from Osx-tTA;TetO-Vegfc mice were filled with lymphatic vessels. Femurs from Osx-tTA;TetO-Vegfc mice also displayed structural abnormalities. Cortical bone was thinner and more porous in Osx-tTA;TetO-Vegfc mice than Osx-tTA mice. Interestingly, all Osx-tTA;TetO-Vegfc mice also displayed chylothorax, a common complication in GSD.
Conclusion: In conclusion, we show that overexpression of VEGF-C by chondrocytes, osteoblasts, and osteocytes, induces the formation of lymphatic vessels in bone and bone structural defects. We believe that Osx-tTA;TetO-Vegfc mice could serve as an animal model of GSD and that these mice could be used to develop a better understanding of the pathogenesis of GSD and to identify therapies for this devastating disease.

11:15-11:23 346 ***ARTERIOVENOUS MALFORMATION EXPRESSION OF TRANSFORMING GROWTH FACTOR β-1 AND RELATED RECEPTORS***

Tara Rosenberg1, Ting Wei2, Haihong Zhang2, Jessica Boswell2, Jenika Sanchez2, James Phillips2, Gresham Richter2

1Baylor College of Medicine/Texas Children's Hospital, 2University of Arkansas for Medical Sciences

Purpose: Introduction: Arteriovenous malformations (AVMs) are very complex lesions, and the role of transforming growth factor β1 (TGF-β1) in their growth/development is not well understood. Objectives: We sought to measure the expression of TGF-β1 and related receptors in AVM tissue/serum and compare to normals.
Methods: Human AVM tissue (n=12), normal tissue (n=12), AVM patient serum (n=13) and normal patient serum (n=8) were collected from both pediatric and adult patients. The majority of the AVMs that were excised involved the head and neck. Tissue levels of TGF-β1, TGFBRI, TGFBRII, and Smad4 were assessed with Western blot analysis. Expression and localization of tissue TGF-β1 protein were determined with immunohistochemistry. Tissue messenger RNA expression of TGF-β1and its related receptors TGFBRI, TGFBRII, TGFBRIII, and ENG were measured by real-time PCR and levels compared. Quantification of serum TGF-β1expression by ELISA was performed.
Results: TGF-β1 expression was statistically higher in AVMs versus normal tissues (p=0.043). No significant difference was detected for TGFBRI, TGFBRII or Smad4. Immunohistochemistry illustrated strong positivity for TGF-β1 in all AVM tissue, predominantly in perivascular cells, but was weaker in normal tissue. The AVM tissue levels of TGF-β1 mRNA and of ENG were significantly higher than in normal controls (p=0.000069 and p=0.038, respectively). The serum TGF-β1 levels of AVM patients were higher than those in the control group (p=0.032).
Conclusion: Arteriovenous malformation tissue expresses significantly higher levels of TGF-β1 than normal tissue, and patients demonstrate elevated circulating concentrations. These findings indicate that the TGF-β1 pathway may be a target for future therapeutic agents.

11:23-11:31 9 ***Elevated Expression of MMP-9 in Human Lymphatic Malformation***

Ting Wei, Haihong Zhang, James Suen, Gresham Richter

University of Arkansas for Medical Sciences

Purpose: Lymphatic malformations (LMs) are one of the most common childhood head and neck masses. The etiology and pathophysiology are not well understood. Abnormal expression of Matrix Metalloproteinase-9 (MMP-9) has specifically been targeted as a significant causative factor in excessive tissue remodeling which underlies multiple pathologic processes. This study was designed to detect the expression of MMP-9 in human LMs and explore preliminarily the possible role of MMP-9 in the expansive growth of LMs.
Methods: Fresh human LMs (n=10) and normal tissues (n=12) were harvested, immediately frozen or fixed. Quantitative assessment and localization of MMP-9 in tissues were performed by real-time PCR, Western blot, zymography and immunohistochemistry assays. Sera collected from LM patients (n=13) and healthy volunteers (n=10) as normal controls were used to detect serum MMP-9 expression by ELISA assay.
Results: Real-time PCR showed that mRNA expression of MMP-9 in LMs was approximately 14-fold increased as compared with normal tissues (P=0.006). Western blot analysis demonstrated that four MMP-9 species were detected in all of the LM samples, 3 out the four had enzymatic activities; however in normal tissues, the main MMP-9 species was MMP-9/TIMP-1 complex which had no enzymatic activity. Immunohistochemistry assay illustrated that MMP-9 was moderately to strongly positive in most of the LM samples (8 out of 10) comparing with weakly positive in normal tissues (11 of 12) and predominantly located in lymphatic endothelial cells, vascular endothelial cells and perivascular matrix. ELISA assay showed 2-fold increase of serum MMP-9 level in LM patients compared with normal controls (P=0.046).
Conclusion: Expression of MMP-9 is significantly elevated in human LM lesions. The high expression level leads to active extracellular matrix degradation and remodeling which can be used to explain the expansive growth of LMs. MMP-9 pathway is a novel treatment target and anti-MMP-9 pharmacotherapy is potentially effective to treat refractory clinical cases.

11:31-11:45 178 ***The miRNA Profile of Human Lymphatic Malformations***

Brandon Sumpio1, Brent Schultz1, Stephanie Douglas1, Andre Alcon1, Mark Youngblood1, Soonwo-ok Hong1, Richard Antaya1, Milton Waner2, Teresa O2, Alejandro Berenstein3, Deepak Narayan1

1Yale School of Medicine, 2Yale University School of Medicine, 3Mount Sinai Hospital

Purpose: Lymphatic malformations (LM) are dilated lymphatic vessels that are disconnected from the rest of the lymphatic system. The etiologies of LMs are still unknown, which has hindered the development of more advanced approaches to managing this disease. MicroRNAs (miRNAs) are short (19-22 nucleotide), non-coding, single stands of RNA that post-transcriptionally repress protein expression. They are involved in a majority of human physiology, from embryogenesis to tumorigenesis. By characterizing the miRNA expression profiles of 12 LMs and comparing their miRNA to normal human lymphatic endothelial cells, this paper seeks to better understand the disease.
Methods: RNA was extracted from human LM specimens and control human lymphatic endothelial cells for microarray analysis. The microarray data from LM and control endothelial cells was pooled and student's t-test was used to compare the data. miRNA bioinformatics databases were used to predict the miRNA regulators of a given gene. Pathway analysis was performed using Qiagen Ingenuity Pathway Analysis (Redwood City, California).
Results: The ten most up- and down-regulated miRNA's compared to normal lymphatic endothelial cells are shown in Table 1. Only two of these—miR-181b-5p and miR-551b-3p—are predicted to regulate Prox1 and GATA, genes known to be involved with LMs and lymphangiogenesis, respectively. Other miRNA transcripts that were not found in the top ten, but aberrantly expressed were found to regulate GATA2, Prox1 and VEGFR3, genes also associated with lymphangiogenesis (Table 2). Pathway analysis of the miRNA data showed that the CD36 pathway is inhibited by these miRNA's (Fig 1). The CD36 pathway is the thrombospondin-1 receptor that functions to inhibit lymphangiogenesis through the inhibition of VEGF-c and VEGF-d expression in lymphatic channels.
Conclusion: We have identified miRNAs that may play a role in pathogenesis of lymphatic malformations. Furthermore, we have identified a pathway that could serve as a novel drug target for suppressing lymphangiomas.

11:45-12:15 | DC 2 - Difficult Case Presentations II | Juan Pablo II Room

Chairs: María Cordisco, Dov Goldberg

11:45-12:00 319 ***EXTENSIVE ARTERIOVENOUS MALFORMATION OF THE BRAIN AND MANDIBLE ASSOCIATED WITH NEVUS SEBACEOUS SYNDROME (SCHIMMELPENNING SYNDROME)***

Julie Powell1, Louise Laberge2, Catherine Farrell2, Michèle David2, AnneVeronique Pelletier2, Elisabeth Rousseau2, Josee Dubois3

1CHU SainteJustine, U of Montreal, 2CHU Sainte Justine, 3CHU SteJustine

Purpose: Discussion of an unusual association and therapeutic challenge
Methods: Case presentation
Results: History: This 8 yo girl was born with an extensive nevus sebaceous of the right hemiface, scalp, neck and upper thorax. She also had a right ocular choristoma and coarctation of the aorta. She developed severe seizures at four months of life as well as developmental delay typical of Nevus Sebaceous (Schimmelpenning) syndrome. Her brain MRI at that time was normal except for leptomeningeal fat metaplasia around the pons. At age 7, an infiltrating AVM of the mandibular bone and the left hemiface were discovered following an episode of massive bleeding from the gum: she also has a brain AVM involving the pons. During the last year, she underwent several emergency embolizations for severe bleeding, with improvement of the mandibular AVM. A 6-month treatment with Sirolimus was not helpful. Genetic testing is pending.
Conclusion: Discussion: To our knowledge, only 2 cases of Nevus sebaceous syndrome associated with AVMs have been reported in the literature, one intracerebral and the other intraspinal. In recent years, post-zygotic HRAS and KRAS mutations have been identified in nevus sebaceous/ Schimmelpenning syndrome and these two conditions are now considered as RASopathies. Cerebral and intraspinal AVMs are seen in CM-AVM syndrome associated with RASA1 mutation, also a RASopathy. As HRAS, KRAS and RASA1 are part of the RAS/MAPK pathway, the association observed in this case is probably more than coincidental. Suggestions for further management would be appreciated.

12:00-12:15 211 ***Refractory Congenital Chylous Ascites Requiring Multiple Denver Shunt Revisions and Paracentesis***

Kathy Schall, Chadi Zeinati, Lori Howell, Dean Anselmo

Children's Hospital Los Angeles

Purpose: We present a difficult case of a term baby with known lymphedema of her left upper extremity presenting at three months of life with progressive abdominal distension.
Methods: After appropriate informed consent was given, a retrospective case review was completed.
Results: Extensive diagnostic workup (ultrasound, MRI, lymphoscintigraphy, and paracentesis) confirmed congenital chylous ascites. Initial medical management (medium chain triglyceride diet, NPO, TPN, Octreotide, diuretics) failed to resolve the ascites. She underwent esophagogastroduodenoscopy (EGD) with duodenal biopsies which revealed lymphangiectasia. Continued ascites led to subsequent surgical management that consisted of preoperative enteral fat loading followed by laparotomy with ligation of retroperitoneal lymphatics and application of peritoneal fibrin sealant. Despite this measure, her ascites recurred and was again attempted to be managed medically with recurrence and numerous therapeutic paracentesis. After ascites recurrence, a peritoneovenous shunt was placed. This shunt has required four revisions, omentectomy, and one shunt replacement over the past six months due to fibrin clogging and ascites recurrence. Patient had recurrence of increasing ascites and shunt was found to be occluded. Surgical management ensued with methylene blue loading, exploratory laparotomy, lymphatic channel ligation and cauterization and peritoneovenous shunt takedown. Ascites was refractory, requiring multiple rounds of therapeutic paracentesis. MRI was done showing ascites with appearance of lobulated macrocytic LM and she underwent drain placement and sclerotherapy with continued ascites.
Conclusion: She is now 6 years old with continued ascites requiring paracentesis and plans of continuing with another round of inpatient drain placement and sclerotherapy.

12:15-13:30 LUNCH

13:30-14:45	SE 4 - Session 4: Sirolimus for Vascular Anomalies	Juan Pablo II Room

Chairs: Cameron Trenor, Juan Carlos Lopez Gutierrez

13:30-13:40 106 ***Developmental Pharmacokinetics of Sirolimus: implications for dosing in neonates and infants with vascular anomalies***

Tomoyuki Mizuno1, Chie Emoto1, Tsuyoshi Fukuda1, Paula MobberleySchuman1, Adrienne Hammill1, Denise Adams2, Alexander Vinks1

1Cincinnati Children's Hospital Medical Center, 2Cincinatti Children's Hospital

Purpose: We recently reported sirolimus to be efficacious and well tolerated in patients with complicated vascular anomalies. Nevertheless dosing information for this pediatric population is very limited, especially for neonates and infants. The purpose of this study was to characterize the developmental trajectory of sirolimus clearance in very young patients using data from our pharmacokinetically guided clinical trial. In addition, we developed an age-appropriate dosing algorithm to facilitate achievement of the appropriate sirolimus target concentrations.
Methods: A total of 316 sirolimus pre-dose concentrations were obtained from 24 patients aged 3 weeks to 4 years participating in a concentration-controlled sirolimus Phase 2 study in children with complicated vascular anomalies. Sirolimus pharmacokinetic (PK) parameters were calculated using Bayesian estimation with a recently published population PK model (MW/Pharm, Mediware, Czech Republic). Allometrically scaled sirolimus clearance was modeled as a function of age using a sigmoidal Emax model (NONMEM 7.2, ICON, USA). Using the developmental PK model, sirolimus doses required to reach a trough target concentration of 10-15 ng/mL were simulated across the different age groups from 0-24 months.
Results: Allometrically scaled sirolimus clearance increased with age up to 24 months. The non-linear relationship between age and allometrically scaled clearance was well described by the sigmoidal Emax model. Based on the developmental PK model, predicted sirolimus maintenance doses were estimated as 0.4, 0.6, 0.9, 1.3 and 1.6 mg/m2 every 12 hours for the 1, 3, 6, 12 and 24 months age groups, respectively.
Conclusion: This study quantitatively described the relationship between sirolimus clearance and age in neonates and infants. An age-appropriate dosing algorithm was developed that will facilitate sirolimus target concentration attainment. This algorithm in combination with therapeutic drug monitoring will allow precision dosing in very young children receiving sirolimus treatment for complicated vascular anomalies.

13:40-13:50 361 ***Neonates require lower sirolimus doses to achieve therapeutic levels for treatment of vascular anomalies***

Kristin Shimano1, Janel LongBoyle2, Erin Mathes3, Anna Meyer2, Kristina Rosbe2, Christopher Dowd2, Daniel Cooke2, Ilona Frieden2

1University of California San Francisco, 2University of California, San Francisco, 3UCSF

Purpose: Neonates with vascular anomalies causing critical complications, including airway compromise from microcystic lymphatic malformations (LM) of the neck, or coagulopathy due to Kasabach Merritt Phenomenon (KMP), require early initiation of medical therapy. Standard (e.g. Lexicomp) recommendations for dosing of sirolimus in vascular anomalies start at 7 months of age. Guidelines for dosing in very young infants, who have different hepatic metabolism of many drugs, are needed.
Methods: We performed a retrospective chart review of 5 neonates with vascular malformations or tumors treated with sirolimus. Dose, frequency, trough levels, and pertinent labs were reviewed, along with clinical notes regarding treatment response and side-effects.
Results: Three patients with LM and two patients with KMP were treated with sirolimus starting at age 5 days to 4 weeks. Three of the patients quickly became supra-therapeutic (trough >25ng/mL) when starting at a dose of 0.8mg/m2 BID, and a fourth patient rapidly achieved a therapeutic level (15ng/mL) after only 3 days, suggesting that he would also have become supra-therapeutic if continued at the initial dosing. Based on these experiences, a fifth infant was started at a lower dose (0.5mg/m2) at 6 days of life, and subsequently achieved goal troughs of 4-10ng/mL at a dose of 0.9mg/m2 every other day. One infant had elevated systolic blood pressures with the elevated drug levels. Another had a wound secondary to pressure from his tracheostomy; elevated sirolimus levels have been shown to contribute to poor wound healing. One had elevated triglycerides. No other significant laboratory abnormalities were found. Infants who started out at supra-therapeutic dosing were titrated to doses of 0.8 mg/m2 every other day or 0.4 mg/m2 daily.
Conclusion: We propose sirolimus dosing in neonates be started at 0.4 mg/m2 daily, lower than the starting dose for older infants. Drug levels should be monitored frequently to avoid supra-therapeutic levels.

13:50-14:00 261 ***Retrospective and Prospective Results of the Use of Sirolimus in the Treatment of Generalized Lymphatic Anomaly and Gorham Stout Disease***

Kiersten Ricci1, Adrienne Hammill1, Cameron Trenor2, Paula MobberleySchuman1, Carol Chute3, Mary Sue Wentzel3, Alexander Vinks3, Manish Patel3, Gulraiz Chaudry2, Anita Gupta3, Jennifer Eile4, Arnold Merrow3, Roshni Dasgupta3, Belinda Dickie3, Richard Azizkhan5, Lin Fei3, Lindsey Hornung3, Ilona Frieden6, Nelson Stephen7, Julie Blatt8, Julia GladeBlender9, Catherine McCuaig10, Anna Synakiewicz11, Denise Adams12

1Cincinnati Children's Hospital Medical Center, 2Boston Children's Hospital, 3Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA, 4Boston Children's Hospital, Boston, MA, USA, 5University of Nebraska College of Medicine and Children's Hospital and Medical Center, Omaha, NE, USA, 6University of California San Fransisco, San Francisco, CA, USA, 7University of Minnesota, Minneapolis, MN, USA, 8UNC Health Care System, Chapel Hill, NC, USA, 9Columbia University Medical Center, New York, NY, USA, 10University of Montreal, Montreal, QC, Canada, 11Medical University of Gdansk University Hospital, Gdansk, Poland, 12Cincinatti Children's Hospital

Purpose: The purpose of this study is to evaluate the safety and efficacy of sirolimus in the treatment of patients with complicated lymphatic malformations, specifically Generalized Lymphatic Anomaly (GLA) and Gorham Stout Disease (GSD).
Methods: This study analyzed combined data from a multicenter systematic retrospective review of medical records of patients treated with sirolimus between January 2007 and June 01, 2014 and from the prospective Phase 2 FDA-funded study, Clinical Trial Assessing Efficacy and Safety of the mTOR Inhibitor Sirolimus in the Treatment of Complicated Vascular Anomalies. Disease improvement was determined by radiologic imaging, quality of life (QOL) measurements, and clinical status assessments. Sirolimus dosing regimens, toxicities and side effect causality were also evaluated.
Results: Of the evaluable patients, nineteen had complicated lymphatic malformations including 13 with GLA and 6 with GSD. As expected, no patients had complete resolution of clinical symptoms and radiologic disease on sirolimus therapy. Overall partial disease response was 84% (92% GLA, 67% GSD) with 79% of patients with improved QOL, 63% with improved clinical status and 39% with improved radiological response. Improvement occurred in 83% of patients with pleural effusions and 50% with pericardial effusions; no patients with pre-existing pleural or pericardial effusions worsened on therapy. Disease progression occurred in 1 GSD patient due to reported decreased QOL. Five patients experienced grade 3 or 4 drug toxicities without requiring dose reductions. Most common side effects were bone marrow suppression, mucositis/stomatitis and hypertriglyceridemia.
Conclusions: Sirolimus is a safe and well-tolerated treatment that appears to reduce symptoms and/or stabilize disease in patients with GLA and GSD. Given the known significant morbidity and mortality rates in patients with complicated lymphatic malformations, future treatment studies need to address these specific phenotypes.

14:00-14:10 70 ***Rapamycin effects on Kasabach-Merritt phenomenon coagulopathy***

Olivia Boccara1, Eve Puzenat2, Thierry Leblanc3, Stéphanie Proust4, Smail HadjRabia5, Christine Bodemer5

1Necker Hospital, 2CHU Besançon, France, 3Robert Debré Hospital, France, 4CHU Angers, France, 5Necker Hospital, France

Purpose: The coagulopathy of Kasabach-Merritt phenomenon (KMP) is frequently protracted after thrombocytopenia resolution. We describe the effects of rapamycin on the coagulopathy of KMP.
Methods: Retrospective/prospective analysis of D-dimer levels evolution in patients treated with rapamycin for a KMP compared with patients treated with other treatments, before rapamycin use, for whom clinical and biological data were available.
Results: - 5 infants (3 females, 2 males), aged from 1 to 30 months at diagnosis, were treated with rapamycin. The tumor was located on the inferior limb (n=2), face (n=1), trunk (n=1), peritoneal cavity (n=1). Rapamycin was implemented orally, 1 mg/kg/d, once a day, as a second line treatment after anti-agregant agents (n=3) or corticosteroids+vincristine (n=2). Platelet count was always below 10,000/mm3, except in one infant for whom rapamycin was given in a relapse setting, before platelet count dropped below 50,000/mm3. Platelet count normalized in 10 days to 2.5 months (average: 1.5 months). In all patients but one D-Dimer levels normalized within 6 months. - control group: 6 patients (1 females, 5 males), from birth to 24 months of age at diagnosis, were treated with anti-agregant agents (n=2), vincristine (n=1), embolization (n=1), interferon-alpha (n=1). The tumor was located to the limb (n=3) or the trunk (n=3). D-dimer remained elevated for 1 to 7 years (average: 2.3 y) after treatment initiation, while platelet count normalized in 1 to 14 months (average: 7 months).
Conclusion: KMP is due to massive platelet trapping within the tumor, because of pathological interaction between platelets and lymphatic endothelium. The coagulopathy with elevated D-Dimer is a consequence of platelet activation and is frequently a protracted phenomenon because of long lasting low grade platelet trapping. Rapamycin inhibits lymphangiogenesis and therefore blocks the platelet trapping, explaining its dramatic efficacy on both the thrombocytopenia, and the long lasting coagulopathy.

14:10-14:20 317 ***The use of combination therapy (sirolimus + zoledronic acid) for the treatment of bony disease in complicated vascular anomalies***

Adrienne Hammill1, Joseph Pressey1, Mary Sue Wentzel1, Carol Chute1, Paula MobberleySchuman1, Denise Adams2

1Cincinnati Children's Hospital Medical Center, 2Cincinatti Children's Hospital

Purpose: Bisphosphonates have been used as adjuncts to therapy in cases of bony metastases, becoming standard of care in frequently metastatic tumors such as renal cell carcinoma. There is preclinical evidence to suggest that the combination of mTOR inhibition and zoledronic acid may be synergistic, in both osteosarcoma cell lines (Moriceau 2010) and breast cancer cell lines (Lan 2013). Here we describe early results of combination therapy in a cohort of patients with bony disease related to vascular anomaly.
Methods: We developed a standardized protocol for combination therapy with oral sirolimus and intravenous zoledronic acid. We applied this protocol to a number of patients who had insufficient response to sirolimus alone. Data were gathered through retrospective chart review for this case series.
Results: 5 patients were treated with the combination of sirolimus plus zoledronic acid. 2 patients experienced high fevers following the first dose of zoledronic acid (only). All experienced symptomatic improvement by 6 months of therapy.
Conclusion: The use of zoledronic acid in combination with sirolimus can provide additional benefit to those patients with the most severe bony disease and symptoms not fully relieved by single agent sirolimus therapy. Additional prospective studies should be considered in order to further investigate the biological basis of this increased response and long-term effects on bone health.

14:20-14:26 220 ***Rapamycin as Novel Treatment for Refractory to Standard Care Lymphatic Anomalies***

Laurence M. Boon1, Jennifer Hammer1, Steven Duez1, Emmanuel Seront2, Anne Van Damme3, Claire Hoyoux4, Caroline Chopinet5, Frank Hammer6, Philippe Clapuyt7, Miikka Vikkula8

1Center for Vascular Anomalies, Division of Plastic and Reconstructive Surgery, Cliniques universitaires Saint Luc, Universite catholique de Louvain, 1200 Brussels, Belgium, 2Center for Vascular Anomalies, Department of Medical Oncology, Cliniques universitaires Saint Luc, Universite catholique de Louvain, 1200 Brussels, Belgium, 3Center for Vascular Anomalies, Pediatric Oncology, Cliniques universitaires Saint Luc, Universite catholique de Louvain, 1200 Brussels, Belgium, 4Departement of Pediatric HematoOncology, CHR Citadelle, 4000 Liège, Belgium, 5Departement of Pediatric HematoOncology, CHRU Lille, 59000 Lille, France, 6Center for Vascular Anomalies, Department of Interventional Radiology, Cliniques universitaires Saint Luc, Universite catholique de Louvain, 1200 Brussels, Belgium, 7Center for Vascular Anomalies, Pediatric Radiology, Cliniques universitaires Saint Luc, Universite catholique de Louvain, 1200 Brussels, Belgium, 8Human Molecular Genetics, de Duve Institute, Universite catholique de Louvain, 1200 Brussels, Belgium

Purpose: Despite sclerotherapy and/or excision, lymphatic malformations (LM) often recur. No molecular therapy exists. The identification of activating PIK3CA mutations, which cause activation of mTOR, as a frequent cause of LMs pinpointed a target for such a therapy. To assess the efficacy and security of rapamycin (mTOR inhibitor) on difficult-to-treat extended lymphatic anomalies no more amenable to conventional management.
Methods: Informed consent was obtained and approved by our ethical committee. The trial was registered at clinicaltrials.gov. Eleven patients (3 to 45 years of age) were enrolled: 3 with large facial microcystic LM, 3 with mediastinal and pulmonary LM, 1 with extensive LM of the lower extremity, 2 with GLA and 2 with Klippel-Trenaunay syndrome. Clinical symptoms included: functional impairment (n=11), chronic daily debilitating pain (n=8), cosmetic disfigurement (n=8), recurrent infections (n=6), obstruction of vital organs (n=3), chronic anemia (n=2), and daily oozing and ulceration (n=2). Patients were seen on a monthly basis. Efficacy was evaluated by : anamnesis of symptoms (functional, cosmetic and psychological), pain evolution, quality of life questionnaire, clinical parameters, photos of the visible lesion and blood sampling. Side effects were noted according to CTCAE v3. Volumetric MRI was performed before initiation and at yearly bases.
Results: Ten patients reached 12 months follow-up. All except one experienced almost complete relief of pain and symptoms, and improved function and self-perceived quality of life. One patient (extensive Klippel-Trenaunay syndrome) continued to have local infections and functional restraint, but with lower frequency. Side effects were minor. A statistically significant reduction in lesional volume was observed with MRI at one-year follow-up.
Conclusion: This trial suggests that rapamycin can be a therapeutic option for patients with refractory-to-standard-care lymphatic anomalies. As rapamycin is likely a life-long treatment, it should not be considered for small, localized and asymptomatic LMs that respond to standard care.

14:26-14:32 222 ***Rapamycin as Novel Treatment for Refractory to Standard Care Venous Malformations***

Laurence M. Boon1, Jennifer Hammer1, Steven Duez1, Emmanuel Seront2, Anne Van Damme3, Elisa Boscolo4, Joyce Bischoff5, Frank Hammer6, Philippe Clapuyt7, Miikka Vikkula8

1Center for Vascular Anomalies, Division of Plastic and Reconstructive Surgery, Cliniques universitaires Saint Luc, Universite catholique de Louvain, 1200 Brussels, Belgium, 2Center for Vascular Anomalies, Department of Medical Oncology, Cliniques universitaires Saint Luc, Universite catholique de Louvain, 1200 Brussels, Belgium, 3Center for Vascular Anomalies, Pediatric Oncology, Cliniques universitaires Saint Luc, Universite catholique de Louvain, 1200 Brussels, Belgium, 4Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio USA, 5Department of Surgery, Boston Children's Hospital, Boston, MA 02115, USA, 6Center for Vascular Anomalies, Interventional Radiology, Cliniques universitaires Saint Luc, Universite catholique de Louvain, 1200 Brussels, Belgium, 7Center for Vascular Anomalies, Pediatric Radiology, Cliniques universitaires Saint Luc, Universite catholique de Louvain, 1200 Brussels, Belgium, 8Human Molecular Genetics, de Duve Institute, Universite catholique de Louvain, 1200 Brussels, Belgium

Purpose: Venous malformations (VM) are composed of ectatic veins with scarce smooth muscle cell coverage. They often cause deformity, pain, local intravascular coagulopathy or bleeding. Despite sclerotherapy and/or excision, lesions often recur. Targeted pharmacological therapies are not available. To assess the efficacy and security of rapamycin, an mTor inhibitor, which targets the disease-causing, activated PI3K-AKT signaling pathway, on subjects affected with difficult-to-treat extended VMs and/or complex slow-flow vascular anomalies, no more amenable to conventional management.

Methods: Informed consent was obtained and approved by our ethical committee. The trial was registered at clinicaltrials.gov. Ten patients (8 to 64 years of age) with refractory-to-standard-care VM were enrolled. Clinical symptoms included: chronic daily debilitating pain (n=8), esthetic and functional impairment (n=9) and daily gastrointestinal bleeding (n=3) despite several sessions of sclerotherapies and/or surgery. Patients were seen on a monthly basis by two specialists. Efficacy was evaluated by : anamnesis of symptoms (functional, cosmetic and psychological), pain evolution, quality of life questionnaire, clinical parameters, photos of the visible clinical lesions and blood sampling. Side effects, according to CTCAE v3, were noted. Volumetric MRI was performed before initiation and at a yearly bases.

Results: Eight patients reached 12 months follow-up. All patients experienced almost complete relief of pain and symptoms, improved functional restraint and self-perceived quality of life. Side effects were principally mucositis (n=7), mild headache (n=8), fatigue (n=7) and diarrhea (n=5). A statistically significant reduction in volume was observed with MRI in most patients that reached one-year follow-up.

Conclusion: This trial suggests that rapamycin is a possible therapeutic option for patients with refractory-to-standard-care VM and/or complex slow-flow vascular anomaly. As Rapamycin is likely a life-long treatment, it should not be considered as treatment for small, localized and asymptomatic slow-flow vascular malformations that respond to standard care.

14:32-14:45 46 ***The mTOR Inhibitor Sirolimus for the Treatment of Complicated Vascular Anomalies: A Retrospective Review of Medical Records***

Paula MobberleySchuman1, Denise Adams2, Ilona Frieden3, Dov Goldenberg4, Rajkumar Venkatramani5, Kai Li6, Moise Levy7, Tony Penington8, Rod Phillips8, Lisa Orme8, Michael Jeng9, Vicky Price10, Amy Geddis11, Stephen Nelson12, Julie Blatt13, Beth Drolet14, Mike Kelly14, Ionela Iacobas15, Marc Hendricks16, Megha Tollefson17, Julia GladeBender18, Anna Synakiewicz19, Karen Fernandez20, Catherine McCuaig21, Cameron Trenor22, Francine Blei23, Fiona Kritzinger24, Shoshana Greenberger25, Megan Metcalf1, Christine Brookbank26, Mary Sue Wentzel1, Lin Fei1, Adrienne Hammill1

1Cincinnati Children's Hospital Medical Center, 2Cincinatti Children's Hospital, 3UCSF, 4University of Sao Paulo Medical School, 5Texas Children's Hospital, 6Children's Hospital of Fudan University, 7Dell's Children's Medical Center, 8Royal Children's Hospital, Melbourne, 9Lucile Packard Children's Hospital, Stanford University, 10Dalhouise University, Halifax, NS, 11Rady Children's Hospital, 12Univeristy of Minnesota, 13UNC Health Care System, 14Children's Hospital of Wisconsin, 15Drexel University, St. Peter's University Hospital, 16Red Cross War Memorial Children's Hospital, 17Mayo Clinic, Rochester MN, 18Columbia University, 19Medical Univeristy of Gdansk, Poland, 20Children's Hospital of Illinois, 21Univeristy of Montreal, 22Boston Children's Hospital, 23North Shore LIJ Healthcare System, 24Thriving Kids, Cape Town, South Africa, 25Sheba medical Center, Ramat Gan, Israel, 26Cincinnanti Children's Hospital Medical Center

Purpose: The purpose of this study is to review and describe dosing, response, and side effects of sirolimus, as well as long-term outcomes of children with complicated vascular tumors and malformations treated with sirolimus at multiple institutions throughout the world.

Methods: A systematic retrospective international multisite case review of patients with complicated vascular tumors and malformations treated with sirolimus for a minimum of 3 months between January 2007 and June 2014. This project involves long-term follow up of our patients treated with sirolimus as well as data from other institutions' experiences and other vascular anomalies centers.

Results: In total, 24 sites contributed patient data from 9 countries representing 6 continents. A total of 160 patient records were reviewed. Table 1 below shows the diagnoses for these patients.

Diagnosis	Type (N)	Subtype (N)
Tumor (53)	Hemangioma (1)	
	KHE/ Tufted Angioma (32)	KHE with KMP (18)
		KHE without KMP (9)
		TA with KMP (5)
Malformation (87)	Lymphatic (32)	Generalized Lymphatic Anomaly (6)
		Gorham Syndrome (4)
	Venolymphatic (19)	Blue Rubber Bleb Nevus (5)
	Capillary Lymphatic Venous (26)	Klippel Trenaunay(14)
	CLOVES (4)	
	Capillary Lymphatic AVM (6)	
	CAT/ MLT (0)	
Other(34)	Overgrowth Syndrome (13)	
	PTEN (5)	
	Lymphangiectasia Syndrome/ Channel Disorder (7)	
	Kaposiform Lymphangiomatosis (6)	
	Nasopharyngeal Angiofibroma (3)	

Dosing regimens, response, side effects and causality, long term outcomes as well as long term effects were examined. 93% of patients had an overall response to sirolimus, with 97% of patients or parents reporting improvement in quality of life, 83% reporting improvement by imaging, and 91% reporting improvement in clinical status. Ten patients had grade 4 infections (3 possibly or probably related, 4 unlikely or unrelated), none were Pneumocystis pneumonia. Most common side effects were bone marrow suppression, mucositis/stomatitis and hypertriglyceridemia. No long term side effects were reported and greater than 60% of patients remained on treatment for 2 years or longer.

Conclusion: Although there is no current published standard of practice for sirolimus for the treatment of vascular anomalies, this multinational retrospective study shows it to be an overall effective and safe treatment and expands the cohort of patients with complicated vascular anomalies treated with sirolimus to over 200 patients.

14:45-15:05 DC 3 - Difficult Case Presentations III — Juan Pablo II Room

Chairs: Carla Castro, María Garzón

14:45-14:55 164 ***CHALLENGES IN MANAGEMENT OF A MASSIVE CERVICO-FACIAL LYMPHATIC MALFORMATION IN A NEONATE AFTER MULTIMODAL THERAPY***

Minna Wieck, Shannon Castle, Lori Howell, Chadi Zeinati, Dean Anselmo

Children's Hospital Los Angeles

Purpose: Large head and neck lymphatic malformations (LM) can be difficult to treat and exert a high morbidity and potential mortality due to their location.
Methods: Here we describe a challenging case of a large macrocystic LM that recurred despite aggressive multimodal therapy and ultimately led to the patient's death.
Results: A prenatal diagnosis of large cervical LM was made and an EXIT procedure was scheduled, however the patient was born prematurely by an urgent EXIT procedure at 33 weeks. MRI showed multiple macrocysts over his lower face and neck bilaterally with mediastinal extension. Over the first two months of life, he underwent drain placement and multiple courses of doxycycline sclerotherapy into roughly 18 macrocysts. At 7 weeks of life, he underwent extensive surgical debulking which resulted in an initial reduction in LM size. In the subsequent weeks, the LMs reaccumulated and he developed profound scalp and facial edema. Percutaneous sclerotherapy and drainage were repeated with little improvement, and so a course of sirolimus was administered but the LMs and edema persisted. He also developed a chylothorax which was successfully managed with chest tube placement and octreotide. At 3 months, he underwent tracheostomy but continued to require significant ventilator support. He also had a gastrostomy tube placed but enteral feeds could not be advanced due to emesis and agitation. Ultimately, he developed more frequent episodes of desaturations and bradycardia which led to his death at 4 months.
Conclusion: Based on this experience, we must consider carefully the role and order of implementation of sclerotherapy, surgery, and medical management of these large head and neck LMs.

14:55-15:05 185 ***Unclassified vascular tumor due to somatic HRAS/GNAQ mutation. Response to rapamycin. Should we consider Trametinib***

Eulalia Baselga1, Pau Castel2, silvia bague3, esther roe4, nuria pardo5, fania zamantha muñoz4, miquel sanchez4, sabina luna6, lluis puig4

1, 2Memorial Sloan Kettering Cancer Center, 3Pathology.Hospital de la Santa Creu i Sant PAu, 4Dermatology. Hospital de la Santa Creu iSant Pau, 5Pediatrics. Hospital de la Santa Creu i Sant Pau, 6Ophtalmology. Hospital de la Santa Creu i Sant Pau

Purpose: To present an unclassified vascular tumor underneath a port-wine stain in which next generation sequencing has demonstrated a somatic GNAQ and HRAS mutation. Based on this results treatment trametinib is being considered.
Methods: CASE REPORT: 15 y.o girl presented shortly after birth for a "port-wine stain" on her left cheek, ear, parotid area and scalp. She received 6-7 PDL laser treatment during the first 2 years of life and was stopped because lack of response and she developed an underlying tumor. MRI demonstrated an hyperintense mass that involved the parotid gland, pterygopalatine fossae, up to orbital ridge. There were multiple connexions between arteries and veins but there were no fluid voids. A skin biopsy demonstrated a vascular tumor in the dermis and subcutaneous tissue with some features of hobnail hemangioma of intermediate malignancy in a few areas and other less cellular areas with dilated blood vessels. Glut-1 and D2-40 staining were negative and WT-1 staining was positive. The tumor continued to grow in volume and caused marked distortion of the left cheek. Therapeutic trials with systemic corticosteroids, propranolol and sildenafil were unsuccessful. Rapamycin was finally instituted with partial response Because this vascular tumor had never been well characterized clinically or histologically DNA from tissue was sequenced with the next generation sequencing. Two different somatic mutations in GNAQ (Q209R) and HRAS(Q61L.GNAQ Q209R is a previously described mutation in Sturge-Weber patients and port-wine stains and HRAS Q61L has been recently described in unclassified vascular tumors and pyogenic granuloma-like tumors. Phase I and II clinical trials have demonstrated that patients with solid tumors such as melanoma, lung and pancreatic cancers with HRAS mutations response to MEK inhibitor trametinib we are considering this treatment as a more targeted therapy for our patient. Safety in children is our major concern.
Conclusion: Genetic studies can be helpful in directing theraphy for unclassified vascular tumors

15:05-15:30 Coffee Break

15:30-15:45 PP - Poster Pearls Juan Pablo II Room

Chairs: Ilona Frieden, Raúl Matassi

15:45-16:50	SE 5 - Session 5: Lymphatic Malformations and Syndromic Vascular Malformations	Juan Pablo II Room

Chairs: Steven Fishman, Jonathan Perkins

15:45-15:53 181 ***Early orthodontic and orthognathic correction of mandibular skeletal abnormalities in patients with cervicofacial lymphatic malformation***

Teresa O1, Milton Waner2, Vasiliki Karlis3, Stuart Super4

1,2Vascular Birthmark Institute of New York, AVM Center, Lenox Hill and Manhattan Eye, Ear, and Throat Hospitals, 3Oral and Maxillofacial Surgery, New York University College of Dentistry, 4Lenox Hill Hospital, Oral and Maxillofacial Surgery at NYU College of Dentistry

Purpose: Patients with "beard distribution" cervicofacial lymphatic malformations(LMs) may develop skeletal abnormalities in the same anatomic location of disease. Previous studies have noted outward flaring of the mandibular ramus, anterior displacement of the mandible, relative ipsilateral facial hypertrophy, and anterior positioning of the maxilla. The open-bite deformity is a common finding leading to functional difficulties with malocclusion, oral incompetence and speech intelligibility. There are also aesthetic and psychosocial concerns. We demonstrate the feasibility and effectiveness of early correction of mandibular skeletal abnormalities in lymphatic malformation.
Methods: Retrospective chart review of patients with class III malocclusion and anterior open bite deformity undergoing orthodontic and orthognathic treatment was performed(2013-2015). Medical records including pre-and postoperative photographs, dental films, and 3D-CT were reviewed. All patients underwent Lefort I maxillary osteotomy to advance the maxilla. The mandible was treated with bilateral rami osteotomies or sagittal split osteotomies.
Results: All(4) patients underwent preoperative orthodontics prior to orthognathic surgery. Their ages 11, 11, 17, and 22 respectively. Three females and one male(17 year old) were treated. In 2 patients the surgery was staged. The maxilla was advanced 3-6mm anteriorly, and differentially impacted posteriorly 3-4mm. One patient required an iliac crest bone graft to downgraft the maxilla. Two patients also had reshaping and shortening (5-10mm) of the inferior border of the mandible. One patient had bilateral gonial angle osteotomies to rotate the angles inferomedially. All patients had closure of the open bite with resultant Class 1 (normal) occlusion. Followup was 12-14 months.
Conclusion: Cervicofacial LMs cause skeletal mandibular deformities leading to functional, aesthetic, and psychosocial morbidity. Traditionally, orthognathic surgery has been reserved for later adolescence and adulthood. With advances in plating technology, the early correction of these skeletal defects is feasible and advantageous. Surgery corrects facial proportions and bite deformity allowing improved speech, feeding, and oral competence.

15:53-15:57 288 ***Management of Lymphedema with Suction-Assisted Lipectomy***

Reid Maclellan MD, MMSc and Arin Greene MD, MMSc

Boston Children's Hospital / Harvard Medical School

Background: Lymphedema is the chronic, progressive swelling of tissue due to inadequate lymphatic function. Surgical management includes removal of affected tissues or operations that create new lymphatic connections. The purpose of this study was to determine the efficacy of one type of excisional procedure, suction-assisted lipectomy, for extremity lymphedema.
Methods: Patients treated in our Lymphedema Program between 2007 and 2015 with liposuction that had post-operative follow-up were reviewed. The diagnosis of lymphedema was made by physical examination and confirmed with lymphoscintigraphy. Patient gender, age, type of lymphedema (primary or secondary), location of disease, infection history, and volume of lipoaspirate were recorded. Outcome variables were improvement in patient symptoms, reduction of extremity volume, and complications.
Results: Fifteen patients were included, mean age was 45 years (range, 17-71) (Figure 1). Six patients had secondary upper extremity lymphedema, 9 patients had lower limb disease. Eight patients had a history of repeated cellulitis involving the lymphedematous extremity. Mean lipoaspirate volume was 1612 mL (range, 1200-2800) for the upper extremity and 2902 mL (range, 2000-4800) for the lower limb. Post-operative follow-up averaged 3.2 years. The mean reduction in excess extremity volume was 73% (range 48% to 94%). Patients with follow-up reported improved extremity function, reduction in episodes of cellulitis, and better quality of life; none exhibited recurrence.
Conclusions: Suction-assisted lipectomy is an effective technique to reduce extremity volume for patients with moderate or severe lymphedema. The procedure gives a long-term reduction in limb size, reduces the prevalence of infections, and improves quality of life.

15:57-16:01 290 ***Suction-Assisted Lipectomy May Improve Physiologic Function in Patients with Lymphedema***

Reid Maclellan MD, MMSc and Arin Greene MD, MMSc

Boston Children's Hospital / Harvard Medical School

Background: Surgical management of lymphedema includes removal of affected tissues (excisional procedures), or operations that create new lymphatic connections (physiologic procedures). The purpose of this study was to determine if suction-assisted lipectomy (an excisional procedure) has physiologic effects and improves lymphatic function.
Methods: Inclusion criteria for patients with lymphedema treated with liposuction between 2007 and 2015 were: (1) documentation of pre- and post-operative Stemmer sign (the inability to pinch the skin on the dorsum of the affected hand or foot) and (2) lymphoscintigraphy. Patient gender, type of lymphedema (primary or secondary), duration and location of disease, and infection history were recorded.
Results: Two out of 6 patients who met inclusion criteria developed a normal Stemmer sign post-operatively indicating improved lymphatic function. Patient #1 had a 6 year history of secondary upper extremity lymphedema, no infections, and a lipoaspirate of 1200 mL. Patient #2 had a 10 year history of primary lower extremity disease, absent infections, 2800 mL of lipoaspirate (74% volume reduction), and post-operative lymphoscintigraphy that illustrated improved lymphatic drainage (Figure). Duration and location of disease, history of infections, and type of lymphedema was not different between patients with improved and unchanged lymphatic function (p=0.42).
Conclusions: Suction-assisted lipectomy which reduces extremity volume by removing excess subcutaneous adipose, also may improve lymphatic function.

16:01-16:09 152 ***Surgical concerns in a large cohort of patients with lymphatic malformation***

Nader Ghaffarpour

Karolinska University Hospital

Purpose: Sclerotherapy is the primary treatment for lymphatic malformations (LM), however some patients require surgery. The aim of this study was to identify the patient of high risk for surgery in a cohort of patients with LM, all eligible for sclerotherapy with OK-432.
Methods: Between 1998 and 2013, we enrolled 138 patients diagnosed with, LM all eligible for sclerotherapy with OK-432 at Astrid Lindgren Children´s hospital in a retrospective study. The malformations were categorised according to the International Society for the Study of Vascular Anomalies. The subgroup of the cohort who had undergone surgery was analysed.
Results: In total, 19/138 (7,3%) patients required surgery. Three patients were primarily operated because of the risk of compromise of the airways from using sclerosing agents. One patient needed emergency surgery due to major swelling after sclerotherapy affecting vital functions. Both the primarily operated and the emergency surgery case had mediastinal involvement. These cases were operated with a medial sternotomy and had no postoperative complications. Unsatisfactory results were the cause for the operation in 11 patients with LM in the head/neck region, one on the trunk and three lesions on multiple regions. In these patients, the outcome of sclerotherapy was considered to be unsatisfactory after a median number of six sclerotherapy sessions (range 1-11). The type of malformation that required an operation due to unsatisfactory results from sclerotherapy was microcystic in four cases, macrocystic in one case and mixed lesions in 10 cases. All these patients were safely operated but experienced various degrees of wound healing problems.
Conclusion: Sclerotherapy in LM with mediastinal involvement may require long-time post treatment intensive care with protection of the airways. Surgery is a safe alternative in such cases. Unsatisfied results after sclerotherapy with OK-432 can be operated but require postoperative wound treatment strategy.

16:09-16:17 265 ***Use of lymphoscintigraphy in pediatric lymphoedema***

Sophie Turpin, Raymond Lambert, Catherine McCuaig

University of Montreal; CHU Sainte Justine

Purpose: Lymphoedema in children and adolescents is a rare condition. The purpose of our study was to evaluate the role of lymphoscintigraphy in a pediatric setting.
Methods: Lymphoscintigraphies performed in our institution since 2001 for lymphoedema were reviewed. Patients with Klippel-Trenaunay were excluded. Lymphoscintigraphy was performed after interdigital injections of Tc99m-sulfur colloid. The presence or absence of radiotracer migration, lymph node visualization, dermal backflow were evaluated. Findings were correlated with patient characteristics and clinical history to differentiate between primary lymphoedema due to aplasia or hypoplasia and secondary lymphoedema.
Results: 54 lymphoscintigraphies were performed in 51 patients. There was 16 boys (aged 5.4 +–4.7 yo,) and 35 girls (aged 12.6 +– 4.5 yo). Six patients had suspected secondary lymphoedema. Eight studies were normal and 6 likely normal taking in consideration technical problems with injection. Among those, 4 patients with unilateral disease had symmetrical migration of the tracer after walking. No migration of the tracer, suggestive of aplasia was found in 10 studies (3 boys,

7 girls). Four patients had bilateral lymphedema and another secondary lymphoedema. Patients were young (8.5+-6.8 yo). Delayed migration of the tracer, with hypoactivity of the lymph nodes, suggestive of hypoplasia was found in 29 studies (8 boys, 20 girls). Three patients had secondary lymphoedema and seven bilateral disease. Patients were older (12 +-4.7 yo). Dermal backflow was found in 13 studies (4 boys,7 girls). 50% of patients with secondary lymphoedema had dermal back flow and 16% of patients with primary lymphoedema.
Conclusion: Lymphoscintigraphy was able to confirm or exclude lymphedema in our patients. A drainage pattern suggestive of aplasia was found in younger patients with suspected congenital lymphoedema, and hypoplasia in older patients with suspected lymphoedema praecox. However, there was overlap between primary and secondary lymphoedema drainage patterns.

16:17-16:25 268 ***An Observational Study of Long-term Outcomes in Complicated Lymphatic Anomalies: The Lymphatic Anomalies Registry***

Megan Aitro, Katherine Broecker, Meghan O'Hare, Ahmad Alomari, John Mulliken, Steven Fishman, Raja Shaikh, Gulraiz Chaudry, Cameron Trenor

Boston Children's Hospital

Purpose: Lymphatic anomalies are a subset of vascular anomalies. There is limited knowledge on the natural history, long-term outcomes, risk factors of morbidity and mortality, and response to treatments.
Methods: The Lymphatic Anomalies Registry is an IRB-approved, secure clinical database of patients with vascular anomalies with significant lymphatic complications. Patients were recruited from existing referrals to our center and physician or self-referrals through the internet (www.lymphaticregistry.org). Patients lost to followup were enrolled retrospectively only, while active patients were consented for prospective data collection. Data is collected through medical record review, standardized patient interview, and an annual survey. Enrolled diagnoses include Gorham-Stout Disease, Generalized Lymphatic Anomaly/Lymphangiomatosis, CLOVES, Klippel-Trenaunay Sydrome, central conducting lymphatic anomaly and Kaposiform Lymphangiomatosis among others.
Results: We have enrolled 474 patients with 242 active patients consenting for prospective data collection and 232 patients retrospectively enrolled from 6 continents. Median age 11 years (range 4 months to 63 years old). Initial analyses have defined the presenting features of KLA, poor efficacy of sildenafil, outcomes of 190 patients with effusions, and the association of brain imaging and seizures in CLOVES. Annual follow-up data provides us with a longitudinal profile of how these diseases develop over time. Analysis of patients with neonatal effusions, GSD/GLA and bone complications is ongoing.
Conclusion: We are expanding this registry to a multicenter study for patient enrollment. We have recently opened a linked biorepository to archive biological samples. Data from this registry will serve to validate risk-stratification, illuminate natural history and generate preliminary data for clinical trials to improve outcomes for these rare and challenging patients.

16:25-16:33 322 ***Complications from Surgical Excision for the Treatment of Lymphatic Malformations - a 10-year Institutional Review***

Don Hoang1, Tiffany Yang1, Kathy Schall2, Minna Wieck2, Donna Nowicki2, Chadi Zeinati2, Dean Anselmo2, Lori Howell2

1University of Southern California, 2Children's Hospital Los Angeles

Purpose: Treatment options for lymphatic malformations (LMs) include percutaneous sclerotherapy, surgical resection, or a combination thereof. Published studies report resolution rates of 95.2% for sclerotherapy of macrocystic LMs (84.2% overall), while microcystic lesions are typically surgically excised which results in a reported 66% resolution rate. The purpose of our study was to compare complication rates of surgical resection alone versus a combination of surgery and sclerotherapy in the treatment of extra-abdominal LMs at a single multidisciplinary vascular anomalies center.
Methods: A retrospective chart-review included 177 patients diagnosed with lymphatic malformations from August 2003-June 2015. LMs that were intra-abdominal or not treated with surgery were excluded. Forty-Eight total surgical patients' complications were compared with chi-square testing based on their treatment with surgery or a combination of sclerotherapy and surgery. Follow-up ranged from 2 days to 933 days post-operation.
Results: For 48 surgical patients with lymphatic malformations, 48% underwent surgical resection only, 19% were treated with surgery and post-operative sclerotherapy, and 33% with pre-operative sclerotherapy and surgery. The overall complication rates were as follows: 25% of patients developed a post-op seroma, 20% developed edema, 16% had a wound infection, 13% developed chronic draining wounds, and 11% resulted in wound breakdown following treatment. Wound infection rates were higher in patients undergoing surgery if combined with pre-operative sclerotherapy compared with those undergoing surgery alone (44% vs 13%;$p<0.05$). Post-op edema rates were higher in patients treated with surgery

followed by sclerotherapy than in patients treated with surgery alone (56% vs 17%;p<0.05); however, no statistical differences were observed for other wound problems post-operatively (Table 1).
Conclusion: Treatment of LMs with pre-operative sclerotherapy appears to exacerbate the rate of post-operative wound infection. Treatment of LMs with surgery followed by sclerotherapy also increases the rate of post-operative edema. Given that the most common postsurgical complications were post-operative seroma and edema associated with surgical treatment, surgical drain placement and prophylactic compression garments should be utilized judiciously to anticipate these complications regardless of whether sclerotherapy is used as an adjunctive therapy.

16:33 - 16:41 229 ***Functional Characterization of FOXC2 Mutations Identified in Patients with Primary Lymphedema***

Matteo Bertelli1, Raul Ettore Mattassi2, Maurizio Ricci3, Daniela Tavian4, Sandro Michelini5

1Magi's Lab Human Medical Genetics Institute, Rovereto (TN), Italy, 2Center for Vascular Malformations, Castellanza (VA), Italy, 3Laboratory of clinical Analysis; Clinical Institute Humanitas, Castellanza (VA), Italy., 3Medicina Riabilitativa, Azienda Ospedaliero- Universitaria Ospedali Riuniti di Ancona, Torrette, Italy, 4Laboratory of Cellular Biochemistry and Molecular Biology, CRIBENS, Catholic University of the Sacred Heart, Milan, Italy, 5Department of Vascular Rehabilitation, San Giovanni Battista Hospital, Rome, Italy

Purpose: Dominant mutations in the FOXC2 gene cause a form of lymphedema that usually develops around puberty. FOXC2 is a member of the forkhead/winged-helix family of transcription factors and plays essential role in different developmental pathways and physiological processes. Most of FOXC2 mutations described so far either truncate the protein or are missense mutations in the forkhead domain causing a loss of function. The haplo-insufficiency is associated with generalized hyperplasia of lymphatic system in mice as well as in humans. We previously described six unrelated families with primary lymphedema in which patients showed different FOXC2 mutations. We present here the results of the functional characterization of these new six mutations.
Methods: All of those six mutations, four missense mutations (p.A3G, p.S370T, p.L487P, p.A492V), one frameshift mutation (p.M276DfsX186) and the last one a stop mutation (p.Q420X), were located outside of the forkhead domain. To evaluate their pathogenic potential, we examined their subcellular localization and performed a transactivation assay using a luciferase construct with FOXC1 response elements.
Results: All FOXC2 mutated proteins, were able to localize correctly into the nucleus. A reduction in the ability to activate FOXC1/FOXC2 response elements was detected in 50% of mutations, while the remaining mutations caused an increase of protein transactivation activity
Conclusion: A correlation between lymphatic hypo or hyperplasia and activating or inactivating mutations has been observed. Our data suggest that the unbalanced FOXC2 activity causes a dramatic perturbation of lymphatic vessel formation leading to lymphedema.

16:41-16:50 74 ***Facial Infiltrating Lipomatosis Contains Somatic PIK3CA Mutations in Multiple Tissues***

Javier Couto, Matthew Vivero, Joseph Upton, Bonnie Padwa, Matthew Warman, John Mulliken, Arin Greene

Boston Children's Hospital, Harvard Medical School

Purpose: Facial infiltrating lipomatosis (FIL) is a rare congenital disorder that causes overgrowth of one side of the face. We previously reported that the subcutaneous adipose tissue contains somatic PIK3CA mutations. The purpose of this study was to determine whether the entire face is overgrown because of paracrine signaling by mutant cells only in the fat, or if all tissues are mutated.
Methods: We obtained FIL tissue from 3 patients during a clinically-indicated procedure and isolated skin, subcutaneous adipose, muscle, buccal fat, bone, and mucosal neuromas. Endothelial cells then were separated from other cell types. Droplet digital PCR (ddPCR) was performed on DNA from each tissue to determine the presence and frequency of PIK3CA mutant alleles.
Results: PIK3CA mutations (p.H1047R, p.H1047L) were found in all tissues from each patient studied. Mutant allele frequencies were: skin (5.5%-11.4%), subcutaneous adipose (16.2%-20.1%), muscle (5.6%-28.2%), buccal fat (23.2%-29.0%), bone (24.6%), and mucosal neuroma (12.5%-12.8%) (Figure). Mutant allelic frequencies in cell populations were: endothelial (1.5%-5.2%) and non-endothelial (28%-49.2%).
Conclusion: PIK3CA mutations are present in all overgrown tissues in FIL (not only subcutaneous adipose tissue); non-endothelial cells are enriched for the mutation. The disease likely results from a mutation in an early pluripotent cell, rather than subcutaneous adipose causing secondary overgrowth of adjacent structures.

16:50-17:20	DC 4 - Difficult Case Presentations IV	Juan Pablo II Room

Chair: Daniela Kramer

16:50-17:05 157 ***Lymphangioendotheliomatosis? Medical Treatment Failure***

Josee Dubois1, Ewurabena Simpson2, Kheirie Issa2, Catherine C. McCuaig3, Catherine Ann Farrell3, Michele David3

1CHU Ste-Justine, 2Children's Hospital of Eastern Ontario, 3CHU Sainte-Justine

A healthy 7-month-old girl presented in November 2013 for a scleral hemorrhage of her right eye with extensive bruising and petechiae over her right ear. Four days later, the physician noticed splenomegaly with violaceous discoloration of her earlobe and unusual eczematoid plaque of her right cheek.
Ultrasound revealed a heterogeneous splenomegaly with hypoechoic areas. MR of the head and neck revealed an extensive infiltrative lesion of the face associated with a significant lymphatic component and an involvement of the laryngopharyngeal area. Biopsy of the occipital lesion was initially compatible with a multifocal lymphangioendotheliomatosis with thrombocytopenia but was subsequently diagnosed as Kaposiform lymphangiomatosis. She has an ongoing Kasabach-Merritt phenomenon. She had multiple intercurrent complications, including several episodes of gastrointestinal bleeding, tamponade requiring pericardial fenestration and respiratory compromise requiring tracheostomy. Recently, hypothyroidism was diagnosed.
Multiple medical therapies were tried, usually in combination: sirolimus, dexamethasone, prednisone, propranolol and weekly vincristine, as well as a short course of interferon. Embolization of the spleen and the face were performed, as well as sclerotherapy of the face. Sirolimus and weekly vincristine in combination with steroids maintained a certain clinical stability but have had little impact on the coagulopathy and have not led to significant regression of the face and ENT lesions.

17:05-17:20 282 ***Sigmoidoscopy Assisted Sclerotherapy for Intractable Bleeding Post Left Hemicolectomy for Diffuse Left Colonic Venous Malformation***

Anne Marie Cahill, Abhay Srinivasan, Thane Blinman

Children's Hospital of Philadelphia

Purpose: To describe rigid proctoscopy assisted direct injection of sodium tetradecyl foam for treatment of a residual diffuse post operative rectal pouch venous malformation for intractable life threatening hemorrhage.
Methods: 18-year-old male with a known diagnosis of Klippel-Trenaunay Weber Syndrome and diffuse venous malformation of the distal colon, sigmoid and rectum presenting with severe lower GI bleeding non responsive to massive transfusion. A CT angiogram (CTA)demonstrated a grossly enlarged rectosigmoid colon with a diffuse venous malformations from distal left colon to anus distending and displacing the bladder into the right abdomen. In addition enlarged mesenteric veins were noted throughout the left colonic mesentery. The CTA was negative for active extravasation but a tagged red cell scan demonstrated the likely source of bleeding to be the sigmoid colon. Emergent rectosigmoid resection with a left decompression colostomy was performed with a portion of the rectum and anus retained due to the risk of potential fatal hemorrhage form massively dilated mural veins. The residual rectal pouch and anus continued to bleed post-operatively requiring continual blood transfusions. Open sigmoid colectomy, hartmann's, descending colosomty
Results: Under rigid proctoscopic guidance the residual rectal pouch venous malformation was accessed at multiple sites using small bore needles and sodium tetradecyl foam was injected under fluoroscopic guidance. At cessation of procedure no further bleeding was noted form the anus which had been actively bleeding at initiation of procedure. Broad spectrum antibiotic coverage and pain control was aggressively managed and the patient was discharged 1 week post sclerotherapy without any evidence of further bleeding.
Conclusion: Endoscopically assisted direct injection sclerotherapy of accessible colonic venous malformation provides a minimally invasive alternative to surgical resection in selected cases.

Friday April 29, 2016

Juan Pablo II

08:00-10:00	**Session 6: Intramuscular Vascular Malformations and Selected Topics**
10:00-10:30	**Difficult Case Presentations V**
10:30-11:00	**Coffee Break**
11:00-12:30	**Session A: Interventional Radiology**
12:30-13:30	**Lunch**
13:30-14:45	**Session 7: Vascular Malformations 2**
14:45-15:15	**Difficult Case Prentations VI**
15:15-15:45	**Closing Ceremony**

Aula Magna

11:00-12:30	**Session B: Laser & Surgery**

Auditorio 1

11:00-12:30	**Session C: Collaborative Research - Sirolimus, OVAMA STUDY, OTHER**

08:00-10:00	SE 6 - Session 6: Intramuscular Vascular Malformations and Selected Topics	Juan Pablo II Room

Chairs: Greshan Richter, Michel Wassef

08:00-08:10 36 ***Development of A Set of Core Outcome Measures for Vascular Malformations (OVAMA Project): An International E-Delphi Consensus Study***

Sophie E.R. Horbach1, Chantal M.A.M. van der Horst2, Dirk T. Ubbink3, OVAMA consensus group4, Phyllis I. Spuls5

1Plastic and reconstructive surgery, Academic Medical Center (AMC) Amsterdam, 2Plastic and reconstructive surgery, Academic Medical Center (AMC), Amsterdam, the Netherlands, 3Surgery and Epidemiology, Academic Medical Center (AMC), Amsterdam, the Netherlands, 4OVAMA project, 5Dermatology, Academic Medical Center AMC), Amsterdam, the Netherlands

Purpose: One of the main limitations of vascular malformation research studies is the heterogeneity in outcome measures used for the evaluation of treatment outcome. With the Outcome measures for VAscular MAlformations (OVAMA) project, we aim to reach consensus on a core outcome set for peripheral (extracranial) space-occupying vascular malformations to be used in clinical research studies.
Methods: The OVAMA project follows the steps of the HOME (Harmonising Outcomes Measures for Eczema) roadmap. This study represents step 2 of the OVAMA project: an international e-Delphi consensus study. A list of 36 possible relevant outcome measure domains, based on the current literature and expert opinions, will be proposed to all relevant stakeholders (worldwide clinical experts, researchers, patients and parents) in a 3-round Delphi consensus procedure using digital surveys. Participants will repetitively score the importance of these outcome measure domains on a 5-point Likert scale. In each round, the results of the previous round will be fed back to the participants. All participants will have the opportunity to propose other relevant outcome measure domains in the first and second round.
Results: The final list of core outcome domains, consisting of domains on which consensus is reached (80% agreement on importance) in the expert and patient/parent groups, will be discussed in an international OVAMA meeting.
Conclusion: This e-Delphi consensus study, step 2 in the OVAMA project, will identify the core outcome measure domains for vascular malformations. Our next study will focus on the selection of appropriate outcome measurement instruments.

08:10-08:20 299 ***PHACE Syndrome International Clinical Registry and Genetic Repository: Update on Genetic Investigation.***

Kala Schilter1, Francine Blei2, Wendy Demos1, William Dobyns3, Beth Drolet4, Ilona Frieden5, Denise Metry6, Elizabeth Worthey7, Dawn Siegel1

1Medical College of Wisconsin, 2Lenox Hill Hospital, 3University of Washington, 4MCW, 5University of California, San Francisco, 6Baylor College of Medicine, 7Hudson Alpha Institute for Biotechnology

Purpose: PHACE syndrome is an acronym for the association of a large facial Hemangioma with Posterior fossa malformations, Arterial anomalies, Cardiac defects, and/or anomalies of the Eye (OMIM #606519). The etiology of PHACE syndrome is not known. 84% of PHACE patients have cerebrovascular anomalies, 56% of them arterial dysgenesis, and 47% anomalous course and/or origin of the arteries, suggesting disruption of normal developmental processes. Majority of arterial and brain anomalies are found ipsilateral to the hemangioma as well as within anterior circulation suggesting both factors early in specific development, as well as implicating the neural crest lineage. Genetic studies on PHACE syndrome including X-inactivation analysis, copy number variation analysis, and candidate locus analysis have not identified a genetic etiology. Based on the extensive phenotypic data of PHACE patients as well as previous genetic studies, we hypothesize a genetic component, likely somatic mosaic, causing the manifestations observed in PHACE syndrome.
Methods: The PHACE Syndrome International Clinical Registry and Genetic Repository established in 2006, currently has approximately 210 patients enrolled. Whole exome and/or whole genome sequencing has been performed on 13 tissue samples and 24 blood samples (13 paired with tissue and 11 blood alone) from PHACE syndrome patients, as well as 12 parental samples. WES and WGS data were generated on the Illumina HiSeq 2500 platform and aligned by the Burrows-Wheeler Alignment MEM algorithm (v0.7.7). The resulting .bam files were processed by the established intermediate workflow steps recommended by the Broad Institute, and the resulting outputs were subjected to variant calling with the Genome Analysis Toolkit v 3.2-2 Unified Genotyper and Haplotype Caller algorithms (GATK, Broad Institute). Variant calls from each algorithm were analyzed separately. Data analysis included investigation into variants in 3 or more PHACE patients, variants within proband tissue and absent in other samples, variants within proband tissue and blood and absent in parents, as well as variants inherited from parents in a recessive or compound heterozygous pattern. Variants of interest are prioritized by genes involved in neural crest migration and/or developmental lineage, and variants found within 29 genes implicated in angiogenesis and vasculogenesis.
Results: Previous genetic studies did not reveal X-linked variants or variants of copy number within PHACE patients. No shared pathogenic mutations have been identified in 3 or more PHACE patients. Initial analysis has not revealed causative variants in either factors of the neural crest lineage or factors involved in angiogenesis and vasculogenesis.
Conclusion: Utilizing what is known about PHACE syndrome and the possible cell types and lineages has directed the exploration of potential factors involved in this highly variable disorder. Ongoing analysis and exploration into the pathways involved in the development of PHACE syndrome features including endothelial cell development and proliferation are underway. More detailed investigation into factors involved in vascular development is planned. Potential interactions of environmental and genetic factors are being considered.

08:20-08:28 41 ***Patient Information on the Internet: Readability and Quality of Websites Regarding Hemangioma and Vascular Anomalies***

Andrew McCormick, Kara Davis, Lorelei Grunwaldt, Noel Jabbour

Vascular Anomalies Center UPMC

Purpose: The internet is increasingly a source of healthcare information utilized by parents, especially in rarer pathologies such as vascular malformations. The quality, validity and thoroughness of these websites is variable and unregulated. The goal of this study was to evaluate the quality and understandibility of websites related to vascular malformations.
Methods: The terms "hemangioma", "vascular malformation", and "vascular anomalies" were searched in Google. The first 30 websites meeting inclusion and exclusion criteria were evaluated. Quality and readability were assessed using the DISCERN criteria and the Flesh-Kincaid Reading Grade Level (FKGL), respectively. Date of last update, HONcode accreditation, and the website category were recorded.
Results: Most websites were owned by academic institutions (n=19, 63.3%). The mean DISCERN score for all websites was 2.97, or a partially valid source of information on a 1-5 scale. The average reading level estimated by FKGL was grade 12; only one website was scored at less than a grade 9 level. Two websites were HONcode accredited. Of the 18 sites giving an explicit date of last update, 12 (67.7%) had been updated in the previous 12 months.
Conclusion: Websites relating information about vascular anomalies may not be understandable to the general public, including parents. Health care providers should be cognizant of the quality and availability of such information as it may impact parent perspectives and bias toward treatment options.

08:28-08:36 76 ***HHT in Children: Symptomatic pediatric presentations of arteriovenous malformations (AVMs) in previously undiagnosed families***

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1Cincinnati Children's Hospital Medical Center, 2University of Cincinnati Medical Center

Purpose: To describe the symptomatic presentation of AVMs in pediatric patients (ages 0-31) subsequently found to have HHT.
Methods: We performed a retrospective chart review of patients followed by our HHT Center. We identified those patients who presented with symptomatic AVMs in the pediatric period (ages 0-31) prior to a diagnosis of HHT being made within the family. Information was gathered regarding details of presentation, treatment, other signs/symptoms of HHT (Curacao Criteria), and disease-causing mutation.
Results: We identified 11 AVMs which presented symptomatically in 10 patients (ages 12 days to 24 years) with no family diagnosis of HHT and no prior screening. Nine of 11 AVMs required intervention. Three patients who initially presented with brain AVMs were also found to have pre-symptomatic pulmonary AVMs when screening was completed. Eight of 10 patients were found to have a family history consistent with HHT once the diagnosis was considered. TABLE-see attached
Conclusion: Pediatric presentations of HHT-related AVMs can predate development of other Curacao criteria (nosebleeds, telangiectasias, and even family history) in these patients. These AVMs can cause significant morbidity in our pediatric patient population. Therefore, it is important to both 1) have a low threshold for testing in cases of possible HHT in pediatric patients, and 2) follow the international consensus guidelines for screening of affected individuals (in families where a genetic mutation is known), as well as for at-risk individuals in cases where genetic testing cannot identify a mutation or has not yet been performed.

08:36-08:44 359 ***HHT-related pulmonary AVMs (PAVMs) in children: efficacy of endovascular therapy***

Philip John1, Felix Ratjen2, Nigel Fernandopulle2

1The Hospital for Sick Children, Toronto, 2The Hospital for Sick Children

Purpose: To report our experience of endovascular closure of PAVMs in children with HHT.
Methods: A 18-year retrospective review (ending 2015) of clinical records, imaging studies and angiographic endovascular procedures (embolization) was performed on 20 consecutive children with HHT.
Results: 42 PAVMs (22 "simple", 20 "complex") were embolised in 20 pts (M:F=14:6, age range 1mo-15y, mean 7.4y). Single PAVMs were present in /multiple PAVMs were present in 12 pts had single and 8 pts had multiple PAVMs. Primary endovascular closure was achieved in 36/42 PAVMs (86%), incomplete primary closure in 6/42 (14%). 30 embolised PAVMs (16 pts) had CT scan at 1yr post therapy showing persistent closure in 29/30 (97%) and recannalisation in 1. Repeat angiography was undertaken in 12 PAVMs (in 12 pts) because of incomplete primary closure (6 PAVMs), recannalisation of a previously treated lesion (1 PAVM) or "new" PAVMs (5 PAVMs) requiring treatment were seen at the 1 yr post initial therapy CT scan. Time interval between initial and repeat angiography = 5.8yrs (range 1-11years). Retreatment closure was then achieved in 9/12 PAVMs (9 pts) and incomplete closure in 3/12 PAVMs(3 pts). Overall endovascular closure was achieved in 39/42 PAVMs (93%) in 17/20pts (85%). Incomplete closure occurred in 3/42 (7%) PAVMs in 3/20 pts (15%). One patient developed transient hypotension during embolization. There was no procedural-related mortality. Two pts died from massive hemoptysis & cardiorespiratory failure related to their underlying pulmonary disease.
Conclusion: In childhood endovascular closure of PAVMs by embolization is well tolerated, with low-risk, high efficacy and good durability. The high prevalence of complex types limits the overall durability in this patient population.

08:44-08:52 231 ***Non-syndromic Low-Flow Mixed Venous/Lymphatic Malformation of Skeletal Muscle of the Extremity (Fibro-Adipose Vascular Anomaly): a Clinicopathologic Study of 23 Cases***

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Purpose: Non-syndromic low-flow intramuscular malformations are often misdiagnosed as hemangioma or AV malformation, impacting management. Recently, a distinctive subtype of intramuscular mixed venous/lymphatic malformation was described termed fibro-adipose vascular anomaly (FAVA). Here we report 23 cases consistent with this lesion emphasizing distinquishing histomorphology and variable clinical severity.
Methods: Archival cases of extremity intramuscular "hemangioma" or "malformation" with low-flow MRI characteristics were identified and re-evaluated, including podoplanin/elastin staining. Clinical, MRI, operative and follow-up data were reviewed, excluding PHTS/other vascular syndromes, yielding 45 cases. From these, 22 typical VMs with gaping veins/prominent thrombi were pulled, providing a comparison group.
Results: Twenty-three patients (14F,9M), median age 16.3y (0-37) developed intramuscular lesions of calf (8), thigh (10), forearm (2), upper arm (2), foot (1). Twenty-two had variable pain; one was asymptomatic and one developed contracture. Follow-up on 22 patients (mean 19.3 mo, range 1-60) showed recurrence in 7 and persistent contracture in one despite resection and sclerotherapy. All showed large irregular veins surrounded by clusters of thin veins in a "honeycomb" pattern, fibrofatty change (23/23), abnormal lymphatics confirmed by D2-40 immunostain (14/16), lymphoid aggregates (22/23) and hemosiderin deposits (16/23). Twenty had distinctive indeterminate vessels with concentric hypertrophy and narrow lumina resembling small arteries but with absent/aberrant internal elastica (16/16). Venous thrombi were uncommon (4/23). In contrast, ordinary VMs showed large collapsed veins with frequent thrombi (22/22) and rarely other features. Thick, indeterminate vessels were suggested only focally in 1/22. Seventeen ordinary VMs were painful, indicating that pain is not a reliable criterion in separating these lesions.
Conclusion: Non-syndromic intramuscular mixed venous/lymphatic malformations, for which designation "FAVA" has been suggested, have distinctive histopathologic features distinquishing it from ordinary VMs and variable clinical severity ranging from asymptomatic to equinus contracture. Indeterminate vessels resemble arteries but lack internal elastic lamina and shouldn't be misinterpreted as arterial component in these low-flow malformations.

08:52-09:00 37 ***Developing a cryoablation protocol for management of Fibro-Adipose Vascular Anomaly (FAVA)***

Ahmad Alomari and Samantha Spencer

Boston Children's Hospital

Purpose: To discuss the protocol and technique of image-guided percutaneous cryoablation in management of FAVA
Methods: A retrospective cohort study of 30 patients with FAVA who underwent percutaneous cryoablation from September 2013 to November 2015. The protocol and technique used and clinical outcomes were evaluated.
Results: Using the novel cryoablation protocol, there was good peri procedural and follow up outcome. Patients tolerated the procedure well and had good recovery with this protocol with no major complications. There was significant improvement in pain as measured on brief pain inventory, which dropped by 3 (pain now) to 3.7 (pain in the past 24 hrs.) points. There was less interference of pain to most of the evaluated aspects of patients' everyday social life. Concurrent symptoms like swelling, physical limitations, skin hyperesthesia also improved. Clinical response was greatest at 2 to 5 months follow up after cryoablation with a more acceptable patient satisfaction thereafter.
Conclusion: A safe image-guided percutaneous cryoablation protocol in management of FAVA aimed at a good outcome is feasible.

09:00-09:08 297 ***Correlation of Complex Phenotypes in Vascular Overgrowth Syndromes with Genotype Data from Targeted Sequencing.***

Kala Schilter1, Eulaila Baselga2, Patricia Burrows3, Illona Frieden4, John Jensen3, Catherine McCuaig5, Elena Pope6, Dawn Siegel1, Megha Tollefson7, Beth Drolet8

1Medical College of Wisconsin, 2Hospital de la Santa Creu i Sant Pau, 3Children's Hospital of Wisconsin, 4University of California, San Francisco, 5CHU Sainte-Justine, 6Hospital for Sick Children, 7Mayo Clinic, 8MCW

Purpose: Vascular overgrowth syndromes [VOS] are complex vascular anomalies comprising vascular malformations, segmental cutaneous abnormalities, regional overgrowth and regional skeletal anomalies, caused by multiple post zygotic mosaic mutations within the PI3K/AKT/mTOR signaling pathway. Severity and prognosis are variable and are most likely explained by the specific genetic alteration. We hypothesize that the variability seen in VOS is due to coexistence of multiple variance in more than one VOS related gene. The purpose of this study is to identify specific mutations in a group of patients with VOS and determine whether or not they predict the clinical and imaging phenotypes.
Methods: Genotype data from DNA extracted from affected tissue for 25 vascular overgrowth patients was generated via targeted exome sequencing of 129 genes within the comprehensive cancer gene set from the Washington University School of Medicine. This panel included AKT1, AKT3, GNAQ, GNAS, MTOR, PIK3CA, PIK3R2, PTEN, RASA1, TSC1, TSC2 and more. All variants from the targeted sequencing panel will be evaluated. Genes previously identified in overgrowth syndromes or related syndromes are first evaluated for any variants. Nonsynonymous and premature stop variants will get priority although all variants within vascular overgrowth genes will be noted for possible modifier effects. Variants are evaluated for their presence in the literature or connection to related disorders, variant allele frequency, and frequency in the general population databases. Clinical and imaging phenotype will be determined from review of clinical photographs and imaging studies to document cutaneous dysplasia, common somatic anomalies, tissue planes affected by overgrowth and nature and extent of vascular malformation.
Results: Analysis is currently ongoing. 17 patients have gone through initial analysis and likely causative germline or mosaic mutations have been identified in 11 patients. Initial analysis has also revealed 6 patients harboring variants in more than one causative gene. 8 patients have yet to be analyzed.
Conclusion: Correlations of genotype data with detailed phenotype data are underway. Preliminary data has revealed the importance of multifactorial genetic effects in vascular overgrowth phenotypes. Genotype information can also help to elucidate diagnosis and help direct clinical management. A more all-inclusive screening of genes within the known etiological pathways as well as related proliferative pathways in VOS can reveal additional insight into this highly variable spectrum of disorders.

09:08-09:16 101 ***Predictors of thrombosis complications in pediatric patients with vascular malformations***

Pablo Sepúlveda, Alejandro Zavala, Pamela Zuñiga

Pontificia Universidad Católica de Chile

Purpose: Patients with vascular malformations can develop localized intravascular coagulation, being the thrombotic events the most frequent form of presentation. This can produce pain and complicate the evolution of the illness. Through this study, we have identified clinical and laboratory factors associated to this type of complications.
Methods: This is a study observational retrospective, of cases and controls. Realized with compiled data from a period of 6 years (2008-2014) at the Pontifical Catholic University of Chile's Clinical Hospital. From the data base we have analyzed 110 patients diagnosed with vascular anomalies. To investigate the factors associated with increased risk of thrombosis odds ratios (OR) were calculated. Multivariate logistic regression analysis was performed to search for the best model predictive of complications.
Results: In the bivariate analysis we found significant association between high levels of D-dimer with thrombotic complication ($p < 0,01$), with calculated OR 17,1, for values over 500 ng/mL. Besides the surface ≥ 10 cm2 and the presence of tangible phlebolith were associated to significant higher risk, with an adjusted OR 6,18 and adjusted OR 20,17 respectively. In the multivariate analysis we found that with higher age, matching with the beginning of adolescence, the risk of thrombotic complication increased in 1,33 times ($p=0,013$), the surface presence ≥ 10 cm2 was associated to 8,19 times more risk ($p=0,042$) and the presence of tangible phlebolith(s) to 85.29 times more risk ($p < 0,01$). We observed the extended partial thromboplastin time (APTT)as a protective factor, nevertheless, this last result was not significant ($p=0,056$).
Conclusion: Vascular malformations characteristics as a bigger extension and the presence of tangible phlebolith, in addition with laboratory elements as high levels of D-dimer and extended APTT must be considered to decide using profilactic anticoagulant therapy in children. Adolescence would be a riskier age to reconsider this decision.

09:16-09:24 98 ***Pulmonary Thromboembolic Events in Patients with Congenital Lipomatous Overgrowth, Vascular Malformations, Epidermal Nevi (CLOVES) and Klippel-Trenaunay Syndrome (KTS)***

Joseph Reis, Ahmad Alomari, Cameron Trenor, Samantha Spencer, Steven Fishman, Gulraiz Chaudry

Boston Children's Hospital

Purpose: Patients with CLOVES and KTS have enlarged persistent embryonic veins, which are incompetent and prone to thromboembolism. The purpose of the study is to determine the incidence of symptomatic pulmonary embolism (PE) in these patients, screen for the presence of abnormally dilated veins in this population and evaluate the effectiveness of medical and endovascular treatments.
Methods: A retrospective review was conducted of 219 patients referred to the Vascular Anomalies Clinic (VAC) at our institution over an 18 year period with a final diagnosis of CLOVES or KTS. The patients that developed PE were screened for thromboembolic risk factors in addition to phlebectasia and the presence of persistent embryonic veins. Treatment outcomes following endovascular and medical therapies were reported.
Results: A total of 7 KTS patients out of 117 (6%) and 9 CLOVES patients out of 102 (9%) suffered PEs. Seven patients (44%) developed PEs following surgery. All patients were treated with anticoagulation and 12 (75%) patients underwent subsequent endovascular treatment. Two of the patients died of pulmonary emboli. Fifteen patients (94%) had abnormally dilated central veins or persistent embryonic veins. No patients prophylactically treated with endovascular closure of dilated embryonic veins had evidence of PE.
Conclusion: Patients with CLOVES and KTS are at risk for pulmonary emboli and should be prophylactically treated with endovascular closure of dilated persistent embryonic veins. Optimal therapy includes using both medical and endovascular treatments to address hypercoagulability and phlebectasia.

09:24-09:32 329 ***Abnormal Brain Imaging and Seizure Risk in 34 patients with CLOVES Syndrome***

Katherine Broecker, Sanjay Prabhu, Jacqueline Fabricius, Meghan O'Hare, Darren Orbach, Cameron Trenor

Boston Children's Hospital

Purpose: Congenital Lipomatous Overgrowth, Vascular anomalies, Epidermal nevi, and Scoliosis or skeletal anomalies (CLOVES) can be associated with other manifestations, including brain malformations and seizures, similar to other disorders with mutations in PIK3CA. Our goal was to identify brain imaging predictors of seizure risk in patients with CLOVES.
Methods: Through the Lymphatic Anomalies Registry (www.lymphaticregistry.org), 84 patients with CLOVES were retrospectively reviewed for a history of seizures. Of patients with available imaging, 13 patients with seizures were compared to 21 age-matched control CLOVES patients without seizures. Brain imaging of these 34 patients was reviewed by two blinded neuro-radiologists, assessing for polymicrogyria, hemimegencephaly, heterotropia, and corpus callosum abnormalities.
Results: Of 34 patients, 13 (38%) had seizures compared to 21 (62%) controls without seizures. The mean age at the time of imaging for seizure patients was 2.3 years compared to 7.3 years in control patients. Eight patients (61.5%) presented with seizures between birth and the age of 2. Six patients were treated with anti-epileptics and two have refractory epilepsy. One patient underwent curative hemispherectomy at age 1. Five of 13 seizure patients had developmental delay, ranging from motor or speech delays to global developmental delay. Of 13 patients with CLOVES and seizure, 9 (69%) had polymicrogyria, 10 (77%) had hemimegencephaly (seven of these with facial asymmetry), 3 (23%) had heterotopia and 6 (46%) had abnormalities of the corpus callosum. No control patients had polymicrogyria or heterotopia, one had hemimegencephaly and two had abnormalities of the corpus callosum. Additionally on imaging, multiple patients with CLOVES and seizure had other cortical findings including lissencephaly, a large arachnoid cyst, and a cavernous venous malformation.
Conclusion: Abnormal brain imaging is associated with seizure in patients with CLOVES, which may have implications for management of these patients.

09:32-09:40 276 ***Cutaneovisceral Angiomatosis with Thrombocytopenia (CAT) / Multifocal Lymphangioendotheliomatosis with Thrombocytopenia (MLT): Consensus Diagnostic Criteria and Outcomes of 48 patients***

Cameron Trenor1, Meghan O'Hare1, Yvonne Chiu2, Meaghan Barrett2, Patricia Burrows2, Michael Kelly2, Paula North2, Harry Kozakewich1, Beth Drolet3

1Boston Children's Hospital, 2Medical College of Wisconsin, 3MCW

Purpose: CAT/MLT is a rare vascular disorder characterized by multifocal skin and visceral lesions, thrombocytopenia, and bleeding. Transfusion-dependent gastrointestinal hemorrhage contributes to morbidity especially in infancy. Consensus diagnostic criteria, atypical presentations and long-term outcomes data are lacking.
Methods: Our IRB-approved retrospective cohort study utilized dual center registries of 48 patients fitting the diagnostic criteria of CAT/MLT to unify diagnostic criteria and elucidate clinical features and long-term outcomes. Patients were referred in dual center registries by physician and patient referral. A multidisciplinary, collaborative meeting developed consensus-derived diagnostic criteria, standard patient evaluation, and initial treatment recommendations.
Results: Consensus diagnostic criteria are classic multifocal skin lesions, characteristic histology of skin biopsies, visceral/organ involvement, and thrombocytopenia. Patients meeting 3 of 4 criteria were defined as probable CAT/MLT (14%) and all four criteria were CAT/MLT (82.6%). Presentation at birth occurred in 65.2% of patients; 86.0% were full term infants and 54.2% were female. Multifocal skin lesions were described in 91.3% of patients and gastrointestinal lesions were present in 72.9%. The majority (87%) of patients experienced bleeding and 91.1% had thrombocytopenia with a median platelet nadir of 37,000/ul (3,000-464,000/ul). Atypical sites of CAT/MLT lesions include lung, bone, eye, pericardium and brain. Mean length of follow up was 4.7 years (range 0.2 -23.6 years). Resolution of GI bleeding occurred at median of 1.2 years (range 3 months-9 years) while thrombocytopenia resolved at a median 2.5 years (range 1 month - 15 years). Parent-reported efficacy was >50% for corticosteroids (21/32 patients), thalidomide (4/7 patients) and bevacizumab (2/3 patients).
Conclusion: CAT/MLT is not isolated to cutaneous and visceral presentation. Infants may require treatment but, in most but not all patients, CAT/MLT is a resolving disease. Collaborative study of this rare vascular anomaly facilitated consensus diagnostic criteria and review of nomenclature and highlights atypical features and long-term outcomes.

09:40-09:48 47 ***Primary Intestinal Lymphangiectasia. A Protein-Losing Enteropathy in the context of Generalized Lymphatic Anomaly***

Juan Carlos Lopez-Gutierrez1 and Victoria Diaz Marugan2

1, 2La Paz Children´s Hospital

Purpose: To demonstrate that Primary Intestinal Lymphangiectasia (PIL) described by Waldmann in 1961 in 18 patients with "idiopathic hypercatabolic hypoproteinemia" , results from a disruption of lymphatic circulation and, therefore, corresponds to a secondary event in the context of Generalized Lymphatic Anomaly and is not a primary disorder of unknow etiology as marked in most articles referred to this entity.
Methods: Analysis of intestinal lymphatic involvement in patients with diagnosis of PIL between 1965 and 2013 was performed . 21 patients were included. 10 patients were diagnosed before 5 years-old (1 prenatal), 8 between 5 and 18 years-old and 3 older than 18 years-old. The follow-up period varied between 1 and 34 years. One patient had Noonan syndrome and two patients were siblings. Clinical data (growth, digestive symptoms, frequency of infections, presence of associated lymphatic malformation , lymphedema, thrombosis episodes , coagulopathy and osteolysis), blood and fecal parameters, imaging studies, endoscopy results ,biopsies analysis ,treatments and outcome were collected from medical records . Endoscopy ,histological study, MR imaging and Lymphoscintigraphy was undertaken in all patients. Dynamic Intranodal lymphangiography was performed in 8 patients.
Results: Central lymphatic channel obstruction was identified in 12 patients (57%) . Associated LM was present in 16, diarrhea in 10, chylothorax in 11, chylous ascites in 10, pericardial effusion in 6, coagulopathy in 3 and osteolysis in 7.
Conclusion: Following analysis of symptoms, imaging studies , clinical courses and final outcomes we consider Primary Intestinal Lymphangiectasia not an entity, but a consequence of the lymphatic flow impairement in the thoracic duct which develops chylous reflux into the intestinal lymphatics. Therefore, we propose the term Primary Intestinal Lymphangiectasia to be replaced by Protein-Losing Enteropathy in the context of a Channel type Lymphatic Malformation or Generalized Lymphatic Anomaly.

09:48-10:00 34 ***Sclerotherapy for Low Flow Vascular Malformations of the Head and Neck: A Systematic Review of Sclerosing Agents***

Sophie E.R. Horbach1, Max M. Lokhorst2, Peerooz Saeed3, Claire M.F. de Goüyon Matignon de Pontouraude3, Aniki Rothová4, Chantal M.A.M. van der Horst2

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Purpose: Sclerotherapy has become the gold standard for the first-line therapy of most venous and lymphatic malformations of the head and neck. Numerous sclerosing agents are used to treat these low flow vascular malformations, but to date, it remains unclear which sclerosing agent is superior in terms of effectiveness and safety.
Methods: In a systematic review of the literature (1995-present), we compare the effectiveness and complications of the sclerosing agents most commonly used for cervicocraniofacial venous and lymphatic malformations.
Results: The literature search yielded 1155 articles, 36 (1552 patients) were included in the systematic review. The quality of evidence was low. Pingyangmycin, absolute ethanol, OK-432, ethanolamine oleate, bleomycin, polidocanol, doxycycline and sodium tetradecyl sulphate were the most reported sclerosing agents. All seem effective, the mean overall response varies from 71 to 100%. Complications occurred more frequently after ethanol (18%), compared to other sclerosing agents (0-6%). Cellulitis and ulceration were encountered following most sclerosing agents, but skin necrosis was particularly observed after ethanol. Facial nerve paralysis occurred only after OK-432 (0.05%) and ethanol sclerotherapy (6%).
Conclusion: This systematic review could not identify a significantly superior sclerosing agent in terms of effectiveness, due to the low quality of the available evidence. Until stronger evidence is available, the difference in complication rates is potentially the deciding factor in the choice between sclerosing agents. Since a significantly higher complication rate and more severe local complications were encountered after absolute ethanol, we cannot recommend this agent for sclerotherapy of cervicofacial vascular malformations.

10:00-10:30 | DC 5 - Difficult Case Presentations V | Juan Pablo II Room

Chairs: Bernardo Gontijo, Magdalena Sojo

10:00-10:15 294 ***Percutaneous Sclerotherapy of Midline Scalp Venous Malformation with Assisted Balloon Occlusion via the Superior Sagittal Sinus***

Anne Marie Cahill1, Robert Hurst2, Bryan Pukenas2

1Children's Hospital of Philadelphia, 2Hospital of the University of Pennsylvania

Purpose: To describe successful balloon occlusion and direct percutaneous injection of a scalp venous malformation with venous outflow to the superior sagittal sinus.
Methods: 8 yr old boy presenting with a swelling of his scalp, significantly increased in the supine position and intermittent pain. MRI with contrast revealed a venous malformation of the scalp with no cranial defect and no obvious venous drainage.
Results: Contrast injection of the venous malformation via a percutaneous access demonstrated delayed venous outflow drainage to the superior sagittal sinus. Via femoral access a Hyperform 7x7mm balloon was placed in the superior sagittal sinus at the site of venous drainage and three sites were treated with 30% NBCA was injected at four sites using a percutaneous approach. 6 week follow up revealed thrombosis of the venous malformation and the patient was asymptomatic with no further alteration in lesion size with positioning.
Conclusion: Balloon occlusion of the superior sagittal sinus is a feasible option for temporary occlusion of draining veins from type 2/3 scalp venous malformations.

10:15-10:30 183 ***Complex case of combined AVM and AV fistulas in a Parkes Weber Syndrome (PWS). The Yin Yang of transarterial and venous embolization***

Gilles Soulez1, Patrick Gilbert1, Marie-France Giroux1, Vincent Oliva1, Josee Dubois2

1CHUM-University of Montreal, 2CHU Ste-Justine

Purpose: This 28 year-old man with PWS of the leg presented with edema, calf ulceration and cardiac failure.
Methods: On angiography, the patient had multiple large AV fistulas arising from the femoral profunda and multiple AVMs coming from iliofemoral feeders. AVFs were embolized with amplatzer plugs and a covered stent. Multiple embolization sessions of AVMs with ethanol and glue were performed to decrease the inflow. Then, transvenous embolization of the profunda femoral draining vein was performed with coils. No anticoagulation was given before or after the procedure.
Results: After the 18th embolization session, the patients developed an extensive DVT of the left leg deep venous system. He was treated heparin/ Coumadin. Six months later, we observed a dramatic improvement of the leg edema and a complete closure of arteriovenous shunting but he still have a 5 cm aneurysm of the iliac artery.
Conclusion: Questions for discussion: 1. Should we prescribe anticoagulation after transvenous embolization of AVMs to prevent acute thrombosis? 2. How to prevent pulmonary embolism, IVC and iliac vein too large for IVC filtration? 3. What is the potential of iliac aneurysm progression versus remodeling with slower but high resistance flow?

10:30-11:00 Coffee Break

11:00-12:30 PS A - Parallel Session A: Interventional Radiology Juan Pablo II Room

Chairs: Patricia Burrows, Ricardo García-Mónaco

11:00-11.10 111 ***Preclinical testing of a bioresorbable and sclerosing embolizing gel made of chitosan and STS in a high flow fistula and aneurysm model (endoleak)***

Gilles Soulez1, Fatima Zhetabi2, Vincent Dumont-Mackay2, Elias Assaad2, Ahmed Fatimi2, Heon Helene2, Sophie Lerouge3

1CHUM-University of Montreal, 2CHUM Research center, 3CHUM research center

Purpose: To demonstrate the advantages of a biodegradable embolizing sclerosing agent over an embolizing but non-sclerosing agent in a canine endoleak model reproducing a high flow fistula in iliac aneurysms.
Methods: Chitosan (CH)-based radiopaque hydrogels were prepared with or without a sodium tetradecyl sulfate (STS) sclerosing agent. Their rheological, injectability and embolizing properties were assessed in 0.024 inch microcatheters. To reproduce the rheology of an arterio-venous fistula, 18 bilateral common iliac aneurysms were constructed in 9 dogs with venous patches and anastomosed to the caudal artery to create an outflow vessel. A stent-graft was inserted with a proximal gap to create a pressure gradient and a flow (endoleak) in the aneurysm and the collateral artery. Leaking aneurysms were randomly embolized with CH and CH-STS. The primary endpoint was endoleak persistence at 3 or 6 months, based on CT scan findings confirmed on macroscopic tissue slides. Secondary endpoints were, gel migration, the evolution of the aneurysm mean diameter with time, as well as aneurysm healing and inflammation scores based on pathology examination.
Results: In vitro experiments showed that both products gelled rapidly, with good initial mechanical properties, which continued to increase with time. Both were able to occlude flow up to physiological pressure, and were injectable through microcatheters. In the high-flow fistula model, the injection of CH-STS sclerosing gel tended to reduce the risk of endoleak persistence (2/9 aneurysms), compared with CH non-sclerosing agent (6/9 aneurysms) (p=0.068).Two cases of gel migration and tail necrosis were observed. The gel was not visible on follow-up CT-scans. Histological analysis showed moderate inflammation around both gels, with a comparable intensity score in both CH and CH-STS groups.
Conclusion: Flow occlusion, combined with endothelial denudation, appears as a promising paradigm for the treatment of high-flow fistula. Bioresorbability, easy injectability and temporary radio-opacity are other advantages of this new embolizing agent.

11:10-11:20 13 ***Embolization of Pulmonary Arteriovenous Malformations: A Comparison of the Micro Vascular Plug System, Amplatzer Vascular Plugs and Coils***

Matthew Towsley, Stacey MacKenzie, Sally Mitchell, Clifford Weiss

Johns Hopkins Hospital

Purpose: Transcatheter embolization remains the treatment of choice in Pulmonary Arteriovenous Malformations (PAVMs), whether using the detachable coil, Amplatzer Vascular Plug (AVP) or the recently developed MicroVascular Plug System (MVP). Coil embolization has been the traditional approach, but recanalization rates ranging from 5-15% and the need for multiple coils has led to delivery systems that provide rapid occlusion with a single plug. This study compares all three embolic devices in the treatment of PAVMs.
Methods: With approval from the institutional review board, all patients treated for PAVMs January 2012 - July 2015 were reviewed. Only patients receiving a single device category (Coil, AVP or MVP) were included. The study contained 45 patients with 142 PAVMs (13 men, 32 women, mean age 43y±24y). 24 PAVMs were treated with coils, 39 with AVPs and 23 with MVP. Technical success was defined as occlusion of the feeding artery supplying the PAVM without evidence of residual flow. We examined total procedure time, fluoroscopy time, contrast dose and cost of deployed devices.
Results: All procedures were technically successful. At a mean follow-up of 122 days using computed tomography angiography (18/45 patients), recanalization occurred in 4 coil cases, 4 AVP cases and 0 MVP cases. The results are displayed in table. T-tests were performed between the embolic devices, with cost being the only statistically significant variable at $p<0.01$ when comparing coils v. AVP and coils v. MVP.
Conclusion: AVPs had the lowest procedure and fluoroscopy time, and were the most cost effective. MVPs improved procedure time and were more cost effective than coils with the added benefit of microcatheter delivery allowing embolization of smaller PAVMs.

11:20-11:30 256 ***Onyx embolization of pediatric head and neck Arteriovenous Malformations utilizing a two microcatheter technique***

David Case1, Paul Rochon2, Ann Kulungowski3, Daniel Wells2, Jason Rich2, Rajan Gupta4, David Kumpe2, Joshua Seinfeld2

1University of Colorado Department of Neurosurgery, 2University of Colorado, 3The Childrens Hospital, Denver Colorado, 4Kaiser Permanente

Purpose: Endovascular treatment of arteriorvenous malformations (AVMs) has taken on a greater role in the pediatric population. Adequate nidus embolization without clinically significant non-target embolization/reflux is challenging. We describe a case series using a specific 2 microcatheter technique for pediatric AVM embolization with Onyx. We aim to demonstrate the efficacy and safety of this technique in the pediatric population.
Methods: Patient Selection: Head and neck AVM cases treated with Onyx embolization were reviewed from the past 5 years. 5 pediatric patients between 2010 and 2015 were treated with Onyx embolization utilizing a 2 microcatheter technique. 2 patients had mandibular arteriovenous malformations, 1 patient had a posterior neck arteriovenous malformation, and 2 patients had cerebral arteriovenous malformations. Vascular malformation anatomy, location, and procedural details were recorded. Technique: During 1-4 procedures per patient smaller arterial feeders were embolized first to maximally decrease the intranidal pressure at the time of the occlusion/ embolization of the major residual feeder. The dominant residual feeder was then embolized using two microcatheters. Coils followed by Onyx were initially deployed through the proximal catheter to form a dense plug. This was allowed to solidify for 20-30 minutes and then aggressive embolization of the nidus was performed through the distal catheter.
Results: All 5 patients had excellent treatment results with complete (3) or near complete (2) obliteration of the vascular malformation nidus. No procedural complications were noted, specifically no strokes, hemorrhages, or unintentionally retained catheter fragments occurred.
Conclusion: Pediatric AVMs are a challenging disease entity to treat. A 2 microcatheter technique for Onyx embolization in conjunction with prior embolization of smaller arterial feeders is a safe and efficacious treatment option. This technique allows for maximal nidus penetration while minimizing the risk of non-target embolization/reflux. In our small case series, we achieved excellent results with near complete to complete obliteration of the vascular malformation nidus.

11:30-11:40 263 ***Percutaneous Sclerotherapy of intra-orbital Lymphatic Malformations using bleomycin***

Galli Eduardo

Hospital de Niños Ricardo Gutierrez, Buenos Aires, Argentina.

Purpose: to describe the clinical, imaging findings, percutaneous treatment and short term follow-up of a serie of 5 patients presenting with intraorbital lymphatic malformations.
Methods: 5 patients (from 2 to 29 years) underwent percutaneous schlerotherapy with bleomycin under angiographic and echographic guidance.
Results: all of patients presented with exoftalmos and visual symptoms. Diagnostic was confirmed by MRI and CT. Treatment reduced size of lesions and improved intra-ocular pressure and symptomatology without complications.
Conclusion: Percutaneous sclerotheraphy using bleomycin provides a safe and effective treatment for orbital lymphatic malformation.

11:40-11:50 27 ***Bleomycin for Early Intervention of Extracranial Arteriovenous Malformations: A Prospective Study***

Yunbo Jin1, Yun Zou1, Lin Xiaoxi2, Xi Yang3, Hui Chen1, Gang Ma4, Chen Hua1

1Shanghai 9th People's Hospital at Shanghai, 2Department of Plastic and Reconstructive Surgery, Shanghai Ninth People's Hospital, School of Medicine, Shanghai Jiaotong University, 3Shanghai ninth people's hospital, 4Department of Plastic and Reconstructive Surgery, Shanghai Ninth People's Hospital, Shanghai Jiaotong University, School of Medicine

Purpose: There is no optimal treatment method for Extracranial Arteriovenous Malformation (AVM) at early stage up to now. This study explores AVM treatment with bleomycin as a potential early intervention strategy.
Methods: We enrolled 50 patients with lower-stage (I/II) AVMs diagnosed by digital subtraction angiography (DSA). Patients were administered intralesional injections of bleomycin at a 15mg dosage (adults) or below 1mg/kg (children)once monthly for a six-month period. Subsequent DSA was scheduled with a 3-month interval after the six treatments to assess the efficacy of bleomycin. The safety of all procedures was diligently maintained.
Results: Twenty-seven patients with completed data were enrolled in the study: four men (14.8%) and 23 (85.2%) women, with a mean age of 21.7 years (range 2-44 years). Twenty-three of the 27 patients (85.2%) showed disappearance rates over 50% on their DSA, including eight patients (29.6%) whose AVMs completely disappeared. No patient's AVMs became worse. Out of all 153 procedures (average dose: 14.8 mg), only two injections (in two respective patients) had temporary major (Class C, Society of Interventional Radiology) complications, and zero patients experienced serious long-term complications.
Conclusion: Bleomycin is safe, effective, and practical for the treatment of early-stage AVMs. This innovative treatment method is a favorable strategic choice for early AVM intervention, and according to our observations, may cure or prevent worsening of lower-stage AVMs.

11:50-12:00 149 ***Endoscopy-assisted percutaneous treatment of laryngeal low flow vascular malformations.***

Sergio Sierre1, Dario Teplisky2, Alejandro Cocciaglia1, Hugo Botto1, Hugo Rodriguez1, Mary Nieto1, Matias Garriga1, José Lipsich3

1Hospital de Pediatria "Juan P. Garrahan", 2Hospital de Pediatría "Juan P. Garrahan, 3Hospital de Pediatría "Juan P. Garrahan"

Purpose: To describe our experience with the endoscopy-assisted percutaneous treatment of airway tract low flow vascular malformations (LFVM) with laryngeal involvement in pediatric patients.
Methods: Retrospective review of 11 children with laryngeal obstruction related to LFVM. Seven boys, age range [1-14 ys-old]. There were 3 venous malformations, 4 lymphatic and 4 combined venous-lymphatic malformations. All patients were treated by means of percutaneous sclerotherapy assisted with fibrolaryngoscopy. Five children had tracheostomy cannulas before the first course of treatment, due to severe airway obstruction. Bleomycin was the sclerosing agent in all cases. All procedures were performed under general anesthesia, and under fluoroscopy and endoscopic guidance. One to 4 sessions/patient (mean 2.5) were performed during the study period. Treatment response and outcome were assessed with fibrolaryngoscopy and clinical examination.
Results: All patients presented a significant reduction of the LFVM volume (>75%) with associated clinical improvement and resolution of airway obstruction symptoms. Patients with tracheostomy were decannulated after a mean of 3 months of treatment. No complications were found in these series.
Conclusion: Endoscopy-assisted percutaneous sclerotherapy of airway LFVM with laryngeal involvement seems to be effective and safe and might be considered as a valuable minimally invasive treatment option in patients with vascular malformations with laryngeal involvement.

12:00-12:10 179 ***Mandibular High-Flow Malformation Embolization with Onyx: Initial Experience in a Tertiary Pediatric Institution***

Anthony Guzman1, Robert Hurst1, David Stanton1, Joli Chou1, Steven Wang1, Anne Marie Cahill2

1Hospital of the University of Pennsylvania, 2Children's Hospital of Philadelphia

Purpose: To report our initial experience with ethylene vinyl alcohol copolymer (ONYX; ev3/Covidien, Irvine, CA) in treating mandibular high flow malformations (HFMs) in a tertiary pediatric center.
Methods: Two male patients, age 12 (patient 1) and age 13 (patient 2) with the diagnosis of HFM who underwent percutaneous ONYX embolization were identified. Patient 1 presented with a slow-growing, painful left mandibular swelling with loose teeth and hemorrhage that required packing. MR imaging demonstrated left mandibular arterial prominence and dilated low flow spaces. Patient 2 presented with a painless, pulsatile right mandibular mass. CT showed an expansile lytic lesion of the right mandibular body with prominent vasculature suggestive of HFM.
Results: In patient 1, intra-arterial PVA embolization of a third order branch of the left lingual artery and left inferior alveolar artery was performed to little effect, and thus fluoroscopy-guided percutaneous ONYX embolization of the nidus was performed. In patient 2, intra-arterial embolization of right facial, lingual, and inferior alveolar arteries was performed with balloon-assisted occlusion with limited effect, followed by percutaneous ONYX embolization of the nidus. In both cases, post-procedural angiography demonstrated nidal occlusion. No complications occurred. The patients were discharged after precautionary overnight monitoring. At 1 year, Panorex imaging of patient 1 demonstrated the presence of Onyx material and bone fill at the nidal site. The patient is pain-free, is undergoing orthodontics and playing contact sports. Similarly, at 1 year, CT angiography of patient 2 demonstrated intra-nidal Onyx and no evidence of enhancing nidal lesion. The patient has had no further bleeding with complete fixation of the overlying teeth.
Conclusion: Percutaneous ONYX nidal embolization may be an effective adjunctive technique for the treatment of intraosseous mandibular high-flow malformations.

11:00-12:30 | PS B - Parallel Session B: Laser & Surgery | Aula Magna Room

Chairs: Milton Waner, Carsten Philipp

11:00-11:10 137 ***The relationship between flow velocity and therapeutic effect on port-wine stains: A prospective self-control study***

Jiafang Zhu, Tianyou Wang, Wenxi Yu, Gang Ma, Yijie Chen, Yajing Qiu, Hanru Ying, Lin Xiaoxi

1Department of Plastic and Reconstructive Surgery, Shanghai Ninth People's Hospital, School of Medicine, Shanghai Jiaotong University

Purpose: Port-wine stain (PWS)is a benign congenital vascular malformation. Laser therapy is the choice for treatment of PWS. Unfortunately, this approach has limited efficacy, with only 10-20% of patients experiencing complete blanching of the PWS. Laser Doppler imaging is a measure reported to detect the hemodynamics of the pws. In order to find a better way to assess the prognosis of port-wine stains outside the face, laser doppler imaging is used here looking for a connection between flow velocity and therapeutic effect.
Methods: Prospective self-control study of 20 patients with PWS large in size outside face treated with a 595 nm laser alone or in combination with other lasers, including Nd:YAG laser. Hemodynamics of the patients were detected before treatment and the patients were treated for three times. After treatment was completed, the therapeutic effect was evaluated with both photographs and Chromameter.
Results: In all, 20 patients were included. 15 patients were on the upper extremities and 5 patients were on the lower extremities. The flow velocity of the upper arm/thigh was 0.81 in average, the lower arm/leg was 0.95 in average, and hand/feet was 1.3 in average, while the the average blanching rate evaluated by Chromameter for these sides was 36-42%, 21-24% and 15-18%. This difference was statistically significant (P = 0.04), which suggests that flow velocity may be an effective method to assess the prognosis of the pws.
Conclusion: Laser doppler imaging is effective and safe to assess the prognosis of PWS. The efficacy of the PDL is affected by the location of pws, which is inversely proportional to the flow velocity of the lesion.

11.10-11:20 6 ***Endovascular diode Laser treatment in venous malformations of the upper aerodigestive tract.***

François Simon1, Nicolas Le Clerc1, Didier Salvan1, Elisabeth Sauvaget2, Benoît Faucon1, Michel Borsik1, Philippe Herman1, Annouk Bisdorff1

11APHP, Hôpital Lariboisière - Université Paris 7, Paris, 2Hôpital Saint Joseph, Paris

Purpose: Venous malformations of the upper aero-digestive tract can cause pain, dysphagia, obstructive sleep apnea and rarely bleeding issues. We studied the effectiveness of 980 nm diode endovascular laser therapy.
Methods: This is a 2007-2014 retrospective study in our vascular anomalies center. Data on patients' clinical history, polysomonography, MRI and treatment was collected. Patients were contacted for Epworth and EAT-10 scores to evaluate sleepiness and dysphagia before and after laser therapy. Apnea-Hypopnea Index was also statistically compared in obstructive sleep apnea patients.
Results: We included 32 patients (mean age 41) presenting obstructive sleep apnea (n=18) and dysphagia (n=13). With a mean follow-up of 39 months, average Epworth score fell from 17.3 to 10.4 (p=0.015), EAT-10 score from 8.2 to 3.5 (p=0.002) and Apnea-Hypopnea Index from 47.5 to 24.7 (p=0.01). 89% of the sleep apnea patients required Continuous Positive Pressure before down to 50% afterward laser therapy (p=0.016).
Conclusion: Diode endovenous laser treatment seems to be a safe and effective treatment option in venous malformation of the upper airways. A multimodal approach must be discussed in a specialized multidisciplinary clinic to best tailor treatments for each patient.

11:20-11:30 25 ***A Prospective Self-Controlled Study of Topical Timolol Cream versus 595nm Pulsed Dye Laser in Treatment of Superficial Infantile Hemangiomas***

Gang Ma1, Pinru Wu2, Hui Chen3, Yunbo Jin3, Xiaoxi Lin3

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Purpose: Infantile hemangioma (IH) is the most common soft-tissue tumor of infancy. The mainstay approach to uncomplicated lesions is 'wait and see', but active intervention is sometimes preferred to avoid the unpredictable risk of cosmetic disfigurement. Recently, timolol maleate, a topical nonselective beta-blocker, has been reported as a potentially effective treatment for superficial IHs. This prospective self-control study was designed to evaluate the efficacy and safety of the relatively new technique termed ablative fractional laser-assisted drug delivery for enhancing the topical timolol for the treatment of superficial and mixed IHs.
Methods: A total of 23 children (16 girls and 2 boys) completed with 20 proliferative IHs (15 superficial and 5 mixed) and 3 involuting IHs (1 superficial and 2 mixed). A fractional CO2 laser system was applied to the skin surface of IH using DeepFx mode (25-35 mJ per pulse, 5% density, single pulse) at one week interval. Topical timolol maleate 0.5% ophthalmic solution was applied under occlusion for 30 minutes four to five times daily for an average treatment duration of 12 weeks (5-24 weeks). Clinical improvement was evaluated by a visual analog scale (VAS).
Results: Of the 23 patients, VAS improvement of color was significant different between AFXL + Timolol and Timolol alone sites (P=0.007), AFXL + Timolol and untreated sites (P=0.04), AFXL alone and Timolol alone sites (P=0.021) in proliferative IHs indicating a greater reduction of color improved by fractional CO2 laser assisted timolol delivery. The mean VAS of AFXL + Timolol sites was similar as AFXL alone sites while a little higher than the score of Timolol sites in involuting IHs.All of these sites had an average VAS of thickness reduction of more than 60% at the end of treatment and 80% after six months of follow-up in proliferative IHs, and 70% and 85% respectively in involuting IHs.The plasma timolol concentration was not detected with the sensitivity of 20 pg/ml in all patients after the first administration of topical timolol. None of the patients showed significant signs of relapse. No systemic complication or skin side effects were observed in any of the patients.
Conclusion: This study showed that fractional CO2 laser assisted transdermal delivery of topical timolol is a safe and effective method for the treatment of superficial and mixed IHs. This combined modality can accelerate the involution of both proliferative and involuting IHs.

11:30-11:40 23 ***Different responses to laser therapy of Port-Wine Stains: a histopathological study based on Facial Anatomic Subunit***

Lin Xiaoxi1, YU Wenxin1, MA Gang1, WANG Tianyou1, ZHOU Henghua2, Dongze Lv1, Yajing Qiu1, Hui Chen1, Jiafang Zhu1

1Department of Plastic and Reconstructive Surgery, Shanghai Ninth People's Hospital, School of Medicine, Shanghai Jiaotong University, 2Department of Pathology, Shanghai Ninth People's Hospital, School of Medicine, Shanghai Jiaotong University

Purpose: Following pulsed dye laser (PDL) treatment, lateral facial and neck port-wine stains (PWSs) clear quicker and more conspicuously than central facial PWS do.To investigate whether the difference in the efficacy of the treatment between central and lateral facial PWS was related to different histological manifestations.
Methods: Thirteen patients with PWS had biopsies and underwent PDL treatments in both central and lateral facial areas. The hypothesis was tested by correlating the PWS response to PDL with the depth and diameter of the PWS vessels. The clinical efficacy was assessed by chromameter two months after the final PDL treatment, while diameter and depth of PWS vessels were measured in biopsy specimens.
Results: All patients were treated on the central and lateral facial sites. The chromameter evaluation showed that the average blanching rate was 34.01% and 8.68% for lateral and central facial sites, respectively, ($P<0.05$), which suggests a better response to PDL treatment in the lateral than in the central facial area. Histological manifestations showed that ectatic vessels in the lateral regions were primarily located in the upper dermis, whereas in the central facial regions they were extensively distributed from the dermis into the subcutaneous tissue.
Conclusion: Lateral facial PWSs respond better to PDL than PWSs in a central facial location. The differences in histological manifestations especially the depth of the vessels may be responsible for this clinical phenomenon.

11:40-11:50 205 ***Topical rapamycin combined with pulsed dye laser in the treatment of port wine stian: a prospective side-by-side self-control study***

Gang Ma, Wenxin Yu, Hui Chen, Yunbo Jin, Yajing Qiu, Lin Xiaoxi

Department of Plastic and Reconstructive Surgery, Shanghai Ninth People's Hospital, School of Medicine, Shanghai Jiaotong University

Purpose: Port wine stain (PWS) is a congenital capillary vascular malformation where malformed, ectatic blood vessels are present in the papillary and reticular dermis. Pulsed dye laser (PDL) is the most effective treatment for PWS. However, regeneration and revascularization of photocoagulated blood vessels may result in poor therapeutic outcome. Rapamycin, an angiogenesis inhibitor, can reduce the regeneration and revascularization of photocoagulated blood vessels. The aim of this study was to evaluate the efficacy and safety of PDL alone and combined with topical rapamycin in the treatment of PWS.
Methods: We conducted a prospective side-by-side self-control clinical trial. 52 patients with PWS (30 males and 22 femals; median age 14 years, age range 2-32 years) were recruited. Two interventions were evaluated: PDL + placebo and PDL + rapamycin. Each patient received 3 PDL treatment sessions with 2 month interval. Clinical efficacy outcomes were evaluated by blinded, clinical evaluations and by chromameter assessment at 2 months after the intervention. No adverse events were observed in both sites.
Results: 3 (5.77%) patiens showed PDL + rapamycin sites were slightly better improvement compared with PDL + placebo, while 2 (3.85%) patiens showed the opposite results. 47 (90.38%) patiens showed no significant difference between PDL + placebo and PDL + rapamycin sites.
Conclusion: There is no evidence showing significanty different for PDL treatment of PWS with followed topical rapamycin or not.

11:50-12:00 315 ***Interdisciplinary Arthroscopic Laser Treatment of Angiodysplastic Arthritis (Hauert Disease)***

Carsten Philipp1, Friedrich Jahn2, Ute Mueller3, Peter Urban3, Margitta Poetke3, Julia Becker-Koehnlein3

1Zentrum Lasermedizin, Evangelische Elisabeth Klinik, 2Dept. Orthopaedic Surgery & Traumatolgy, Evangelische Elisabeth Klinik, Berlin, Germany, 3Zentrum Lasermedizin, Evangelische Elisabeth Klinik, Berlin, Germany

Purpose: This clinical retrospective study of arthroscopic laser treatments in patients with angiodysplastic arthritis (Hauert Disease) in the knee joint evaluates procedural safety and clinical outcome.
Methods: We used arthroscopic approach without tourniquet and distension with 0.9% saline. Nd:YAG-laser applied via bare fibre (600µm, long pulse mode, 20W) was used to coagulate vascular tissues or release and vaporize fibrotic adhesions. In some cases excess fibrotic tissues were removed by mechanical grasp instruments additionally. Access sites were individually determined by duplex ultrasound. Additional parts of VM outside the joints were treated by Nd:YAG laser. Evaluation was by clinical investigations, MRI and duplex ultrasound imaging, and re-arthroscopy (in case of residuals or new findings), minimal follow up time: 2 years, yearly examinations.
Results: Between 2005 - 2013 sixteen patients (stage I and II) underwent arthroscopic laser treatment of knee joints. All patients presented progressive disease with intraarticular bleeding and progressive functional disabilities. Mean age was 17.8 years at presentation. Indication was settled by positive MRI and/or typical clinical symptoms and positive duplex ultrasound. Ten patients had earlier non-laser treatments (arthroscopic resection, sclerotherapy). None of the patients developed intraoperative or postoperative or later bleedings into the joints. All patients showed functional improvement. Median number of treatments was 1.4 (range: 1-3). Partial loading period with crutches was 5 days (median).
Conclusion: In patients with stage I and II angiodysplastic arthritis of the knee joint arthroscopic laser approach has proven to be safe. During follow up no further joint destruction was noted and functional improvement was found in all patients. Side effects and downtime were low compared with open surgery. Further prospective studies may be encouraged by these results but long time follow up evaluations are requested to evaluate the influence of early laser treatment with regard to the number of consecutive arthrodesis or joint replacements.

12:00-12:10 363 ***Vascular Anomalies of the Lip Challenge the Reconstructive Rule of Thirds***

Daniel M Balkin1, Emily Balkin1, Rachel Lentz1, Erin Mathes2, Ilona Frieden1, William Hoffman1

1University of California, San Francisco, 2UCSF

Purpose: Vascular anomalies of the lip can cause aesthetic deformity and functional impairment. We characterized a cohort of patients requiring reconstructive surgery for vascular malformations of the lip.
Methods: Retrospective review of patients requiring reconstructive surgery for vascular malformations of the lip between 2005-2015.
Results: 30 patients with vascular anomalies of the lip were identified. Female-to-male ratio was 1.5:1. Vascular malformations included hemangiomas (73.3%, 22/30), venous malformations (2/30), Sturge-Weber-related capillary malformations (2/3) or other (3/30). Median age at surgery was 5.6 years (range, 1.2-33.5). Indications for surgery included labial dysfunction (50%) and aesthetic deformity (93.3%). The lower lip was most frequently involved (80%, 24/30). In the lower lip, lateral lip lesions (66.7%, 16/24) were more common than central ones. The majority of lower lip resections involved the vermillion border (75%, 12/24), 58.3% (14/24) were full-thickness, 9/24 (64.3%) involved 1/3-2/3 total lip width and the remainder involved <1/3. In those patients with defects 1/3-2/3 total lip width, only 5/9 (56%) required local flap closure. Of upper lip anomalies (27%, 8/30), central lip lesions (75%) were more common than lateral ones, 50% of resections (4/8) involved the vermillion border, all (8/8) were partial thickness, and 87.5% (7/8) of upper lip reconstructions were achieved with primary closure. Postoperatively, 23.3% (7/30) of patients experienced minor issues with wound healing or infection. Median follow-up was 8.1 months (range, 3 days-8.4 years).
Conclusion: Vascular malformations of the lips often require reconstructive surgery for both aesthetic and functional purposes. The lip reconstructive rule of thirds suggests that lower lip defects involving 1/3-2/3 total lip width require closure with lip switch or local advancement flap techniques. However, our data demonstrate that many of such patients with large defects can be closed primarily. We posit that vascular malformations expand normal lip tissue enabling reconstruction by primary closure.

12:10-12:20 87 ***Surgical management of Verrucous Hemangioma: A case study of 22 patients***

Ho Yun Chung1, Dong Hun Choi1, Seok Jong Lee2, Jong Min Lee3, Seung Huh4

1Dept. of Plastic & Reconstructive Surgery, School of Medicine, Kyungpook National University, 2Department of Dermatology, School of Medicine, Kyungpook National University, 3Department of Radiology, School of Medicine, Kyungpook National University, 4Department of Vascular Surgery, School of Medicine, Kyungpook National University

Purpose: Verrucous hemangioma, a rare disease previously regarded as a kind of vascular tumor is now viewed more as a limited form of vascular malformation. The purpose of this study is to report the effectiveness of surgical management.
Methods: 22 patients from year 2005 to 2015 were admitted to plastic surgery department due to vascular malformation. These 22 patients were diagnosed as verrucous hemangioma in postoperative histologic finding. Age, sex, location, name of operation and recurrence were inspected by reviewing patients note, operation chart.
Results: This study was conducted on 22 patients: 13 were male and 9 were female with mean age of 13.13. Of those 22, 18 patients had a lesion on lower extremity and 4 on upper extremity. 14 patients underwent primary closure for skin and soft tissue defect occurred after excision. Since 8 patients unable to receive primary closure due to extensivity of lesion, 5 received skin graft. Lesions of the other 3 patients were covered by free anterolateral thigh(ALT) flap either because tendons were exposed after excision or applying skin graft was not indicated. 11 patients confirmed to have no recurrence with postoperative vascular USG, MRI follow up. 11 were completely cured clinically. In one patient who received free ALT flap after excising multiple lesions on lower leg, the lesion recurred and this resulted in an overall recurrence rate of 4.5%.
Conclusion: Verrucous hemangioma is a rare disease invading mostly on lower extremities. It is assumed to be curable by surgical management.

12:20-12:30 236 ***Strategies for Immediate Reconstruction of Disfiguring Arteriovenous Malformations of the Lips***

Dov Goldenberg, Esther Choi, Tatiana Moura, Rolf Gemperli

University of Sao Paulo Medical School

Purpose: Lip arteriovenous malformations (AVMs) may assume large dimensions and total resection may create extensive defects. Size is often the most important parameter for treatment planning. Classically, when more than 25% of the lip is affected, extra tissue is required for reconstruction. The aim of this study is to evaluate a treatment strategy, hypothesizing that expansion of adjacent normal tissues simplify reconstruction.
Methods: From 2006-2015, 13 patients with AVMs affecting more than 25% of the lip were included (7 females, mean age 24.7 + 9.7 years). The upper lip was affected in 10 patients. Resection design was planned to ensure complete AVM removal, correction of lip height and lining of skin, muscles and oral mucosa. The correlation between defect size and type of reconstruction was analyzed and compared to the classical principles of lip reconstruction. Type of reconstruction was classified as direct closure, advancement-rotation flaps, opposite lip flaps or distant flaps.
Results: Post-resection defects affected up to 50% of the lip in 5 patients, 50-75% in 4 and were larger than 75% in 4 patients. In 7 patients involvement exceeded lip boundaries, affecting the nose, cheeks or chin. When compared to the conventional principles of lip reconstruction based on defect size, a reduction in additional tissue needs was observed. For defects up to 75% of the lip, closure was obtained by direct approach (6 cases) or rotation-advancement flaps (4 cases) without tissue interposition. Only in 3 patients (with defects larger than 75%) opposite lip flaps (2) or reconstruction with microsurgical flap (1 case) were needed.
Conclusion: The low incidence of lip transposition flaps or distant flaps, even in large defects, was a consequence of the expansive effect of normal tissues and surgical planning. The combination of these factors ensured a more satisfying result and reduced the morbidity of the procedure.

11:00-12:30	PS C - Parallel Session C: Collaborative Research - Sirolimus, OVAMA STUDY, OTHER	Auditorio 1 Room

Chairs: Denise Adams, Laurence Boon, Sophie Horbach

12:30-13:30	LUNCH

Chairs: Margarita Larralde, Julie Prendville

13:35-13:43 224 ***Venous malformations of the knee: surgical experience***

Claude Laurian1, Claudine Massoni2, Michel Wassef3, Emmanuel Houdart3, Franscesca Toni3, Nikolaos Paraskevas3, Annouk Bisdorff Bresson2

1Saint Joseph Hospital, 2Hopital Lariboisiere, 3Lariboisiere Hospital

Purpose: To evaluate outcome of open surgery in the treatment of venous malformations (VM) of the knee's joint, in terms of pain, function and quality of life.
Methods: Retrospective, observational, monocentric study. Forty three consecutive patients undergoing VM knee surgery between 2011 -2014 were included. Data collection was performed using surgical database : reviewing patients clinical records, pre -postoperative MRI, surgical reports and clinical results at long term follow-up .Main outcome end points of this study were: pain, joint mobility, patient's quality of life (= QOL) : individual patients' evaluation on a QOL evaluation sheet . Estimation of residual VM on control MRI evaluated by two independent physicians.
Results: Forty three patients (27 F/16 M; median age 20 y/o, range 5-35 y/o) were included. 15 underwent previous treatments. Surgical indication was intermittent or permanent pain. 34 VM were localized in intra and peri articular knee region, 9 were extensive lower limb VM. 63% of patients presented supracondylar bursa involvement, 22% supracondylar and infrapatellar bursa involvement, 6 % Infrapatellar bursa only ans 9 % VM limited to the patellar retinaculum. 14% of patients had superficial. cartilaginous lesions. 14 patients had associated intervention, with concomitant retinaculum reconstruction or orthopedic procedure. Four postoperative complications required additional procedures Median hospital stay: 5 days. Mean postsurgical active physiotherapy: 2 - 3 weeks. At 6 months FU (median 18 months, range 9-39) : 41 patients (95,3 %) had no more pain and 23 (53 %) had normal joint mobility. On control MRI (n=35) 31 (88%) had no residual VM and 4 (12%) had limited residual VM. At last FU: 93 % were pain free and 81 % with normal joint mobility. Patients' mean quality of life after surgery: 8/10.
Conclusion: Large excision surgery of knee VM is a safe procedure with good results in terms of pain, function and quality of life, requiring in most cases one single procedure.

13:43-13:51 182 ***Autologous fat transfer is effective in Restoring Soft Tissue Contour Deformities after Surgery for Vascular Anomalies***

Teresa O1, Kimberly Chan1, Dylan Roden2, David Shamoulien1, Tara Brennan3, Milton Waner1

1Vascular Birthmark Institute of New York, AVM Center, at Lenox Hill and Manhattan Eye, Ear, and Throat Hospitals,, 2Department of Otolaryngology, New York University Medical Center, 3Department of Otolaryngology, University of New Mexico

Purpose: Soft tissue loss is expected after resection of large vascular tumors or malformations. Autologous fat transfer is a common method utilized to improve asymmetries, however outcomes are rarely evaluated systematically and not previously described for vascular anomalies reconstruction.
Methods: A retrospective chart review from 2012-2015 was conducted on all patients receiving autologous fat transfers for soft tissue defects following vascular anomaly surgery at a tertiary care center. Patients received fat grafts, injections, or both. Pre-and postoperative photos were blindly reviewed by 3 facial plastic surgeons using a 5-point scale. Fat grafts were harvested from the suprapubic crease and placed immediately after excision of a vascular anomaly. Fat injections were performed using liposuction (modified Coleman technique) from the medial thighs or abdomen;fat was processed and injected using 2-3 mm cannulas. The effectiveness of fat transfers was assessed using patients' photos.
Results: There were 32 autologous fat transfer surgeries in 27 patients. Eleven patients received fat grafts, 13 fat injections, and 3 both. Ages ranged from 2-69years(mean 25) with female to male ratio 2.4:1. Majority of patients(81%) had head & neck vascular anomalies, while 19% were of other anatomic subsites. The average volume of fat injected was 16.5 mL(range 0.8-100 mL). The average observer rating score was 2.45 in the fat graft group versus 3.77 in the fat injection group (p-value < 0.001). There was acceptable interrater reliability between the 3 observers (coefficient of concordance = 0.76). Follow-up ranged from 6-22 months. One patient in the fat graft group had a hematoma and another had a salivary fistula after parotid VM excision, while there were no complications in the fat injection group.
Conclusion: Autologous fat transfer improves symmetry after surgical treatment of vascular anomalies. Fat injection is more permanent and creates a more symmetric soft tissue contour compared to fat grafts.

13:51-13:59 283 ***Treatment of Low-Flow Vascular Malformations using MR-guided High-Intensity Focused Ultrasound (MRgFUS): Preliminary experience***

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1Stanford University Medical Center, Department of Radiology, Division of Body MRI, 2Stanford University Medical Center, Department of Interventional Radiology, 3Stanford University Medical Center, Department of Orthopedic Surgery, 4Stanford University Medical Center, Department of Radiology, Division of Interventional Radiology

Purpose: To assess the safety and efficacy of MR-guided FUS as a non-invasive means of treating low-flow vascular malformations.
Methods: From March 2014 to May 2015, four patients were diagnosed as having low-flow vascular malformations by MR imaging, but real-time ultrasound examination failed to demonstrate the lesion or guide a minimally invasive percutaneous intervention. Three males and one female were treated (average age 33; range 18-54 years). Three lesions were in the thigh and one was in the calf. The median maximum dimension was 1.4 cm (range 1.0-4.0 cm) and all were treated using the ExAblate 2100 system operating at 0.95-1 MHz. The mean number of sonications was 42 (range 14-56), with a median energy per sonication of 1521 Joules (range 578-1878) and an average total treatment time of 142 minutes (range 64-202).
Results: No adverse events occurred. At a median follow-up of 7 months (range 4-12), there was a significant reduction in pain (8.8±1.5 to 2±2.3 on a 10-point scale, p=0.02), and a mean reduction in maximal pain of 76%. Follow-up MRI revealed non-perfusion in 3 patients, two of whom remain asymptomatic and one whose pain is improving with physical therapy for chronic muscle atrophy. Partial reperfusion was noted in one patient who began to experience recurrent pain 4 months after the procedure. A second treatment is being planned.
Conclusion: Short-term follow-up of low-flow vascular malformations treated with MRgFUS using the ExAblate 2100 system appears to be safe and effective. These are often challenging lesions and further investigation is warranted into this non-invasive ablative technology.

13:59-14:07 121 ***Expression of Embryonic Stem Cell Markers in Pyogenic Granuloma***

Max Blackwell, Tinte Itinteang, Alice Chibnall, Paul Davis, Swee Tan

Gillies McIndoe Research Institute

Purpose: The expression of embryonic stem cell (ESC) markers is increasingly demonstrated in tumors, including infantile hemangioma. We investigated the expression of ESC markers in pyogenic granuloma (PG).
Methods: The expression of the ESC markers OCT4, SOX2, STAT3 and NANOG in PG samples from six patients was examined by immunohistochemical (IHC) staining, NanoString gene expression analysis and in-situ hybridisation (ISH).
Results: IHC staining demonstrated the expression of pSTAT3, OCT4, SOX2 and NANOG by the endothelium of the microvessels in PG whilst NANOG was also expressed by cells in the interstitium, outside of the microvessels. NanoString analysis showed mRNA expression for STAT3, OCT4 and NANOG which was confirmed to be localized to the endothelium of PG by ISH.
Conclusion: The expression of the ESC markers OCT4, SOX2, pSTAT3 and NANOG, suggests the endothelium of PG displays a primitive phenotype. Cells in the interstitium expressing NANOG may represent a more downstream derivative of the primitive endothelium, or a separate population. The primitive nature of the endothelium and cells in the interstitium reveals novel insights into the biology of PG.

14:07-14:15 271 ***Somatic Activating RAS Mutations Cause Vascular Tumors Including Pyogenic Granuloma***

Young H Lim1, Brandon Sumpio1, Alain Kaldany1, Stephanie Douglas1, Keith Choate1, Christina J Ko1, Richard Antaya1, Jennifer McNiff1, Jing Zhou2, Deepak Narayan2

1Yale School of Medicine, 2Yale University School of Medicine

Purpose: Vascular anomalies are lesions which are categorized as either malformations or tumors, depending primarily on proliferation rate and histological characteristics. Pyogenic granulomas (PGs), or lobular capillary hemangiomas, are benign, spontaneous vascular tumors which are characterized by small vessels organized in lobules. Though various theories have been proposed, the exact cause of PGs and other lobular vascular tumors remains unknown.
Methods: Affected tissue and blood samples were taken from two adolescent patients with lobular vascular tumors. Following DNA isolation, pairwise whole-exome sequencing (WES) of blood and tissue was used to identify somatic mutations driving the formation of PGs. The mutations identified via WES were verified using Sanger sequencing. Immunohistochemical staining for GLUT-1 was performed to ensure that the vascular anomalies were not infantile hemangiomas. Sanger sequencing was also performed on 40 archival PG samples from adolescent patients.
Results: After pairwise WES, a heterozygous KRAS c.35G>A, p.G12D mutation was found in one patient and a heterozygous NRAS c.181C>A, p.Q61K mutation was found in the other patient. Both mutations were confirmed by Sanger sequencing. Archival data yielded four (4/40, 10%) additional patients with somatic RAS mutations. Immunoreactivity to GLUT-1 was negative in all six cases.
Conclusion: Pyogenic granulomas and other lobular vascular tumors have somatic RAS mutations. The identification of such mutations in vascular tumors has both etiological and therapeutic significance. RAS signaling is associated with angiogenesis, therefore the finding of somatic RAS mutations in PGs supports theories relating angiogenic pathways to vascular tumorigenesis. Clinically, vascular tumors are often unresponsive to current therapies such as steroids or β-blockers. If RAS mutations exist in such patients, farnesyl transferase inhibitors or Raf/Mek/Erk inhibitors, which block signaling upstream or downstream of RAS, could provide a promising treatment.

14:15-14:23 118 ***Differential diagnosis of Intramuscular Capillary-type hemangioma***

Tony Penington and Duncan MacGregor

Royal Children's Hospital, Melbourne

Purpose: Intramuscular vascular anomalies have been a source of diagnostic controversy. A condition called 'Intramuscular capillary-type hemangioma' (ICTH) has been described which pathologically are said to show prominent adipose tissue and 'lobules or sheets of capillaries with plump endothelium'. Radiological features are of well-defined T2 hyperintense lesions with fast flow but no evidence of shunting. Pain is described as a less common feature in ICTH than in other intramuscular vascular anomalies.
Methods: All cases of surgically excised or biopsied intramuscular vascular anomalies, including AVMs, for which histopathological sections and adequate preoperative imaging could be assessed at one vascular anomalies service were reviewed. Where possible, pathology and medical imaging were reviewed independently by a specialist pathologist and radiologist respectively, and results compared to identify whether the published criteria for ICTH could be used to identify a distinct subset of intramuscular vascular lesions.
Results: 36 surgical excisions and one biopsy were identified, of which 8 had been preoperatively diagnosed as AVM. 8 cases were excluded due to lack of imaging or pathology. 11 patients had previously undergone sclerotherapy and two of these showed scar tissue only on histology and were also excluded. This left 27 cases for comparison of which 5 were considered to be AVM. On radiological assessment, 11 were thought definitely to be venous malformations (VM), three cases (two from the AVM group) were thought to be AVM, and 13 could be consistent with the radiological criteria for ICTH, although none were thought to be definite. On pathology adipose tissue was present in all but three cases and abundant in many. Sheets of capillary size vessels were seen extensively in three lesions, two of which were in the AVM group, and as focal islands of different size in three more cases, one in the AVM group. One case with focal islands was felt to be definitely VM by radiological diagnosis (phleboliths were present), one was thought to be AVM and the other four were possible ICTH on radiology. Of the two non-AVM cases with capillary vessels, one had significant preoperative pain which persisted after surgery and resolved with a second operation. The other case which had extensive capillary vessels but other unusual features on histology and was thought to be AVM on review of radiology was painless. Pain was a prominent feature of most VMs, and responded well to surgery.
Conclusion: Intramuscular vascular anomalies continue to be a confusing diagnostic area. VM in muscle is not always differentiated from ICTH on imaging but with histology a satisfactory differentiation can be made. The presence of adipose tissue is not of assistance in differentiating ICTH from VM histologically. Sheets of capillary sized vessels are not seen in VM, but have been described previously in AVM, and their presence is confirmed here in cases clinically diagnosed as AVM. The difference between high flow and arteriovenous shunting is the only diagnostic feature which definitely separates ICTH from AVM and a better definition of this is required for diagnostic accuracy.

14:23-14:31 230 ***Intramuscular vascular malformations. An attempt of classification on the basis of clinical, surgical, imaging and pathological aspects***

Moneghini Laura

Pathologic Department-University of Milan

Purpose: The intramuscular vascular malformations (IMVMs) are frequent and may occur at any age, in every part of the body with different clinical manifestations, imaging features and pathological aspects.
Methods: Well documented IMVMs were removed by 44 patients, 18 men and 26 females, in the last 8 years with a follow up. The mean age of presentation was 29 years (range 1 to 69 years). The anatomic locations of the lesions were: 21 limbs (47,7%); 19 head and neck (43,2%) and 4 trunk (9,1%). An attempt to induce sclerosis or embolization was tested in 7 cases (15.9%) before removal of the lesion. All the samples were studied for pathological and immunohistochemical features; 29 cases were also assessed for clinical manifestations, surgical appearances and imaging features (magnetic resonance imaging; ultrasonography; arteriography or venography).
Results: On the basis of this re-evaluation we divided the IMVMs in 4 different histological types: A) High flow IMVMs:6 cases (13,6%); B) Low flow IMVMs: 15 cases (34,%); C) Cavernous low flow IMVMs: 9 cases(43,2%); D) Fibro-adipose vascular anomalies (FAVA):4 cases (9,1). Intermediete aspects beetween the different groups were also considered.
Conclusion: The evaluation of pathological and immunohistochemical characteristics of the different types of IMVMs could allow a better understanding of the imaging features to define the best treatment strategy. In our experience the simply surgical therapy is the best treatment that ensures complete resolution of circumscribed IMVMs. Percutaneous embolization and sclerotherapy could be an adjuvant or palliative treatment before the conventional surgery in A and C, while in B and D IMVMs a simply surgical treatment achieved the best results. Furthermore a more precise hemodynamic study should be planned in order to better identify intermediate flow IMVMs group where a pre-surgical therapy with embolization or sclerosis could be useful.

14:31-14:45 122 ***Angiomatosis of soft tissue as an important differential diagnosis for intramuscular venous malformation***

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Purpose: Sclerotherapy outcome of extremity VMs is difficult to predict. Some lesions respond well but others, especially those locating intramuscularly, may present with persisting symptoms necessitating secondary surgery. The diagnosis of VMs is commonly based on the typical clinical picture and MRI findings with histology analyzed mainly in atypical cases to exclude malignancy. Previous studies, however, report on distinct vascular entities with characteristic histological patterns, such as angiomatosis of soft tissue (AST), fibro-adipose vascular anomaly (FAVA) and PTEN hamartoma of soft tissue (PHOST). These lesions are mimicking venous malformations by clinical and imaging findings, but are less amenable to sclerotherapy and may benefit from surgery (PHOST, AST) or conservative management (FAVA) as a primary treatment. By systematically reviewing histological specimens of lesions diagnosed as VMs but having poor or insufficient sclerotherapy outcome, we aim to improve differential diagnostics and management of these low flow vascular lesions.
Methods: We performed a retrospective review of patient records and imaging of all consecutive patients (n=102) undergoing sclerotherapy for an extremity VM over a period of 6 years and 8 months (1/2007-8/2013). We identified the patients who needed secondary surgery for insufficient sclerotherapy response by 31th of January 2016 and performed a semi-quantitative histological analysis of these operated lesions.
Results: Of the 102 VMs (44 in upper and 58 in lower extremity) treated with sclerotherapy 19 (18.6%) were later operated. Majority (78.9%) of the operated lesions were lower extremity intramuscular lesions. In contrast, only two upper extremity lesions (one subcutaneous and one intramuscular) and three lower extremity subcutaneous lesions required operation after sclerotherapy.
The histological pattern of 13 out of 15 lower extremity intramuscular lesion corresponded to the previously described AST and the histology of all other operated lesions was consistent with common VM. AST had a distinct histological pattern different from VMs. In addition to wide venous spaces, typical features were honeycomb–like thin-walled lymphatic spaces, thick-walled small artery-like vessels with concentric smooth muscle hyperplasia and narrow lumen, clusters of capillaries, lymphocyte aggregates, haphazardly arranged smooth muscle fascicles, and occasional phleboliths. The amount of mature fat and collagen fibers was conspicuous.
The MRI finding of AST was not specific and resembled that of VM. AST lesions were characteristically intramuscular, fairly well demarcated lesions with diverse vascular components, small vessels in addition to dilated veins, heterogeneous gadolinium enhancement, varying amount of fat, occasionally phleboliths, and no flow void-artefacts.
Conclusion: Our study indicates that AST is an important differential diagnosis for intramuscular VMs. Due to the poor sclerotherapy response, identification of AST has major therapeutic implications. Whether these lesions are actually PHOSTs needs to be further investigated by the means of genetic studies.

14:45 – 15:15	DC 6 - Difficult Case Presentations VI	Juan Pablo II Room

Chair: Felipe Velásquez

14:45-15:00 269 ***Use of Sirolimus in Patient with Complex Unresectable Venous Malformation: A Pathway for Surgical Treatment and Cure?***

Dov Goldenberg1 and Denise Adams2

1University of Sao Paulo Medical School, 2Cincinatti Children's Hospital

Purpose: The purpose of this presentation is to report a successful outcome of the association between sirolimus and surgical resection for treating a patient with a previously unresectable complex venous malformation.
Methods: This study reports a 21 years old female patient with an extensive vascular malformation involving the left trunk, with previous episodes of local infection and severe pain. First symptoms occurred in childhood and previous attempts of treatment were performed with sclerotherapy and partial resection. Progression was not avoided and enlargement was associated with intense pain and deformity. CT showed an extensive vascular malformation with predominance of venous component (VM) affecting the full thickness of the thoracic and abdominal wall, left breast with extent to the mediastinum and abdominal cavity. Lesion was considered unresectable. The use of sirolimus was considered. Treatment was initiated at 0.8 mg/m2/dose to achieve levels between 10 and 15 ng/ml. Prophylaxis was instituted for PCP. Measurement of serum levels of sirolimus and laboratorial tests were collected monthly.
Results: The response to medical therapy was evident. Reduction of pain and volume were clinically observed after 30 days. After 6 months, the patient no longer used any analgesics. The volume of the lesion was reduced to approximately one third of the initial volume, and the deep mediastinal and intraabdominal portions became minimal. After 24 months of treatment the VM was reconsidered for surgical resection. The procedure was performed uneventfully, and approximately 80% of the initial volume was removed. Histologic examination including immunohistochemical study confirmed the diagnosis of venous malformation. There were no complications with the healing process and the patient presents with scars positioned in the back and lateral thoracic wall, remains asymptomatic and is followed as an outpatient.
Conclusion: Association of sirolimus and surgical resection was efficient, turning an almost untreatable condition in a case with high potential for cure.

15:00-15:15 102 ***Osler-Weber-Rendu Syndrome with Fibrodysplastic Changes: Implications for Transvenous Embolization of a Pelvic Arteriovenous Malformation***

Lauren Huntress1, Jones Thomas1, Saum Rahimi2, Naiem Nassiri3

1Rutgers-RWJMS, 2Rutgers-RWJ University Hospital, 3Rutgers RWJ University Hospital

Purpose: Osler-Weber-Rendu (OWR) syndrome, also known as hereditary hemorrhagic telangiectasia (HHT), is a rare genetic disorder that commonly features high-flow arteriovenous malformations (AVM) within the pulmonary, intracranial, and visceral circulation. We present a unique case of a 59 year-old female patient with OWR featuring a painful left pelvic AVM with coexisting fibromuscular dysplasia (FMD) of the feeding artery complicating transarterial AVM nidus access. Retrograde transvenous nidus embolization was performed without flow-control adjuncts using a combination of detachable framing coils and Onyx.
Methods: The symptomatic AVM was discovered on computed tomography angiography (CTA) and confirmed on flush abdominal aortography. It was fed by an enlarged, elongated, tortuous, and fibrodysplastic left ovarian artery with aneurysmal left ovarian venous drainers. Microcatheter access of the nidus was achieved retrograde through the venous drainers with draining vein sheath placement controlling the venous outflow and the high-flow shunt through the AVM. Nidus embolization was performed via detachable giant framing coils and Onyx 34.
Results: Completion venogram and angiogram revealed complete obliteration of the nidus with cessation of arteriovenous shunting and no evidence of non-target embolization. There were no complications perioperatively and at 1, 3, and 6-month follow-up. Patient's presenting symptoms resolved without recurrence during that period.
Conclusion: In select angioarchitectural varieties, retrograde transvenous embolization of high-flow peripheral AVMs can be performed safely without the use of flow-limiting adjuncts. This technique can be an additional effective approach for treatment of complex peripheral AVMs in the setting of compromised inflow access. The interplay between the TGF-beta mutations implicated in OWR Syndrome and FMD remains uninvestigated and deserves further scrutiny.

15:15-15:45	Closing Ceremony	Juan Pablo II Room

POSTERS

PANEL #	TITLE	AUTHORS	ABSTRACT #
1	Complex acquired dural AVF can be treated by endovascular means. With meticulous technique complications can be avoided. Many embolic agents are successful in ablating dural AVF in all dural sinuses.	*Wayne Yakes*	**338**
2	CRANIOFACIAL AVM: WHICH POSSIBILITY TO MANAGE? A RETROSPECTIVE STUDY ON 49 CASES	*Raul Mattassi, Giacomo Colletti, Luca Crespi and Walter Pozzoli*	**68**
3	Bordering Procedure: An innovative technique for resection of arteriovenous malformations in the head region	*Mine Ozaki, Aki Ihara, IWASHINA YUKI, Shien Seike, Tomohiro Shiraishi, Akihiko Takushima and Kiyonori Harii*	**219**
4	Pediatric Acral Arteriovenous Lesion: Clinical Presentation and Histopathology	*Javier Couto and Arin Greene*	**306**
5	DIAGNOSIS AND MANAGEMENT OF THORACIC AND SHOULDER ARTERIOVENOUS MALFORMATIONS	*Wayne Yakes*	**326**
6	Ear Arteriovenous Malformation Management	*Wayne Yakes*	**339**
7	Initial Experience with Embolization Treatment of Pulmonary Arteriovenous Malformation using Micro Vascular Plugs	*Stacey MacKenzie, Matthew Towsley, Sally Mitchell and Clifford Weiss*	**12**
8	Can ethanol embolization blanch the skin erythema of extracranial AVM?	*Yun Zhou, Dongze Lv, Yunbo Jin, Chen Hua, Tianyou Wang, Gang Ma, Hui Chen and Lin Xiaoxi*	**135**
9	Management of refractory ulceration caused by arteriovenous malformations with ethanol embolisation	*Yang Xi, Yunbo Jin, Tianyou Wang, Chen Hua, Hui Chen and Lin Xiaoxi*	**139**
11	Efficacy of an AVM Classification System that Directs Endovascular Therapies Accurately.	*Wayne Yakes*	**331**
12	Radical or subtotal resection with microsurgical reconstruction in surgical accessible cases with Extracranial Arteriovenous Malformations: 10 years' follow-up	*Lin Xiaoxi, Wei Li, Yunbo Jin, Gang Ma, Chuan Yan, Jiasheng Dong, Zuoliang Qi and Wei Wang*	**80**
13	INTRACRANIAL PIAL FISTULAS IN PEDIATRIC POPULATION. CLINICAL FEATURES AND TREATMENT MODALITIES	*Flavio Requejo and Juan Marelli*	**112**
15	Comparative study on the Effects of three kinds of different β-receptor blockers on Proliferation and Apoptosis of Mouse Hemangioendothelioma Endothelial Cells in vitro	*xu xianyun, xie qiongjun, Peng Wei, Tao Chao, Huang Haijin, Yan Jinlong, Xu Lu, Ning Huiting, Ma Liangwen, Wen Tingyu, He Xiaodong and Liu Qian*	**120**
16	Unique Functional Characteristics Of Lymphangiomatosis-Derived Endothelial Cells	*Wa Du, Sriram Ayyaswamy, Smruti Rath, Soo-Jin Cho, Ionela Iacobas, Timothy Vece, Sheena Pimpalwar, Judith Margolin, Debra Kearney and Thuy Phung*	**163**
17	mRNA and Protein Expression Levels of SMAD Pathway Constituents in Arteriovenous Malformations	*Conor Smith, Haihong Zhang, Ting Wei, James Phillips, James Suen and Gresham Richter*	**320**
18	Histopathologic evaluation of vascular malformations with characterization of elastic tissue and trichrome staining patterns	*Sara Shalin, Jessica Taylor, Emily Miller, Ting Wei, Jenika Sanchez and Gresham Richter*	**332**
19	Cerebrospinal Fluid (CSF) Leak and Intracranial Hypotension in Blue Rubber Bleb Nevus Syndrome (BRBNS)	*Ahmad Alomari, Cindy Kerr, Maria DaRocha, Mary Sylvia, Erin Spera, Anna Lillis, Gulraiz Chaudry, Cameron Trenor, Meghan O'Hare, Darren Orbach, John Mulliken and Steven Fishman*	**255**
20	CUTANEOUS VASCULAR LESIONS IN CEREBRAL CAVERNOUS MALFORMATIONS: REPORT OF 2 FAMILIES	*Maria del Mar Escudero-Gongora, Ana Bauza, Nicole Knöpfel, Aniza Giacaman, Carlos Saus, Asuncion Pastor and Ana Martin-Santiago*	**273**
21	Capillary malformation-arteriovenous malformation: a clinical review of 68 patients	*Margarita Larralde, Iporre Quiroga Leslie Verónica, Paula Boggio, Paula Carolina Luna and Wilmer Gasca*	**66**

PANEL #	TITLE	AUTHORS	ABSTRACT #
22	CLAPO SYNDROME: New cases reported and genetic data incorporated	*Lara Rodriguez Laguna, Pablo Lapunzina, Kristina Ibañez, Ruben Martin Arenas, Victoria Eugenia Fernandez Montaño, Gema Gordo Trujillo, Elena Vallespin, Rocio Mena de la Cruz, Inmaculada Rueda-Arenas, Maria Victoria Gomez, Angela del Pozo, Juan Carlos Silla-Castro, Victor Martínez-Glez and Juan Carlos Lopez-Gutierrez*	***150***
23	CAPILLARY MALFORMATION OF THE LOWER LIP, LYMPHATIC MALFORMATION OF THE TONGUE AND MINIMAL LOCALIZED OVERGROWTH: "FORME FRUSTE" OF CLAPO SYNDROME ?	*Julie Powell, Afshin Hatami, Catherine McCuaig and Josee Dubois*	***323***
24	Cost-Effective Management of Vascular Anomalies in a Rural Hospital Setting in the New Guinea Highlands	*William Mol*	***16***
25	Shared decision making in vascular malformation care	*Sophie E.R. Horbach, Dirk T. Ubbink, Carine van der Vleuten, Leo Schultze Kool, Mark J.W. Koelemay, Bas Verhoeven, Fabienne E. Stubenrouch, Jim A. Reekers and Chantal M.A.M. van der Horst*	***35***
26	Mutational spectrum of PIK3CA in CLOVES and MCAP syndromes	*Paul Kuentz, Judith St Onge, Thibault Jouan, Yannis Duffourd, Laurence Faivre, Jean-Baptiste Rivière and Pierre Vabres*	***325***
27	Role of PI3K Signaling Pathway Mutations in Lymphangiomas	*Mark Youngblood, Brandon Sumpio, Stephanie Douglas, Soonwook Hong, Carrie Shawber, June Wu, Richard Antaya, Milton Waner, Teresa O, Alejandro Berenstein and Deepak Narayan*	***279***
28	An Analysis of the Expression of Renin-Angiotensin-Aldosterone Axis Components in Infantile Hemangioma with Propranolol Treatment	*James Dornhoffer, Ting Wei, Haihong Zhang, Emily Miller and Gresham Richter*	***175***
29	Elevated Serum Levels of Alpha-fetoprotein in Patients with Infantile Haemangioma Are Not Derived from the Tumour	*Tinte Itinteang, Alice Chibnall, Reginald Marsh, Jonathan Dunne, Sophie de Jong, Paul Davis, Philip Leadbitter and Swee Tan*	***67***
30	Analysis of Follicle-Stimulating Hormone Receptor Expression in Infantile Hemangioma	*Reid Maclellan MD, MMSc, Fu Xi MD, Javier Couto BS, Lan Huang PhD, Matthew Vivero BS, Joyce Bischoff PhD and Arin Greene MD, MMSc*	***264***
31	Risk factors of infantile hemangiomas evolvement	*Дмитрий Комелягин, Alexey Petukhov, Sergey Dubin, Artem Dergachenko, Filipp Vladimirov, Svetlana Yamatina, Elena Striga, Anna Dergachenko, Vladimir Slipenko, Alexandr Ivanov, Dmitriy Romanov, Vladimir Shafranov, Khalida Vafina and Evgeniy Fokin*	***92***
32	Extracellular Matrix Analysis in involuting process of Infantile Hemangiomas	*Ho Yun Chung, Dong Kyu Kim, Seok Jong Lee, Seung Huh, Teresa M O and Milton Waner*	***95***
33	Neuropeptide Y and Its Receptors in Infantile Haemangioma	*Elysia Tan, Max Blackwell, Johnathan Dunne, Paul Davis, Swee Tan and Tinte Itinteang*	***123***
34	Serum miR-518a-3p and miR-518e as potential biomarkers for infantile hemangioma	*Gang Ma, Dongze Lv, Hui Chen, Yunbo Jin, Yajing Qiu and Lin Xiaoxi*	***138***
35	Parotid Hemangiomas require a longer treatment course for resolution	*Geetha Puthenveetil, Jill Stites, Michael Recto, Kevin Huoh, Stuart Nelson and Daniel Jaffurs*	***167***
36	Rapidly Involuting Congenital Hemangiomas: a retrospective case series	*Nicole Knöpfel, Isabel Betlloch, Ana Martín-Santiago, Juan Carlos López-Gutiérrez, Marta Valdivieso, Isabel Febrer and Carlos Saus*	***296***
37	Optical Imaging with Near-Infrared Spectroscopy Demonstrates Hypoxia of Infantile Hemangiomas	*Nicole Weitz, Christopher Fong, Nina Antonov, Lauren Geller, Christine Lauren, Kimberly Morel, Andreas Hielscher, June Wu and Maria Garzon*	***198***
38	Localizing Infantile Hemangiomas: Sites of Predilection	*Anita Haggstrom, Eulalia Baselga, Sarah Chamlin, Beth Drolet, Maria Garzon, Kristen Holland, Kimberly Horii, Christine Lauren, Anne Lucky, Anthony Mancini, Erin Mathes, Kimberly Morel, Brandon Newell, Elena Pope, Kate Puttgen and Ilona Freiden*	***202***
39	Association of infantile hemangioma location with presentation at birth	*Bénédicte Hars, Bertille Bonniaud, Hervé Devilliers, Géraldine Jeudy, Stéphanie Perez-Martin and Pierre Vabres*	***310***

PANEL #	TITLE	AUTHORS	ABSTRACT #
40	Quantification of Severity in Infantile Hemangioma	*David Darrow*	**206**
41	When Do Hemangiomas Need Treatment? A Predictive Scoring System to Screen for Early Referral	*Sarah Chamlin, Jin-Shei Lai, Jennifer Beaumont, Eulalia Baselga, Elizabeth Rancour and Anita Haggstrom*	**208**
42	Hearing Loss in PHACE Syndrome: Clinical and Radiologic Findings	*Bree Zimmerman, Erin Mathes, Mark Mamlouk and Kristina Rosbe*	**245**
43	Aortic Arch Repair in PHACE Syndrome: Complex Anatomy Requiring Complex Solutions	*Seamus Caragher, Peter Frommelt, John Scott, Dawn Siegel and Beth Drolet*	**65**
44	Evaluation of maternal infertility as a risk factor for PHACE syndrome	*Mary Kim, Michelle Cancel, Denise Metry, Estil Y. Strawn, Beth A. Drolet, Yvonne E. Chiu and Dawn S. Siegel*	**262**
45	Multidimensional analysis of data: new insights into infantile hemangioma treatment responses	*Alain Delarue, Ilona Frieden, Christine Leaute-Labreze, Stephanie Gautier And Yann Gaston-Mathe*	**275**
46	Validity of centralized photographic assessment of propranolol treatment response in infantile hemangioma	*Pierre Vabres, Despina Liacu, Christine Labrèze, Pierre Souteyrand, Alain DELARUE and Jean-Jacques Voisard*	**300**
47	Hypothyroidism in the early phase of infantile hemangiomas.	*Bertille Bonniaud, Charlée Nardin, Géraldine Triquet, Stéphanie Perez-Martin, Candace Ben Signor, Frédéric Huet and Pierre Vabres*	**303**
48	Breast hypoplasia as complication of an untreated infantile hemangioma.	*Martin Theiler, William Y Hoffman and Ilona J Frieden*	**305**
49	Conjunctival infantile hemangiomas – a rare occurrence	*Martin Theiler, Eulalia Baselga, Lisa Weibel, Agnes Schwieger-Briel, Erin Mathes and Ilona J Frieden*	**308**
50	Infantile Haemangiomas with Minimal or Arrested Growth: Clinical and Histologic Features	*Philip Bekhor, Ellen Ma, Susan Robertson and CW Chow*	**368**
51	A Prospective Self-Controlled Study of Topical Timolol Cream versus 595nm Pulsed Dye Laser in Treatment of Superficial Infantile Hemangiomas	*Hanru Ying, Yajing Qiu, Wenxi Yu, Yijie Chen, Tianyou Wang, Dongze Lv, Jiafang Zhu, Yunbo Jin, Hui Chen, Gang Ma and Lin Xiaoxi*	**132**
52	Beta Blocker Prescribing Practices Among Vascular Anomaly Experts	*Nancy Bauman, Yao Iris Chang, Jichuan Wang and Francine Blei*	**77**
53	CLINICAL SIGNIFICANCE OF SCREENING ELECTROCARDIOGRAMS FOR THE ADMINISTRATION OF PROPRANOLOL FOR INFANTILE HEMANGIOMAS	*James Phillips, Jenika Sanchez, Andrew Bennett, Adam Johnson, R. Thomas Collins, Larry Hartzell and Jay Kincannon*	**117**
54	PROPRANOLOL IN COMBINATION WITH INFRARED HIGH-INTESITY LASER FOR DIFFERENTIATED TREATMENT OF HEAD AND NECK INFANTILE HEMANGIOMA	*Anna Denis, Ivan Abushkin, Igor Vasilyev, Olga Sudeikina, Olga Romanova and Venyamin Lapin*	**226**
55	Propranolol versus Steroids for the Treatment of Ulcerated Hemangiomas	*Roshni Dasgupta, Bentley Rodrigue, Carol Chute, Denise Adams, Belinda Dickie, Adrienne Hammill And Carlos Alvarez-Allende*	**330**
56	Has Propranolol use eliminated the need for surgical and/or laser intervention in infantile haemangiomas treatment? Over 6,5 years of experience.	*Dariusz Wyrzykowski, Barbara Chrzanowska, Maciej Chojnicki And Piotr Czauderna*	**358**
57	Pharmacokinetics of Topical Timolol for Treatment of Infantile Hemangioma	*Beth Drolet, Scott Denne, Anita Haggstrom, Barrie Harper, Kristen Holland, Laura James, Jan Hau Lee, Hui Min Liew, Andrew Lewandowskip, Dawn Siegel, Adriana Tremoulet and Chiara Melloni*	**247**
58	An Update on Effect and Efficacy of Propranolol for Pediatric Growth and Development	*Rachel Giese, Mario Cleves, Jenika Sanchez, Rachel Goode, Jessica Boswell, James Suen and Gresham Richter*	**360**
59	Social Impact of Facial Infantile Hemangiomas on Preteen Children: Treated Versus Untreated.	*Rachel Haimowitz, Victoria Costa, Yao Cheng, Jichuan Wang, Robert Silverman and Nancy Bauman*	**5**
60	Why patients with infantile hemangioma still require surgical treatment in the propranolol era ?	*Juan Carlos Lopez-Gutierrez and Nataliz Vega*	**48**

PANEL #	TITLE	AUTHORS	ABSTRACT #
61	10 yrs follow up of autolog fatinjection of severe ulcerating hemangiomas	*Agneta Troilius Rubin, Carolin Freccero and Sydney Coleman*	***250***
62	Surgical management of infantile hemangioma using the purse-string technique: impact on the scar.	*Laurence Boon, Julien Coulie and Maude Coyette*	***316***
63	Early resection of infantile hemangiomas: short term and long term outcomes	*Manon Linssen, Dalibor Vasilic, Carine van der Vleuten and Bas Verhoeven*	***221***
64	Diagnosis and Treatment of Hepatic Venous Malformations	*Wayne Yakes*	***333***
65	PNEUMONECTOMY IN A PEDIATRIC PATIENT WITH RENDU-OSLER-WEBER SYNDROME. CASE REPORT.	*Julia Udaquiola, Tomas Ferraris, Nicolas Onna, Tamara Kreindel, Marcelo Serra, Pablo Lobos and Ricardo Garcia Monaco*	***258***
66	Sclerotherapy for the Treatment of Benign Vascular Malformations in the Oral cavity- A Different Approach for Treatment	*Itai Zeevi*	***57***
67	Intralesional lidocaine anesthesia: a novel local anesthesia technique facilitating ethanol sclerotherapy of venous malformation	*Xi Yang, Xiaojie Hu, Yunbo Jin, Hui Chen, Li Hu and Lin Xiaoxi*	***82***
68	PERCUTANEOUS SCLEROTHERAPHY OF EXTENSIVE FACIAL VENOUS MALFORMATION INVOLVING THE SCLERA OF EYE. CASE REPORT	*Galli Eduardo*	***286***
69	How to combine alcohol embolization and surgical therapy to preserve the facial nerves in managing challenging AVM at head neck region?	*Lin Xiaoxi, Yunbo Jin, Ma Gang, Hui Chen, Xi Yang, Chen Hua, Tianyou Wang, Wei Li and Wei Wang*	***327***
70	Ethanol Embolotherapy Management of Pelvic Arteriovenous Malformations	*Wayne Yakes*	***336***
71	The Abernathy Malformation: current requirements from invasive angiography	*Ralph Gnannt and Philip John*	***357***
72	Indications for puncture method of treatment of children with lymphatic and lymphovenous malformations of head and neck area	*Дмитрий Комелягин, Alexey Petukhov, Sergey Dubin, Artem Dergachenko, Filipp Vladimirov, Svetlana Yamatina, Dmitriy Khaspekov, Oleg Topilin, Vladimir Slipenko, Elena Striga, Anna Dergachenko, Orest Topolnitsky, Alexandr Ivanov, Andrey Pasechnikov, Khalida Vafina and Igor Strogonov*	***94***
73	TREATMENT OF TONGUE LYMPHATIC MALFORMATIONS USING PERCUTANEOUS APPROACH IN 6 PEDIATRIC PATIENTS	*Galli Eduardo*	***274***
74	Effectiveness and safety of balloon-assisted sclero-embolotherapy for subcutaneous arteriovenous malformation, AVM: A novel technique for controlling blood flow in AVM	*Masato Aoshima and Kenji Kawakura*	***216***
75	Transcutaneous Glue Extrusion Following Embolization of Arteriovenous Malformations	*Cindy Kerr, Maria Darocha, Anna Lillis, Gulraiz Chaudry Gulraiz Chaudry, Raja Shaikh and Ahmad Alomari*	***318***
76	Intralesional Bleomycin Injections for Vascular Malformations: A Systematic Review and Meta-Analysis	*Sophie E.R. Horbach, Irma M. Rigter, J. Henk Sillevis Smitt, Jim A. Reekers, Phyllis I. Spuls and Chantal M.A.M. van der Horst*	***33***
77	ROLE OF PERCUTANEOUS DIRECT PUNCTURE SCLEROTHERAPY WITH BLEOMYCIN IN THE MULTIMODALITY TREATMENT OF PEDIATRIC HEAD AND NECK ARTERIOVENOUS MALFORMATIONS	*Tara Rosenberg, Leah Braswell, Charles James, Jenika Sanchez, James Phillips, James Suen and Gresham Richter*	***353***
78	MRI-ROI (Region of Interest) Imaging Reconstruction and Regression Measurement in Venous Malformation after Sclerotherapy	*Shengda Qiu, Ziming Zhang, Hui Chen, Xiaofeng Tao, Li Hu, Yunbo Jin, Yang Xi, Chen Hua and Lin Xiaoxi*	***136***
79	THE ROLE OF TRANSARTERIAL LUNG PERFUSION SCINTIGRAPHY (TLPS) IN DIFFERENTIAL DIAGNOSIS HIGH-FLOW AND LOW –FLOW VASCULAR MALFORMATIONS	*Birute Vaisnyte, Daiva Nevidomskyte, Donatas Vajauskas, Marius Kurminas, Virginija Gaigalaite, Darius Palionis and Asta Dukstaite*	***232***

PANEL #	TITLE	AUTHORS	ABSTRACT #
80	ENDOSCOPIC SCLEROSIS IN A BLADDER VENOUS VASCULAR MALFORMATION	*Udaquiola Julia, Varela Ma. Florencia, Ferraris Tomás, Moldes Juan Manuel, Kreindel Tamara, Peralta Oscar Alfredo and Garcìa Monaco Ricardo*	***350***
81	Clinical spectrum of Klippel-Trenaunay syndrome in a third level pediatric hospital in Argentina.	*Dario Teplisky, Gonzalo Altieri Mohedano, Franco Selak, Matias Garriga and Sergio Sierre*	***96***
82	Klippel-Trenaunay Syndrome: study of 160 cases and protocol for Ultrasound Doppler diagnosis	*Nilce Carvalho, J.L. Orlando, F. Ramos Jr., L.C. Biagioni, J.H. Curado, R. Grizzo, H. Campos, A. Katalinic and M. Curado*	***115***
83	Near-Infrared Fluorescence Lymphatic Imaging in a Subject with Klippel-Trenaunay Syndrome	*John Rasmussen, Melissa Aldrich, Rodrick Zvavanjanja, Eva Sevick-Muraca and Matthew Greives*	***266***
85	Cytologic Evaluation of Clinically Suspected Lymphatic Malformations as a Guide to Sclerotherapy	*Amy Davis, Sabri Yilmaz, Megan Natali and Lorelei Grunwaldt*	***58***
86	Is surgery a triggering factor for clinical worsening of lymphatic malformations?	*Olivia Boccara, Bertrand Chrétien-Marquet, Stéphanie Pannier, Stéphane Guéro, Naziha Khen-Dunlop, Smail Hadj-Rabia and Christine Bodemer*	***69***
87	OUTCOMES OF SUBMUCOSAL REDUCTION TECHNIQUE IN PEDIATRIC CASE SERIES OF MICROCYSTIC LYMPHATIC MALFORMATIONS OF THE TONGUE	*Tara Rosenberg, James Phillips, Amber Smith and Gresham Richter*	***349***
88	A single center experience of prenatal diagnosed lymphatic malformation	*Miho Watanabe*	***362***
89	Efficacy of treating large/giant cystic lymphatic malformations (LMs) in the neonatal period.	*Philip John*	***364***
90	Beta-adrenergic receptor expression and mast cells in lymphatic anomalies (Kaposi´s sarcoma and Lymphatic Malformations)	*Pedro Redondo, Isabel Bernad, Michel Idoate, Leyre Aguado, Alejandro Sierra and Marta Ivars*	***148***
91	Bone and Joint Traumas in Vascular malformations are a Case of Emergency: Peculiarities in Management	*Dirk Loose, Juergen Hauert and Wolfgang Lehmann*	***38***
92	Contracture by vascular malformations: causes and treatment.	*Satoru Sasaki, Takehiro Warabi and Chigusa Omote*	***365***
93	Subsequent Management and Outcomes After Primary Surgical Excision of Venous Malformations of the Head and Neck	*Tara Rosenberg, Jenika Sanchez, Theodore Klug and Gresham Richter*	***351***
94	INTRACRANIAL VS EXTRACRANIAL (CERVICO-FACIAL) --ARE THEY DIFFERENT: CASE REPORT	*James Suen, Gresham Richter, Adewumi Amole, Mehmet Akdol and Rudy Van Hemert*	***352***
95	Expression of Components of the Renin-Angiotensin System in Venous Malformation	*Sam Siljee, Emily Keene, Helen Brasch, Paul Davis, Swee Tan and Tinte Itinteang*	***174***
96	Electrochemotherapy (EChT): A Unique Technique for Treating Low Flow Vascular Malformations (LFVMs)	*Jing Hong Li, Peng Liu, Zhi Dong Ye, Jin Zhou and Shu Hua Kang*	***14***
97	Ultrasound-guided sclerotherapy with polidocanol microfoam in symptomatic venous malformations: treatment and follow-up of 160 patients.	*Alejandro Sierra, Pedro Redondo, Juan Cabrera, Leyre Aguado and Jose Ignacio Bilbao*	***145***
98	Sclerotherapy for venous malformations of the glans penis in children.	*Dmitry Romanov*	***201***
99	Combining Interventional radiology and surgery in the treatment of Venous Malformations: Experience with 50 cases.	*Lutz Meyer, Milton Waner, Teresa O, Aaron Fay and Jörg Seemann*	***124***
100	Pregnancy in patients with Klippel-Trenaunay Syndrome	*Sophie E.R. Horbach, Max M. Lokhorst, Charlene E.U. Oduber, Joris A.M. van der Post and Chantal M.A.M. van der Horst*	***62***
101	Revisiting Classic MRI Findings of Venous Malformations: Changes Found with Contemporary Techniques	*Matthew Alexander, Daniel Cooke, Christopher Hess, Ilona Frieden, Natalie Hughes and Andrew Phelps*	***56***
102	Comprehensive Surgical Correction of Serious Soft Tissue or Bone Deformities for Complicated Venous Malformation Cases after Sclerotherapy	*Hui Chen*	***28***

PANEL #	TITLE	AUTHORS	ABSTRACT #
103	Combined Lymphedema and Capillary Malformation of the Lower Extremity	*Reid Maclellan MD, MMSc, Gulraiz Chaudry MD and Arin Greene MD, MMSc*	***278***
104	Management of Primary and Secondary Lymphedema: Analysis of 375 Referrals to a Center	*Reid Maclellan MD, MMSc and Arin Greene MD, MMSc*	***280***
105	Near-Infrared Fluorescence Lymphatic Imaging in a Toddler with Congenital Lymphedema	*Matthew Greives, John Rasmussen, Melissa Aldrich and Eva Sevck-Muraca*	***284***
106	Prenatal diagnosis of cerebral and extra-cerebral high-flow lesion revealing familial CM-AVM syndrome related to RASA1 mutation	*Loic VIREMOUNEIX, Audrey LACALM and Laurent Guibaud*	***287***
107	Prenatal Diagnosis of Vascular Anomalies and Correlation with Postnatal Imaging	*Scott Davis*	***309***
108	A Decade experience with personalized therapy for Bannayan-Riley Ruvalcaba.	*Giannoula Lakka Klement and Christina Roffidal*	***259***
109	Seven-year-old male with a PTEN hamartoma of soft tissue (PHOST) arising in the stomach	*Michael Baker, Belinda Dickie, Arnold Merrow, Denise Adams and Anita Gupta*	***343***
110	Pathological Alterations in the Skin of Infantile and Early Childhood Port Wine Stain	*wenbin tan, Labib Zakka, Martin Mihm Jr and Stuart Nelson*	***212***
111	Vascular anomalies, Pediatric anesthesia, and Neurodevelopment: What is the best practice?	*Camille Bédard-Gauthier and elisabeth hortense*	***160***
112	An innovative surgical method to alleviate refractory cutaneous pain	*Hu Li, Chen Hui, Yang Xi, Jin Yunbo, Ma Gang, Li Wei and Lin Xiaoxi*	***203***
113	RASA1 mutations associated with capillary malformation - arteriovenous malformation: A true AVM?	*Josee Dubois, Amina Bougrine, Catherine Ann McCuaig, Elisabeth Rousseau, Afshin Hatami and Michele David*	***154***
114	Serum Angiopoietins Are Biomarkers For Kaposiform Lymphangiomatosis And Kaposiform Hemangioendothelioma And Respond To Sirolimus Treatment	*Tim LeCras, Paula Mobberley-Schumann, Mary Broering, Lin Fei, Cameron Trenor and Denise Adams*	***17***
115	Lymphangiomatosis involving the mandible and the spleen treated with sirolimus and bevacizumab	*A. Lanoel, A Feliu, E. Nadal, V. Angles, M.R. Cordisco, F. Lubieniecky and A.B. Cervini*	***29***
116	Rapamycin-associated lymphoedema in an infant with Kasabach-Merritt phenomenon	*Olivia Boccara, Smail Hadj-Rabia, Emmanuelle Bourrat, Jérome Coulombe and Christine Bodemer*	***40***
117	Safety and efficacy of a 2mg/m2/day dose of rapamycin as treatment of superficial vascular anomalies in Algeria	*Aicha Salhi*	***61***
118	Treatment of Kaposiform hemangioendothelioma and Tufted angioma with Sirolimus. A case clinical series.	*Agustina Lanöel, Adriana Natalia Torres Huamani, Aurora Feliú, Fabiana Lubieniecki, Laura Galluzzo and Andrea Bettina Cervini*	***180***
119	Sirolimus for the Treatment of Vascular Anomalies in Children	*Joanna Tu, Huy Do, Matthew Lungren, David Hovsepian, Michael Jeng, Ann Marqueling, Mai Thy Truong, Rohit Khosla and Joyce Teng*	***246***
120	Sirolimus for the Treatment of Juvenile Nasopharyngeal Angiofibroma	*Karen Fernandez, Paula Mobberley-Schuman, Megan Metcalf, Christine Brookbank and Adrienne Hammill*	***249***
121	Phase II Study Follow Up: Efficacy and Safety of Sirolimus in the Treatment of Complicated Vascular Anomalies	*Jennifer Davis, Adrienne Hammill, Cameron Trenor, Alexander Vinks, Manish Patel, Gulraiz Chaudry, Mary Sue Wentzel, Paula Mobberley-Schuman, Lisa Campbell, Christine Brookbank, Anita Gupta, Carol Chute, Jennifer Eile, Jesse McKenna, Arnold Merrow, Lin Fei, Lindsey Hornung, Michael Seid, Roshni Dasgupta, Belinda Dickie, Ravindhra Elluru, Anne Lucky, Brian Weiss, Richard Azizkhan and Denise Adams*	***304***
123	Sirolimus for Cervicofacial Lymphatic Malformation	*Julie Strychowsky, Meghan O'Hare, Reza Rahbar, Horacio Padua and Cameron Trenor*	***324***
124	Sirolimus for microcystic lymphangioma in the head and neck region of children with tracheostoma and/or gastrostoma	*Jochen Rössler, Johannes Schelling, Wiebke Schupp, Jörg Elard Otten, Julien Baleine, Michel Mondain and Charlotte Niemeyer*	***369***

PANEL #	TITLE	AUTHORS	ABSTRACT #
125	Sirolimus is highly effective for bleeding and lymph leakage in vascular anomalies	*Jochen Rössler, Johannes Schelling, Etelka Földi, Charlotte Niemeyer, Sandrine Mestre, Michelle Bigorre, Helene Kovacsik, Didier Bessis and Isabelle Quéré*	***370***
126	Denosumab for lymphatic malformation in Gorham Disease of the cervical spine.	*Giannoula Lakka Klement, Anastasia Hryhorczuk and Christina Roffidal*	***291***
127	Intraoperative Talc Administration Decreases Rate of Wound Complications in the Surgical Treatment of Lymphatic Malformations	*Kathy Schall, Tiffany Yang, Donna Nowicki, Don Hoang, Minna Wieck, Chadi Zeinati, Lori Howell and Dean Anselmo*	***162***
128	Comparative study of recurrence after resection and reconstruction of arteriovenous malformation	*Iwashina Yuki*	***217***
129	MANAGEMENT OF PEDIATRIC INTRAMUSCULAR VENOUS MALFORMATIONS	*Minna Wieck, Donna Nowicki, Kathy Schall, Tiffany Yang, Don Hoang, Chadi Zeinati, Dean Anselmo and Lori Howell*	***100***
130	SURGICAL TREATMENT RESULTS OF INTRAMUSCULAR VASCULAR MALFORMATIONS	*Birute Vaisnyte, Dirk A. Loose, Daiva Nevidomskyte, Linas Zaleckas, Virginija Gaigalaite and Darius Palionis*	***105***
131	Angiosarcoma arising in a patient with a 27-year-old lymphatic-venous malformation: a case report	*Chen Hua, Yunbo Jin, Hui Chen, Gang Ma, Yajing Qiu, Xi Yang and Lin Xiaoxi*	***126***
132	Clinical Case Series of Angiosarcoma in the Liver	*Denise Adams, Kalee Grassia, Paula Mobberley-Schuman, Ionela Iacobas, Judith Margolin, Rebecka Meyers, Ewa Bien and Adrienne Hammill*	***190***
133	WT-1- expression in angiokeratoma and verrucous hemangioma; a positive marker for malformation when negative?	*Diane Grélaud and Carolin Freccero*	***97***
134	Congenital smooth muscle hamartoma mimicking cutis marmorata telangiectatica congenita	*Lisa Weibel, Aline Buechner and Martin Theiler*	***292***
135	Unusual Vascular Anomaly in Infantile Boy	*Brandon Sumpio, Alain Kaldany, Richard Antaya and Deepak Narayan*	***295***
136	Angiokeratoma Corporis Diffusum. One Phenotype, Different Ethiologies.	*Paula Luna, Margarita Larralde, MAría Eugenia Abad, Andrea Schenonne, Juan Politei and Marina Szlago*	***166***
137	Congenital Disseminated Pyogenic Granuloma: Characterization of a Rare Multisystemic Disorder	*Wibke Uller, Harry Kozakewich, Gulraiz Chaudry, Anna Lillis, Marilyn Liang, Steven Fishman, John Mulliken, Darren Orbach, Cindy Kerr, Maria DaRocha and Ahmad Alomari*	***165***
138	ERUPTIVE, MULTIPLE, AGMINATED PYOGENIC GRANULOMAS, SUCCESFULLY TREATED WITH TOPICAL TIMOLOL: CASE REPORT	*Daniela Kramer, Camila Downey, Maria Cossio, Claudia Salomone and Carolina Whittle*	***227***

1 *Complex acquired dural AVF can be treated by endovascular means. With meticulous technique complications can be avoided. Many embolic agents are successful in ablating dural AVF in all dural sinuses.*

Wayne Yakes

Vascular Malformation Center

Purpose: To evaluate the role of Retrograde Vein and Direct Puncture Retrograde Vein Endovascular Repair of Large Peripheral AVMs.
Methods: Eighty-seven patients (45 males, 42 females; age: 14 - 72, mean age: 27 years) presented for repair of AVMs involving head and neck, shoulder, chest wall, intra-thoracic, abdominal, renal, pelvic, buttock, and extremities. Ethanol and ethanol/coils were the embolic agents used. Retrograde transvenous catheterizations and vein direct puncture retrograde vein approaches were used in all patients.
Results: Eighty-five of 87 patients are cured at long-term follow-up (f/up: 14 months to 138 months; mean: 42 months) and 2 patients' therapy is ongoing. Complications include 1 pelvic AVM post-Rx small bleed not requiring transfusion; 1 pelvic AVM coils eroded into bladder wall removed uneventfully via trans-urethra endoscopy; 2 infections treated with antibiotics; 2 patients' coils superficially eroded and uneventfully removed; and 1 patient subcutaneous hematoma removed (7/87 patients; 8% minor complications).
Conclusion: Retrograde vein and direct puncture vein access and embolization of AVMs in many anatomic locations have proven curative at long-term f/up of AVMs in multiple anatomic locations with a low complication rate. Reproducible and consistent results of this technique have been reported by Yakes (1990) et al, Jackson (1996) et al and Cho (2008), et al.

2 *CRANIOFACIAL AVM: WHICH POSSIBILITY TO MANAGE? A RETROSPECTIVE STUDY ON 49 CASES*

Raul Mattassi, Giacomo Colletti, Luca Crespi and Walter Pozzoli

Humanitas "Mater Domini"

Purpose: AVM location in craniofacial area is common. They present a difficult task for treatment, due to the specific, complex anatomy of that area and because of great variability in extension and location. General principles of treatment should be adapted to those defects. Result is a significant difficulty in treatment strategy decision. In order to find out indications helpful for approach to craniofacial AVM, a retrospective study of a group of 49 craniofacial AVM, treated in a short period (2011-2015) with similar concepts has been analyzed.
Methods: A group of 46 patients, affected by craniofacial AVM and treated in the period 2011-2015 has been analyzed. Clinical data, including location, extension and evolution of AVM has been recoded. Treatment performed, complication and results were registered with a specific focus on the different locations in order to get more data in that sense.
Results: Most common locations of the malformation were cheek (11 cases: 22%), lips (10 cases, 20%) and scalp (6 cases, 12%). Other sites were front 3, eyelid 2, nose 3, parietal 2, ear 2 and tongue and mouth 2. 3 cases had a diffuse AVM, all involving left site of the face. 2 diffuse cases had repeated bleeding from the mouth. 8 cases were treated conservative because of limited extension, absence of symptoms and no evolution. Overall treatments performed were: catheter embolization 28, percutaneous alcohol embolization 93, surgery 13, laser treatment 9. Total performed treatments were 153; number of treatments media for patient was 3,7. In 9 cases treated for cheek AVM, procedures were: catheter embolization 15, percutaneous alcohol embolization 22, surgery 5 and laser 0. In lips AVM , procedures were: catheter embolization 0, percutaneous alcohol treatment 22, surgery 5 and interstitial laser 6. Results were: healing at control (no residual AVM): 12 (29%), no symptoms but with some AVM remaining 9 (22%), improvement 14 (34%), unchanged 2(5%). Recurrence was recorded in 4 cases (10%). Complications were 1 temporary facial nerve palsy, 2 cases of alopecia in scalp AVM, 1 superficial ulcer.
Conclusion: Management of craniofacial AVM is complex and requires the availability of all four treatment techniques: catheter embolization, percutaneous alcohol sclerosis, surgery and laser. Combination of techniques is the most common approach. Selection and timing of procedures should be adapted to the single case and discussed on a multidisciplinary basis.

3 *Bordering Procedure: An innovative technique for resection of arteriovenous malformations in the head region*

Mine Ozaki1, Aki Ihara1, IWASHINA YUKI2, Shien Seike1, Tomohiro Shiraishi1, Akihiko Takushima1, Kiyonori Harii1

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Purpose: Large arteriovenous malformations (AVMs) require extensive resection to reduce the risk of recurrence, as well as perioperative strategies to minimize blood loss. Embolization and sclerotherapy have been employed before definitive resection as part of a multidisciplinary approach. In our experience, despite multiple interventions such as partial resection or embolization and sclerotherapy, considerable bleeding is often encountered during resection of head and neck AVMs due to the presence of numerous feeder vessels. Difficulty of complete extirpation then leads to continued expansion of the lesion and treatment 'failure'. To stage the resection and reduce operative time and blood loss, we recently developed the technique of "bordering" before final resection. The circumference (border) around the lesion was divided into two to three parts with only one part incised at any one time. The technique is described in the following steps.
Methods: Firstly, the boundary between the lesion and surrounding healthy tissue was determined using ultrasonography. Secondly, the skin was completely incised down to periosteum, ligating any feeder vessels encountered. The length of the skin incision was mostly limited to approximately 10 to 15cm, depending on the operation progress and amount of bleeding encountered. Thirdly, the lesion was partly elevated from the underlying bone through the borderline incision. Perforating vessels from the bone were managed by ligation or rapid application of bone wax. This step was especially critical for large lesions with multiple osseous connections. The skin and subcutaneous layer were the closed. When the entire circumference of the lesion had been incised over a period or weeks, definitive resection and reconstruction was carried out. Between 2014 and 2015, three patients with head and neck AVMs were treated using this method. Bordering was performed two (n=2) or three times (n=1). All cases had immediate free flap reconstruction at the time of final resection.
Results: The mean amount of intraoperative blood loss was 130ml for each bordering episode and 757ml for total resection. Mean operative time was 203 minutes for bordering and 731 minutes for total resection. No growth of the lesion and no complications were observed in between bordering sessions.
Conclusion: Bordering technique allows for a significant reduction in blood loss and operative time during at the time of final resection. This is due to previous ligation of the feeder vessels and scar formation at the boundary preventing new ingrowth. Staging the operation is a safer and more controlled approach to large AVMs in head and neck and reduce the physical burden on both patient and surgeon.

4 *Pediatric Acral Arteriovenous Lesion: Clinical Presentation and Histopathology*

Javier Couto and Arin Greene

Boston Children's Hospital, Harvard Medical School

Purpose: Acral arteriovenous lesion is a rare vascular anomaly described primarily in adults. The natural history and etiopathogenesis of this lesion is not understood; it may be a vascular tumor or malformation. The purpose of this study was to characterize the clinical presentation and histopathology of acral arteriovenous lesions in the pediatric population.
Methods: We reviewed the clinical records of patients with acral arteriovenous lesions between 1990 and 2015 that were diagnosed histopathologically. Patient age, gender, location, and lesion size were documented. Morbidity was investigated (e.g. bleeding, pain, deformity). Histological sections were analyzed to determine the pathogenesis of the lesion.
Results: Fifteen children were included (9 males, 6 females). The mean age of onset of the lesion was 8.0 years (range 0-19). Lesion location was: lip (n=8), eyelid (n=4), ear (n=1), cheek (n=1), and upper extremity (n=1). Average area was 0.4 cm2 (range 0.04-1). Three patients (20%) had a history of bleeding; none caused pain. Ten (66.7%) patients noted the area was increasing in size gradually. Histologically, acral arteriovenous lesions showed large tortuous indeterminate-type channels with hyperplastic endothelium and a thick wall consisting of smooth muscle cells and collagen. Elastin staining showed a network of fine elastic fibers throughout the wall and a few fibers at the periphery; smaller channels had similar morphology and seemed to transition to dilated veins.
Conclusion: Acral arteriovenous vascular anomalies do not occur solely in adults. Currently the pathogenesis is unknown; the lesion might be classified as a tumor, a malformation, or a reactive process precipitated by trauma.

5 DIAGNOSIS AND MANAGEMENT OF THORACIC AND SHOULDER ARTERIOVENOUS MALFORMATIONS

Wayne Yakes

Vascular Malformation Center

Purpose: To determine the efficacy of Endovascular Repair of Thoracic and Shoulder Arteriovenous Malformations (AVMs). Previous reports have documented the futility of nBCA and amputation in treating these lesions in this specific anatomy.
Methods: Twelve patients (8 female, 4 male) presented for repair of shoulder and thoracic AVMs. Three patients had extension of AVM to the supraclavicular and axillary areas. Two patients had multiple AVMs. Seven patients had previous failed therapies (embo: PVA/coils/gelfoam; surgeries: excisions/arterial bypass). All patients underwent ethanol endovascular AVM repair; four patients had additional coil embolizations (132 treatments). Patient age range 18-76 years; mean age 36.
Results: Eleven patients are cured at long-term arteriographic follow-up (follow-up 22 – 192 months; mean follow-up: 42 months). One patient with bilateral shoulder AVM and multiple other AVMs therapy is on-going. Complications include two patients with minor superficial blisters, one patient with transient left radial nerve injury with complete recovery and one patient with clot embolus to hand, Rx with urokinase w/distal 3rd phalanx removed. Thus, major complications were 2/132 procedures, one being transient.
Conclusion: A report of shoulder AVM repair in JVIR documented failure of nBCA approach even coupled with quadrant amputation whereby recurrence was universal. These authors stated that shoulder AVMs were not possible to treat. This report documents that cure of these difficult lesions is possible with ethanol endovascular approaches and direct puncture approaches. No other publications in world literature documents cure of AVMs in this anatomy. Long-term cures are noted with the use of ethanol, and ethanol and coils to successfully treat these complex, problematic lesions. A low major complication rate is noted. This patient series finally documents a curative procedure for this daunting lesion.

6 Ear Arteriovenous Malformation Management

Wayne Yakes

Vascular Malformation Center

Purpose: To determine the efficacy of Ethanol Endovascular Repair of Ear Arteriovenous Malformation (AVMs).
Methods: Ten patients (7 female, 3 males; age range 6-39 years; mean age: 22 years) with ear AVMs presented for therapy. Two patients had failed prior embolizations (PVA/coils/nBCA/steroids) and 2 patients had other therapies (laser/excisions/grafting). All presented with a grossly enlarged painful ear, and 5 patients had intermittent bleeding. All patients underwent transcatheter and direct puncture ethanol treatments. (86 procedures).
Results: All 10 patients were cured of their AVM at long-term follow-up (mean follow-up: 52 months). One patient had transient partial VII nerve palsy. Two patients had minor blisters and ear injuries that healed on the outer tragus.
Conclusion: Ethanol endovascular repair of Ear AVMs can achieve cures in this vexing lesion that previously was treated with resection of the ear and with high recurrence rates. This series documents long-term cures of AVMs of the ear and scalp that were not treatable by endovascular approaches as previously documented in the world's literature. Permanent treatment of the auricular AVMs is documented and no recurrence occurred in any patient. Only one article is published (group from Shanghai, China) emulating this technique, that I taught them.

7 *Initial Experience with Embolization Treatment of Pulmonary Arteriovenous Malformation using Micro Vascular Plugs*

Stacey MacKenzie, Matthew Towsley, Sally Mitchell, Clifford Weiss

Johns Hopkins Hospital

Purpose: Transcatheter embolization has become the standard of care in the treatment of Pulmonary Arteriovenous Malformations (PAVMs). Despite long procedure times, numerous coils required to occlude a single PAVM and recanalization rates ranging from 5% to 15%, the most widely used embolic device is still the detachable coil delivered through a microcatheter. An alternative to coil embolization is the Amplatzer Vascular Plug (AVP, St Jude Medical). AVPs allow for quick delivery of a single occluding device. AVPs, however, cannot be delivered through a microcatheter, limiting their utility to larger PAVM with larger feeding arteries. The new MicroVascular Plug System (MVP, Reverse Medical) was designed to combine the best of both devices, allowing occlusion of small vessels in a quick and predictable manner with a single embolic device through a microcatheter. This study was performed to evaluate the effectiveness of the MVP in the treatment of PAVMs.
Methods: With the approval of the Institutional Review Board, a retrospective review was performed on all patients with PAVM treated with MVP between October 2014 and July 2015. All but one patient had a diagnosis of Hereditary Hemorrhagic Telangiectasia (HHT) and were treated at our institutional HHT Center of Excellence. Technical success was defined as occlusion of the feeding artery supplying the PAVM without evidence of flow through the MVP. Recanalization of the PAVM was assessed using computed tomography angiography (CTA).
Results: A total of 19 patients, 18 with HHT, with 38 PAVMs treated with 48 MVPs were included in the study (5 males, 14 females, mean age 44y, range 5-82y). All procedures were technically successful. Post-procedure follow-up was performed at a mean of 83 days ± 75 days on 6 of the 19 patients. No recanalization was demonstrated on CTA.
Conclusion: The MVP was deemed to be a safe and effective method in the embolization of PAVMs.

8 *Can ethanol embolization blanch the skin erythema of extracranial AVM?*

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Purpose: The absolute ethanol embolization has demonstrated the efficiency in extracranial arteriovenous malformations (AVMs). But no relevant research for the change of cutaneous lesional color has been reported. The study explores the change of skin erythema with a photometer after treatments of absolute ethanol embolization in superficial arteriovenous malformations.
Methods: The study enrolled 13 patients with superficial arteriovenous malformations who has accepted absolute ethanol embolization in recent year. Patients were administered the measure of a photometer before and after the embolization. The measurement locations include the lesional skin and contralateral healthy skin. And the measured value was an average value of three measurements.
Results: 13 patients were measured with photometer in this study. All the patients were staged II stage and have diagnosed by DSA with typical clinical symptoms. Among them, 10 (76.9%) patients' lesions located in the head and face region. And three (23.1%) patients' lesions located in the limb. $P<0.05$ was considered a significant difference in statistical analysis.
Conclusion: The signification improvement in cutaneous lesional color was observed in patients with ethanol embolization. Meanwhile maybe we could regard the photometer measurement,which was widely used for the evaluation of PWS, as one new prognostic criterion of Arteriovenous Malformations.

9 *Management of refractory ulceration caused by Arteriovenous malformations with ethanol embolisation*

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Purpose: To describe the clinical features and treatment outcomes of ulceration caused by arteriovenous malformations (AVMs) after ethanol embolisation.
Methods: From October 2011 to October 2015, we treated 12 patients (six males, six females; mean age, 26.2 ± 11.6 years; age range, 4-43 years) with refractory ulceration caused by AVMs. Ethanol embolizations were performed under fluoroscopy by direct puncture technique or through microcatheter. Treatment outcomes were established by evaluating the outcome of symptoms, tissue lesion sign and the degree of devascularization at follow-up angiography.
Results: Fifty embolotherapy procedures were performed in twelve patients. Four patients (33.3%) experienced complete resolution of abnormal angioarchitecture and were rated as "cure" at follow-up angiography. Complete control of ulceration was achieved in all twelve patients. Two patients (16.7%) experienced superficial skin necrosis that healed spontaneously after 4 weeks. Nine patients (75%) experienced blistering immediately after treatment, the complications were self-limited and minor. There were no major complications.
Conclusion: In a limited series, ethanol embolotherapy was effective and safe in the treatment of refractory ulceration caused by AVMs. Before wide utilization of alcohol embolization, radical surgical resection had been the choice for the complete control of the unhealed ulceration because of blood-steal phenomenon at AVM lesion.

11 *Efficacy of an AVM Classification System that Directs Endovascular Therapies Accurately.*

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Purpose: To determine if AVM angioarchitecture characteristics can be predictive and direct specific curative endovascular procedures accurately and consistently to treat high-flow malformations.
Methods: Angiographic analysis of high-flow vascular malformations determined 4 major angioarchitectures. Type I: Direct arterial/arteriolar to vein/venule connection; e.g., as commonly seen in pulmonary AVF, congenital renal AVF, etc. Type II: Arterial/arteriolar connections to a "nidus" that then have several out-flow veins with no intervening capillary beds in any of the vascular interconnections. Type IIIa: Arterial/arteriolar connections to an aneurysmal vein ("nidus" is the vein wall) that drains into a dominant out-flow vein with no intervening capillary bed in these connections. Type IIIb: Same angioarchitecture as Type IIIa, except that there are more than one (several) out-flow veins. Type IV: "Infiltrative" form of AVM whereby innumerable micro-arteriolar branches fistulize through a tissue (e.g., ear) totally infiltrating it, shunting into multiple out-flow veins. Capillary beds also exist in the tissue and are mixed with the innumerable AVFs. Without the capillaries the tissue could not be viable, therefore must be present.
Results: Type I: Can be effectively treated with mechanical devices; e.g., coils, Amplatzer Plugs, etc. Type II: Can be effectively treated with ethanol embolization. Type IIIa: Can be effectively treated by transcatheter ethanol, retrograde vein catheter access or direct puncture access of the aneurysmal vein and treatment with ethanol and coils, or even by coils alone. Type IIIb: Can be effectively treated as above, but can be more challenging by the vein route as more veins (not a single out-flow vein) require closure. Type IV: Can be effectively treated by transcatheter or direct puncture of the innumerable microfistulous AVFs by embolization with 50% -50% ethanol non-ionic contrast mixture.
Conclusion: This never before reported classification system has a direct impact on determining the curative endovascular and direct puncture embolization procedures and also determines the embolic agents that will successfully treat complex AVMS in the body.

12 *Radical or subtotal resection with microsurgical reconstruction in surgical accessible cases with Extracranial Arteriovenous Malformations: 10 years' follow-up*

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Purpose: Congenital Arteriovenous malformations (AVMs) are congenital vascular anomalies, not proliferative neoplasms, but tend to behave aggressively with unpredictable growth and tissue destruction. Although large AVMs occupies only 1% of vascular anomalies, it remains a great challenge to the physicians.
Methods: This is a retrospective review of 183 patients with congenital AVMs, who presented to our department and received treatments from 1998 to 2004. Among them, 121 patients have been followed up for more than 10 years. Therapeutic options, like embolization with NBCA or PVA, surgery and combination were instituted individually depending on the patient's lesion. NBCA was used as the main embolic material. In many cases of this series, the only way to cure was to completely eradicate the nidus, followed by reconstruction with flaps of abundant blood supply, like microvascular, or island expanded flap.Skin graft is rarely adopted.
Results: All these cases have been followed-up for more than 10 years. Among them, 99 surgically accessible cases show completely controlled or cured with total cured rate of 82% at the end of 2014. But for the surgically inaccessible cases, we had to adopted embolization with PVA or NBCA at that time. The control rate was as lower as 62% to 70% at first two years, but it was highly associated with future recurrence after 2 years's follow up.
Conclusion: Before we adopted alcohol embolization as independent therapy from 2006, surgical excision remained the best option for AVM. In fact it was almost inevitable for AVMs at Stage 3 at that time. The high control rate in this series was associated with radical and aggressive surgery. The outcome demonstrates that radical surgery is still the choice for patients with AVM who could not accept alcohol embolization because of the patient's lesion, availability of resources, fear of complication and the comfort level of the treating physician.

13 *INTRACRANIAL PIAL FISTULAS IN PEDIATRIC POPULATION. CLINICAL FEATURES AND TREATMENT MODALITIES*

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Purpose: The purpose of the study is to describe the clinical manifestations, imaging and treatment modalities of patients having intracranial pial arteriovenous fistulas (PAVFs).
Methods: We retrospectively analyzed the cases of PAVFs from January 2004 to july 2015. Medical charts, diagnostic images, surgical, and endovascular reports were reviewed retrospectively during each of the procedures and follow-up. We recorded patient demographics, clinical presentation, treatment modalities, and outcome.
Results: Thirteen patients, twelve with single PAVFs (one of them with multiple holes) and one with multiple PAVFs were identified, . The median age was 8 years old (20 days to 17 years). Eight patients were male (62 % of cases). Five PAVFs were localized in the posterior fossa eight were supratentorial (62 %). Five patients had intracranial bleeding, three presented seizures, one was studied for chronic head- aches, three manifested by growth retardation, one had hydro- cephalus, and one had a congestive heart failure (CHF) and vein of Galen aneurysmal malformation (VGAM). The latter did not improve after embolization and died few days later. Endovascular therapy was used in eleven, whereas two patients were surgically managed. Total occlusion of the fistula was achieved in all cases.
Conclusion: PAVF affects pediatric population at different ages with miscellaneous clinical manifestations. Endovascular treatment is safe and effective when the venous side of the fistula can be occluded.

15 Comparative study on the Effects of three kinds of different β-receptor blockers on Proliferation and Apoptosis of Mouse Hemangioendothelioma Endothelial Cells in vitro

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Purpose: To primarily study the possible treatment effects and its mechanism of three kinds of different β-receptor blockers in a Mouse Hemangioendothelioma Model (EOMA) in vitro.
Methods: Comparative study on the effects of three kinds of different β-receptor blockers---metoprolol, propranolol and butoxamine, on the proliferation and apoptosis of Mouse Hemangioendothelioma Endothelial Cell (EOMA cells) was conducted in vitro. EOMA cells were cultured in vitro, randomly divided into different groups, three kinds of drugs were added into the medium respectively, after 24 hours intervention, MTT assay and Acridine orange staining assay were conducted respectively to detect cell viability and apoptosis level.
Results: For propranolol, after 24h treatment, significant differences of cell viability and apoptosis were noted ($P<0.05$) at the concentration of 50μmol/L,while continuing to increase to 800μmol/L, the cell survival rate decreased sharply to close to 5%(Figure 1). Acridine orange staining at the 50μmol/L group after 24h revealed many apoptotic cells(Figure 2,3).For metoprolol and butoxamine,significant differences of cell viability and apoptosis were noted ($P<0.05$)at the concentration of 200μmol/L,while continuing to increase to 800μmol / L, the cell survival rate decreased sharply to close to 50%. It was significantly higher than propranolol group at the same concentration ($P<0.05$).It showed a similar trend in Acridine orange staining.
Conclusion: Propranolol can effectively inhibit the proliferation and induce the apoptosis of EOMA cells in vitro; While,the selective β1 receptor blocker-metoprolol and the selective β2 receptor blocker- butoxamine inhibite proliferation and induce apoptosis in EOMA cells was significantly lower than propranolol. Suggest propranolol in mouse hemangioma effect may be related to β1 and β2 receptor synergistic effect.

16 Unique Functional Characteristics Of Lymphangiomatosis- Derived Endothelial Cells

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Purpose: Our aim is to establish cell lines of lymphatic anomalies, investigate the cellular and molecular characteristics of these cells, and use them as biological platform to test new therapies. We report the establishment of primary endothelial cell lines isolated from lesional tissues of a patient with lymphangiomatosis and extensive lymphatic proliferation involving the mediastinum, lungs and mesentery.
Methods: We have developed an immuno-affinity method to purify endothelial cells (EC) from human tissue using anti-human CD31 antibodies coupled to magnetic beads. The purity of EC population from lymphangiomatosis lesions was verified by immunostaining of cells for CD31 and VE-cadherin. The lymphatic differentiation of these cells was verified by staining for LYVE-1 and PROX-1. The proliferative, migratory and angiogenic characteristics of lymphangiomatosis-derived EC and normal EC (from neonatal foreskin) were assessed using in vitro cell proliferation, scratch wound and sprouting angiogenesis assays.
Results: We have successfully purified EC from lymphangiomatosis tissues with >95% purity as verified by CD31 and VE-Cadherin immunostains. These cells also expressed the lymphatic markers LYVE-1 and PROX-1. Lymphangiomatosis EC proliferate much more rapidly and migrate faster than normal EC in in vitro assays. These cells also have increased sprouting angiogenesis as compared with normal EC. Treatment of lymphangiomatosis EC with rapamycin (a mTOR inhibitor that has been used in patients with lymphatic anomalies) effectively inhibited cell proliferation and sprouting angiogenesis. Mechanistically, rapamycin significantly reduced the activities of mTOR complex-1 and complex-2, and inhibited Akt activation in these cells.
Conclusion: We have established primary endothelial cell lines from lymphangiomatosis lesions, and showed that these cells have aberrant functional characteristics. Rapamycin blocked mTOR signaling and effectively inhibited the proliferation and migration of these cells. Lymphangiomatosis EC are valuable biological reagents to investigate the biology of lymphangiomatosis and to test new therapeutic drugs for this disease.

17 mRNA and Protein Expression Levels of SMAD Pathway Constituents in Arteriovenous Malformations

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Purpose: Extracranial arteriovenous malformations (AVMs) are poorly understood. Their vascular phenotype indicates a process of constant remodeling, a process predominately controlled by the TGF-B pathway. Alterations in SMAD expression, downstream effectors of TGF-B, may thereby contribute to AVM formation. This study examines alterations in SMAD mRNA and protein expression in human extracranial AVMs compared to normal tissue.

Methods: Purified RNA from 11 patients with extracranial AVM and 12 normal controls were reverse transcribed and used for real-time PCR. Target genes analyzed were SMAD 1, 2, 3, 4, 5, 6, 7, 9, ALK1, and BMP9. The amplification of all target genes was normalized against 18S rRNA. Abnormal mRNA expression directed western blot analysis for proteins in the SMAD pathway on the same tissue samples. These included SMAD6, SMAD7, SMAD9, ALK1, and BMP9. Western analysis was normalized against GAPDH.

Results: The mRNA levels of SMAD6, SMAD7, SMAD9, and ALK1 in AVM patients were significantly higher than those in normal controls with respective p values of p=.0048, p=0075, p=0084, and p=.0031. SMAD1, SMAD2, SMAD3, SMAD4, and SMAD5 mRNA expression revealed no significant difference between AVM and control samples. There was no amplification of BMP9 in either AVM patients or normal controls. (Figure 1.) Contrasting protein expression revealed reduced levels of SMAD6, SMAD9, ALK1, and BMP9 proteins in AVM patients with respective p values of p=.04, p=.023, p=.01, and p=.005. Protein expression of SMAD7 was not significantly different. (Figure 2.)

Conclusion: This study suggests that abnormal expression of the SMAD pathway is present in extracranial AVM with seemingly disparate patterns in mRNA and protein expression. Interestingly, our results show that while mRNA levels of certain genes are highly elevated in AVM patients, the protein expression level seems to be lower than in normal tissue. This disparity may be a result of post-translational modification. Continued investigation must be performed to continue to elucidate the molecular pathways involved in the development of AVM tissue.

18 Histopathologic evaluation of vascular malformations with characterization of elastic tissue and trichrome staining patterns

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Purpose: Vascular malformations are clinically characterized by fragility and propensity for bleeding. Histologically, they may comprise arterial structures, venular structures, or both, and are characterized by irregular anastomosing of thick- and thin- walled vascular spaces with intervening fibrosis. We investigated the patterns of elastic fiber and collagen staining in vascular malformations.

Methods: Vascular malformations arising from the brain and skin/soft tissue were evaluated by elastic tissue (Verhoeff Von Gieson) and trichrome (Gomorri's method) staining. Nine samples were evaluated by both methods, while six additional malformations were evaluated with elastin staining only.

Results: Trichrome staining revealed thickening of the intimal layers of arteries as well as highlighting the irregular thickness of venous walls within the malformation and some areas of medial degeneration. The elastin stain demonstrated reduplication of internal elastic lamina, fragmentation and disruption of elastic lamina, and irregular thickness of internal elastic lamina. These observed changes confirmed the usual histologic appearance of abnormal vessel structure in vascular malformations aprreciated on hematoxylin and eosin-stained slides, but also detected more subtle abnormalities of histologically normal appearing vessels.

Conclusion: While these changes may reflect innate abnormal development that occurs in the malformation, they may also represent secondary changes due to trauma related to altered blood flow, other mechanical pressure, or manipulation. The observed abnormalities as assessed by elastic tissue and trichrome staining likely correlate to the vascular fragility observed in these lesions.

19 Cerebrospinal Fluid (CSF) Leak and Intracranial Hypotension in Blue Rubber Bleb Nevus Syndrome (BRBNS)

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Purpose: Blue rubber bleb nevus syndrome (BRBNS) is a rare genetic disorder characterized by numerous venous malformations of the skin, gastrointestinal tract and visceral organs. The purpose of this study is to describe the presentation and etiology of cerebrospinal fluid.
Methods: Retrospective review of the medical records, photographs and imaging studies of the databases at Boston Children's Hospital for patients with BRBNS and spinal CSF leak.
Results: Four patients with BRBNS were found to have spinal dural venous malformation (VM). The location of the VM was cervicothoracic (n=3) and lumbar (n=1). Three patients (2 female, 1 male) developed CSF leak and classic signs of intracranial hypotension at the age of 11, 26 and 44 years. The fourth patient (11-year-old male) had non-specific symptoms but without definite signs of CSF leak. In addition to the symptoms caused by multiple venous malformations in the gastrointestinal tract and various organs, valvular disease was noted in 2 patients (severe pulmonary valve regurgitation and trivial atrioventricular valve regurgitation (n=1) and mitral valve prolapse (n=1)).
Conclusion: CSF leak in blue rubber bleb nevus syndrome is likely a late manifestation of spinal dural venous malformation. Further research is needed to examine whether screening imaging studies can predict the development of CSF leak.

20 CUTANEOUS VASCULAR LESIONS IN CEREBRAL CAVERNOUS MALFORMATIONS: REPORT OF 2 FAMILIES

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Purpose: Cerebral cavernous malformations (CCM) are relatively rare vascular malformations that involve the central nervous system but may also affect other tissues as the liver, the retina and the skin. It can present sporadically or inherited in an autosomal dominant pattern with incomplete penetrance. We present 2 families with cerebral cavernous malformations that where diagnosed by the presence of cutaneous lesions in 2 children, aged 12 and 13 years-old.
Methods: Case 1: A 12-year old boy, with no medical history of interest, presented at our department for the evaluation of multiple asymptomatic cutaneous vascular lesions that appeared during the last year. On physical examination the patient presented 2 cherry angiomas, 3 punctuacte capillary malformations, 1 capillary malformation and 2 thrombosed angiomas. Family history was initially negative but an accurate anamnesis revealed that his grandmother had cerebral vascular lesions. Genetic test confirmed mutation in KRIT1 (CCM1) gene. Case 2: A 13-year-old boy presented at dermatology consultation for an angiokeratoma on his knee. Rest of physical examination was unremarkable. He had a family history of CCM and MRI of the brain showed multiple CCM. Genetic test was positive for KRIT1 (CCM1) mutation.
Results: According to the lastest ISSVA clasification, the CCM is included in the venous malformations group. Cutaneous vascular malformations are seen in 9% of patients. Hyperkeratotic cutaneous capillary venous malformation has been classically associated with CCM, although venous nodular malformations, port-wine stain, angiokeratoma, cherry angioma or punctuate capillary malformation have also been described
Conclusion: A detailed anamnesis is mandatory in patients with multiple vascular lesions in order to detect lesions in other locations than the skin that may require further imaging evaluation and therapeutic management.

21 Capillary malformation-arteriovenous malformation: a clinical review of 68 patients

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Purpose: The objective of this study is to report and analyze clinical data of 68 patients with CM-AVM.
Methods: A retrospective clinical review of all the cases of CM-AVM evaluated between 2003 and 2015 was done.
Results: Sixty- eight patients were recorded, 40 females (58%) and 28 males (42%). The average age of presentation was 16 years. Family history was positive in 52 cases (76%). All the patients presented well-defined macular lesions round (33%), oval (32%), heart shaped (28%) or, pinpoint (7%); pink (43%), brownish (37%) or, red (20%). A pale halo was seen in (10% of cases), while increased local temperature was detected in (27% of them). The most important extracutaneous findings were polydactyly, scoliosis and headache. Four subjects presented associated osseous dysplasiia, a lymphatic malformation was detected in one case, a retinal vascular lesion in

another one patient, combined vascular syndromes were diagnosed in two cases and Noonan syndrome in one patient. Four children also had an infantile hemangioma.
Conclusion: Perform image exams when a fast-flow VM is suspected. Is a heterogeneous disorder with phenotypic variability from an isolated MC up to the association with a fast-flow VM with great morbility. Perform image exams when a fast-flow VM is suspected. Should be performed carefull analysis of family history, genetic counseling and follow-up. Important that Dermatologists recognize this entity, probably more frequent than reported in Literature.

22 CLAPO SYNDROME: New cases reported and genetic data incorporated

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Purpose: CLAPO syndrome (Capillary malformation of the lower lip, Lymphatic malformation of the face and neck, Asymmetry of the face and limbs, and Partial/generalized Overgrowth) was described by our team (2008) on 6 unrelated patients. Genetic cause is not known, although somatic mosaicism is suspected, and clinical features partially overlap with PIK3CA-associated somatic overgrowth disorders.
Methods: We have increase the number of patients to 11, we have assessed a complete clinical evaluation, and performed a preliminary gene discovery approach based on Next Generation Sequencing (NGS) custom panel experiments. Paired tissue/blood samples were screened for genetic varianats in about 300 vascular/overgrowth related genes.
Results: Compared with our first report, lymphatic malformations seems to be more frequent in the oral cavity, specifically in tongue or oral mucosa, than neck. In addition, any of the new patients presented generalized overgrowth, all were partial. Capillary malformation of the lower lip (100%) remains the main feature for differential diagnosis. Preliminary genetic analysis did not detect mutations in genes associated with known vascular/overgrowth syndromes such as PROS (PIK3CA), Sturge-Weber (GNAQ) or Proteus (AKT1) among other. However, we cannot rule out genes in the PIK3CA/AKT/mTOR pathway as the genetic cause in CLAPO.
Conclusion: We have updated clinical phenotype in CLAPO syndrome, and we have discarded the presence of mutations in genes known to cause clinical related syndromes, thus confirming our previous hypothesis that CLAPO syndrome is an individual entity with its own genetic cause. Still, the genetic cause of CLAPO remains unknown. To know the genetic cause will allow us to clarify overlapping features between CLAPO and PROS, and to establish future pharmacological treatment options, as done before for cystic lymphatic malformations using mTOR inhibitors. We call for cases to include in our cohort and perform future NGS (exome) experiments.

23 CAPILLARY MALFORMATION OF THE LOWER LIP, LYMPHATIC MALFORMATION OF THE TONGUE AND MINIMAL LOCALIZED OVERGROWTH: "FORME FRUSTE" OF CLAPO SYNDROME ?

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Purpose: CLAPO syndrome (OMIM 613089) is a recently described syndrome associating Capillary malformation of the lower lip, Lymphatic malformation of the face and neck, Asymmetry and Partial/Generalized Overgrowth (Lopez-Gutierrez, 2008). Up to now, only 6 cases are reported as such in the literature. Somatic mosaicism is hypothesized but no genetic mutation has yet been identified.
Methods: Review of 4 pediatric patients with the typical capillary malformation of the lower lip described in CLAPO syndrome.
Results: 4 patients (2 boys and 2 girls) were seen at our institution between 2005 and 2011 with the well-defined capillary malformation involving the central lower lip, slighly overlapping onto the skin, characteristic of CLAPO syndrome. These patients were referred for evaluation of pulsed-dye laser treatment. Mean age at presentation was 10 months (1 month-4 years). At initial presentation, none had clinically visible associated anomalies, in particular no oral lesion, no asymmetry and no overgrowth except for mild hypertrophy of the involved lip. During a mean follow-up of 7 years (4-10 years), localized microcystic lymphatic malformation of the tongue developed between ages 3 and 7 years, with minimal symptomatology in all patients. Careful examination at recent visits did not reveal significant progression of the lip hypertrophy, tongue involvement nor evidence of overgrowth.
Conclusion: We propose that these patients represent a "forme fruste" of CLAPO syndrome and that infants presenting with this typical capillary malformation of the lower lip be examined thoroughly for asymmetry or overgrowth and followed carefully for development of lymphatic malformations of the head and neck, in particular of the tongue. Further observations will help better identify this syndrome.

24 Cost-Effective Management of Vascular Anomalies in a Rural Hospital Setting in the New Guinea Highlands

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Purpose: The management of vascular anomalies is complex; requiring a 'Super-Specialist' Doctor, High Tech Radiological & Tissue Diagnostic support and a state-of-art Operation Theatre in consultation with other 'Super-Specialists' from other related fields of medicine. In the past, patients with suspected vascular anomalies in our country, were referred to Australia or New Zealand. Referring these patients to a well established center, in Australia or New Zealand, would be too expensive and unaffordable to all of them. Therefore, we have devised a cost-effective way to manage these patients. We have then, attempted treatment, in most of them, using whatever resources that is available to us. The main purpose of our study was to devise a Cost-Effective Method to Manage Vascular Anomalies in a Rural Hospital setting, in the New Guinea Highlands.

Methods: We have diagnosed the lesions, mainly from the History, Physical Examination and Intra-Operative Examination. We have then organized our clinical diagnostic method into an Algorithm and a Scoring Chart. Our main treatment method was percutaneous sclerotherapy under general anesthesia, using mainly Absolute (90-100%) Ethanol, which is cheap and readily available to our hospital.

Results: Between April 2008 and April 2013, we have reviewed over 865 cases & have attempted treatment in most of them. Those who have received treatment, the outcome was satisfactory in more than 90% of them. Most of them were followed up for at least a Year. Less then 20% were followed up for 4 Years and revealed satisfactory results for both patients and our team. The main adverse effects were prolonged anaesthesia and skin necrosis; experienced in less than 1% of our patients. There were no deaths among our series.

Conclusion: We have successfully managed cases of Vascular Anomalies in a Rural Hospital Setting; using our Original Clinical Diagnostic Algorithm & Scoring Chart and using Minimal Resources, with Satisfactory Outcomes and Without any Major Complications.

25 Shared decision making in vascular malformation care

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Purpose: Shared decision making (SDM) is an approach in which clinicians and patients communicate together, using the best available evidence, with the goal to arrive at an informed decision about the best therapeutic action. The goal is to combine the physician's knowledge and the patient's preferences and needs when making a therapeutic decision, in the best way possible. The aim of this study was to investigate (1) if patients with congenital vascular malformations have a need for SDM, (2) if we use SDM in our daily practice, (3) if SDM is positively correlated with patient satisfaction.

Methods: Patients with congenital vascular malformations visiting outpatient clinics in 2 academic centers in the Netherlands were asked to complete multiple validated questionnaires focusing on SDM: Control Preferences Scale (CPS), 9-item Shared Decision Making Questionnaire (SDM-Q9), CollaboRATE Scale and a satisfaction score. Treating physicians completed the SDM-Q9 doc questionnaires. Conversations were recorded and assessed for SDM criteria by two independent researchers using the OPTION-5 score.

Results: Sixty-three adults and parents of pediatric patients completed the questionnaires. The vast majority of patients prefers to share responsibility with their doctor in deciding which treatment is best. With our acquired data, we will perform correlation tests to answer our remaining research questions.

Conclusion: SDM is an important communication approach in today's healthcare. Also in vascular malformation care, we should look for ways to improve SDM in our daily practice by education or the use of (digital) decision aids for patients.

26 Mutational spectrum of PIK3CA in CLOVES and MCAP syndromes

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Purpose: Vascular malformations are a hallmark of the PIK3CA related overgrowth spectrum (PROS) which includes CLOVES (congenital overgrowth, vascular and epidermal nevi, skeletal anomalies) and MCAP (macrocephaly-capillary malformation) syndromes. Whereas in CLOVES syndrome, PIK3CA mutations are found in affected tissue only, in MCAP they may also be found in blood or saliva. We sought to determine the diagnostic yield of PIK3CA mutation search on affected tissue or blood depending on clinical presentation.
Methods: We analyzed results of PIK3CA mutation detection USING next generation sequencing (NGS) in a French cohort. Patients were classified either in CLOVES or MCAP spectrum (with central nervous system involvement).
Results: RESULTS. In most patients, PIK3CA was analyzed on at least one affected tissue sample, usually a skin biopsy (n = 155). There were 110 CLOVES (71%) and 45 MCAP cases (29%). Diagnostic yield was 61% for CLOVES and 58% for MCAP. In 31 additional MCAP patients, PIK3CA analysis was performed on blood or saliva only with a lower diagnostic yield (53%), total = 186, CLOVES = 110 (59%), MCAP = 76 (41%). PIK3CA mutations were distributed over the whole gene. In CLOVES spectrum, 12 mutations had previously been reported, and we identified 16 novel mutations. In MCAP spectrum, 27 mutations had previously been reported and we identified 8 novel mutations. Seven common mutations were found both in CLOVES and MCAP, including the three most frequent mutations p.Glu542Lys, p.Glu545Lys and p.His1047Arg. However, they accounted for only 26% of positive cases (n = 107) and were never found in blood or saliva.
Conclusion: CONCLUSION. Molecular diagnosis of PROS should preferably be performed on affected tissue. It is also possible on blood or saliva whenever central nervous system involvement is present, but with a lower diagnostic yield. The mutational spectrum extends far beyond known hot spots, hence complete PIK3CA sequencing is warranted.

27 Role of PI3K Signaling Pathway Mutations in Lymphangiomas

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Purpose: Normal lymphatic malformations are rare, sporadic congenital lesions found in lymphatic-rich tissues. The dilated lymphatic channels become fluid filled and disconnect from the normal lymphatic system. This paper examines the genes associated with the lymphangiomas and classifies subsets of genes that may be important in downstream regulation.
Methods: Eight lymphangioma samples with matching blood underwent whole-exome sequencing (WES) to identify somatic driver mutations. Data was pre-processed using BWA, and further processed with MarkDuplicates (Picard) and BaseQualityScoreRecalibration (GATK). Variant calling was performed with HaplotypeCaller (GATK), and annotated using Annovar. The results of this discovery cohort were validated in an independent group of 30 samples using molecular-inversion probe sequencing. Lymphatic progenitor (CD133 positive) and endothelial cell (CD133 negative) DNA was extracted from a normal patient and analyzed with PCR and Sanger Sequencing for the presence of mutations.
Results: WES identified recurrent alterations to the COSMIC reported gene PIK3CA in three of eight samples. High-coverage targeted re-sequencing confirmed the variants in these three samples, and identified ten additional samples with PIK3CA mutations out of thirty examined (Fig 1). 23% had a E542K mutation and another 23% had a E545K. The majority of the mutations (54%) occurred at 1047 resulting in a Histidine being switched for an Arginine. PCR analysis of lymphatic progenitor and EC analysis showed residues at 1047, but primers length could not confirm 542 or 545.
Conclusion: We have identified mutations in the PI3K signaling pathway that results in lymphatic malformations. PI3k is an intracellular signaling pathway important for regulating cell cycle and cell proliferation. Downstream activators of PI3k include AKT and mTOR. PCR analysis of lymphatic stem cells and EC confirmed that the mutation only existed in lymphangioma patients. PCR analysis proved that these mutations were not in embryonic or normal endothelial cells indicating they must be unique to lymphatic malformations.

28 An Analysis of the Expression of Renin-Angiotensin- Aldosterone Axis Components in Infantile Hemangioma with Propranolol Treatment

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Purpose: Infantile hemangioma (IH) represents one of the most common tumors of infancy. Recently, the beta blocker propranolol was discovered to induce or accelerate the involution of IH, becoming a mainstay of treatment. Investigations of propranolol's mechanism of action have demonstrated the involvement of angiogenic factors (e.g., nitric oxide, VEGF, IGF, etc.). We propose that propranolol induces a beta 1 blockade that reduces renin levels and, subsequently, angiotensin II, thereby preventing induction of these angiogenic substrates. We examined the expression of constituents of the Renin-Angiotensin-Aldosterone (RAA) pathway in IH samples to investigate the role of this pathway in the history and treatment of IH.
Methods: IH samples in proliferation (n=10), involution (n=10), and undergoing propranolol treatment (n=12), and normal tissue (n=11), were subjected to reverse transcriptase quantitative PCR with primers for Renin, Angiotensinogen, ACE, ACE2, and Angiotensin Receptors I and II. These tissues were subjected to Western blot with antibodies against the same factors as well as angiotensin I and II.
Results: PCR analysis showed significant increases in the mRNA levels of Angiotensinogen, ACE, and Angiotensin Receptor 1 in all IH samples versus normal tissue ($p<.05$). Additionally, levels of ACE decreased significantly between proliferating and propranolol-treated IH ($p<.05$). Angiotensin Receptor I levels showed a nonsignificant decrease among treated and involuting IH compared to proliferating samples. Renin, ACE2, and Angiotensin Receptor II showed no amplification. Preliminary protein levels supported PCR findings.
Conclusion: Treatment with propranolol significantly reduces the levels of ACE in IH. In addition, the levels of several constituents of the RAA pathway are elevated in IH tissue compared to normal tissue. This may represent a mechanism by which increased local IH levels of ACE induce elevated levels of Angiotensin II, which may act as an upstream element in the induction of many angiogenic factors shown to be responsible in IH physiology.

29 Elevated Serum Levels of Alpha-fetoprotein in Patients with Infantile Haemangioma Are Not Derived from the Tumour

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Purpose: The observed elevated serum levels of alpha-fetoprotein (AFP) in patients with hepatic infantile haemangioma (IH) led us to investigate whether IH was the source of AFP.
Methods: We measured serial serum levels of AFP in patients with problematic proliferating IH treated with either surgical excision or propranolol. We also investigated the expression of AFP in extra-hepatic IH samples using immunohistochemical staining, mass spectrometry, NanoString gene expression analysis and in situ hybridisation.
Results: Serum levels of AFP normalised following surgical excision or propranolol treatment. Multiple regression analysis for curve fittings revealed a different curve compared to reported normal values in the general populations. AFP was not detected in any of the IH samples examined at either the transcriptional or translational levels.
Conclusion: This study demonstrates the association of proliferating IH with elevated serum levels of AFP which normalized following surgical excision or propranolol treatment. We have shown that IH is not the direct source of AFP. An interaction between the primitive mesoderm derived IH, and the endogenous endodermal tissues, such as liver, via an intermediary, may potentially explain the elevated serum levels of AFP in infants with extra-hepatic IH.

30 Analysis of Follicle-Stimulating Hormone Receptor Expression in Infantile Hemangioma

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Purpose: The life-cycle of infantile hemangioma and follicle-stimulating hormone (FSH) secretion are identical. We have shown that infantile hemangioma expresses the receptor for follicle-stimulating hormone (FSHR). The purpose of this study was to identify which cell type(s) in infantile hemangioma contain FSHR.
Methods: Human infantile hemangioma sections and cells were subjected to immunofluorescence for FSHR. Tissues were co-stained with DAPI and either anti-PDGFR-β or anti-CD31 antibodies to identify nuclei, pericytes, and endothelial cells, respectively. Specimens also were fractionated by fluorescence-activated cell sorting (FACS) into hematopoietic, endothelial, perivascular, and mesenchymal stem cells and were tested for the presence of FSHR by using FSHR antibody. Control specimens consisted of sertoli cells (positive) and normal skin/subcutis (negative).
Results: FSHR was expressed in the endothelial, perivascular, and stem cells of infantile hemangioma by immunofluorescence and FACS (Fig 1). Receptor expression by FACS was greatest in stem cells (37.2%), compared to pericytes (13.5%) or endothelial cells (8.4%).
Conclusions: Endothelial cells, pericytes, and stem cells in infantile hemangioma express FSHR. A precursor cell giving rise to endothelial cells and pericytes expressing FSHR might contribute to the pathogenesis of infantile hemangioma.

31 Risk factors of infantile hemangiomas evolvement

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Purpose: To determine risk factors of infantile hemangiomas evolvement.
Methods: There were surveyed parents, whose children suffered from infantile hemangiomas of various localization. Parents were suggested to anonymously answer25 questions, relating to pregnancy, heredity, appearance and evolution of the disease. 1000 questionnaires were received.
Results: The analysis of the survey revealed the following facts: 1) 70.3% of children with infantile hemangiomas were female; 2) In 62.1% of cases the pregnancy was with different forms of pathology, of which 31.2% had toxicosis, in 20.3% of cases there was revealed the umbilical cord entanglement, in 19.6% - the threat of pregnancy termination, 18.7% - fetal hypoxia, 10.2% - a pathology of placenta; 3) 85.7% of women took medication drugs during pregnancy: Papaverine (suppositories) - 27.4%, Nospanum - 26.8%, Curantyl - 23.9%, Duphaston - 21.9%; 4) 13.1% of children were born at less than 37 weeks of pregnancy and in 9.37% of cases they had a birth weight of 1000-2500 g. Analyzing the hereditary factor, there is found, that 28% of relatives were/are different types of vascular formations: infantile hemangiomas, capillary malformations, varicose veins of lower limbs, various types of vascular tumors; 66% of them are women (most commonly mothers of children suffered from vascular pathologies – 26.5%, and maternal grandmothers – 14.9%.)
Conclusion: Medical-social study found, that a combination of such factors as pregnancy of female fetuses, pregnancy with fetal hypoxia, a threat of pregnancy termination, cord entanglement, pathology of the placenta, intake of drugs influencing the vascular wall, hormonal therapy, and also the occurrence of vascular disease in the anamnesis of mother and female relatives increase the risk of infantile hemangiomas.

32 Extracellular Matrix Analysis in involuting process of Infantile Hemangiomas

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Purpose: Changes in the composition of the extracellular matrix (ECM) occur between the proliferating and involuted phases of infantile hemangiomas (IH), and are associated with angiogenic growth. We examined the composition of the ECM in proliferating and involuted IHs and assessed correlations between the composition of the ECM and whether the IH was in the proliferating or the involuted phase.
Methods: We evaluated IH samples from a cohort of patients who had five proliferating IHs and five involuted IHs. The following ECM molecules were analyzed using enzyme-linked immunosorbent assays and immunohistochemistry: laminin, fibronectin, collagen type I, collagen type II, and collagen type III.
Results: The involuted IHs had higher levels of deposition of collagen type III than the proliferating IHs. The median values (interquartile ranges) were 1.135 (0.946-1.486) and 1.008 (0.780-1.166) (P=0.019), respectively. The level of laminin was higher in involuted IHs than in proliferating IHs, with median values (interquartile ranges) of 3.191 (2.945-3.191) and 2.479 (1.699-3.284) (P=0.047), respectively. Abundant collagen type III staining was found in involuted IHs. Laminin α4 chain staining was clearly present within the basement membrane adjacent to the blood vessels, and was significantly more intense in involuted IHs than in proliferative IHs.
Conclusion: Involuted hemangiomas showed extensive deposition of collagen III and laminin, suggesting that differences in the composition of the ECM reflect stages of the development of IHs. This pattern may be due to the rapid senescence of IHs.

33 Neuropeptide Y and Its Receptors in Infantile Haemangioma

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Purpose: Within neural crest derived tumours such as pheochromocytoma, neuropeptide Y (NPY) has been shown to promote angiogenesis and be released from the cells in response to angiotensin II. This study investigated the expression of NPY and its receptors, NPY-R1 and NPY-R2, in infantile haemangioma (IH).
Methods: Immunohistochemical (IHC) staining was performed on proliferating (n=6) and involuted (n=6) IHs for the expression of NPY, NPY-R1 and NPY-R2. The presence or absence of mRNA and protein corresponding to NPY, NPY-R1 and NPY-R2 was confirmed by NanoString gene analysis and Western Blotting (WB), respectively.
Results: IHC, NanoString and WB showed the presence of NPY-R1 but NPY and NPY-R2 were absent within proliferating and involuted IHs.
Conclusion: The observation of the presence of only NPY-R1 within IH could be explained by two hypotheses. The first is that NPY is not produced within the lesion but is produced elsewhere in the body. The second is that the receptor is stimulated by a different known ligand called PYY. This study reveals a novel role for NPY in IH biology via a putative angiogenic mechanism in promoting proliferation of IH.

34 Serum miR-518a-3p and miR-518e as potential biomarkers for infantile hemangioma

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Purpose: Infantile hemangioma (IH) is one of the most common benign tumors of infancy, with high incidence rate of 4%~5%. At present, GLUT-1 has been recognized as a biomarker for IH, which need to rely on histopathological examination. Serum VEGF is also lack of sensitivity and specificity for detection. Therefore, more specific noninvasive biomarkers should be found for IH. Recently, several studies have indicated that circulating miRNAs hold much potential as novel noninvasive biomarkers for cancer and other disease processes. The objective of this study was to investigate the potential of serum miRNAs as novel biomarkers for IH with a single diseased identical twin model.
Methods: Five pairs of monozygotic twins with with IH in one of them were enrolled in this study. The TaqMan miRNA microarray was used to identify dysregulated miRNAs in the plasma of monozygotic twins. The TaqMan-based miRNA quantitative real-time reverse transcription polymerase chain reactions were used to validate the dysregulated miRNAs.
Results: Eight differently expressed miRNAs were selected in monozygotic twins serum using miRNA array screening, among which miR-518a-3p, miR-518e, miR-519a, miR-512-3p were up-regulated genes, miR-216b, miR-409-5p, miR-544, miR-606 were down-regulated genes. Using TaqMan-based RT-PCR, miR-409-5p and miR-606 did not express in IH and control group, eliminate from the expression profiles. The express of miR-544 in RT-PCR was contrast to array. MiR-519a, miR-512-3p and miR-216b were not significantly expressed in IH and control group. MiR-518a-3p were detected in serum of 40 IH cases, 12 cases (92.3%) were Undetermined among 13control cases. MiR -518e was Undetermined in 3 cases (7.5%) among 40 IH patients, but 12 cases (92.3%) among 13 control patients.
Conclusion: Our findings indicated that serum miR-518a-3p and miR-518e could be important potential biomarkers for the early differential diagnosis in IH. Because of this finding, large-scale investigations are urgently needed to pave the way from basic research to clinical utilization.

35 Parotid Hemangiomas require a longer treatment course for resolution

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Purpose: Infantile hemangiomas are benign vascular tumors with a natural history of rapid proliferation in infancy for 4-6 months followed by partial or complete involution over time. Some have been found to have longer periods of growth, location in the parotid region appears to predispose to a longer proliferative phase.
Methods: We report a systematic retrospective single institution review of a series of twenty patients with Infantile hemangioma involving the parotid region. Chart review of these cases was performed to determine their clinical characteristics and monitor their response to treatment. We compared their course to that of patients with hemangiomas in other locations.
Results: Twenty patients with parotid hemangiomas were referred to our clinic from 2009 – 2015. Three patients did not receive medication due to older age at referral. Seventeen patients started medical therapy, three were lost to followup. Two required tracheostomy for coexisting airway hemangioma causing acute obstruction. Mean duration of treatment for 10 patients who completed treatment was 29 months. Four patients remain on treatment; mean duration of treatment is 14.7 months. All patients received propranolol, three patients received concomitant steroids for 2 months. Significant reduction is size of the hemangioma was noted within 4 months of initiating propranolol therapy in all patients. Two patients had skin ulceration and three needed reconstructive surgery. Six patients had significant regrowth of their lesions when treatment was weaned/stopped at a year of age. All of these lesions responded well when propranolol was reinitiated.
Conclusion: Infantile hemangiomas involving the parotid region have a longer proliferative phase and therefore require longer course of treatment than those seen in other locations. This is important data when counseling parents about duration of treatment course. Further studies are required to characterize the biology of parotid hemangiomas to determine the etiology of the prolonged proliferative phase.

36 Rapidly Involuting Congenital Hemangiomas: a retrospective case series

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Purpose: We describe the clinical characteristics, histopathology and long-term clinical course of rapidly involuting congenital hemangiomas (RICH) and compare our findings with previous reports.
Methods: We conducted a multicentre retrospective review of RICH over a 20-year period. A review of the medical charts, serial clinical photographs, imaging, and histopathological findings was performed.
Results: We identified 38 patients with fully formed vascular lesions at birth that demonstrated a rapid involution course during the first months of life. Twenty-two of 38 patients (57.9%) were male and 15 (42.1%) were female. Two clinical presentation subtypes were identified: tumor type (81.6%) and patch type (18.4%). The most common location was the limbs (55.3%), trunk (26.3%) and only 7 cases involved head and neck. Twenty-one RICH (55.3%) were larger than 5 cm. Prenatal diagnosis was established in only 3 patients and in 1 case intrauterine growth was documented prior to birth. Most lesions were solitary except for 2 patients. Complications were observed in 9 cases (23.7%). Transient thrombocytopenia and coagulopathy was the most common complication (18.4%) associated with congestive heart failure in larger tumors (10.8%). Most of the RICH regressed during the first 15 months and in 8 cases the involution process was only partial (PICH) leaving a NICH-like lesion (7 cases). Most common residuum of RICH was of an atrophic patch and less commonly, lipoatrophy with proeminent veins was observed. Histologic analysis (n=22) showed small to large lobules of capillaries in a fibrous stroma with abnormal draining channels. Immunohistochemical studies demonstrated absence of glucose transporter-1 protein expression in all cases.
Conclusion: Recent studies based on molecular evidence have revealed distinctions and similarities between congenital and common infantile hemangioma. However, it still remains unknown the behavioral divergence in hemangiomas that arise in utero. Emerging advances in molecular research, prenatal imaging and histochemical and cytogenetic studies may provide a greater insight into congenital hemangiomas and contribute to therapy decision.

37 Optical Imaging with Near-Infrared Spectroscopy Demonstrates Hypoxia of Infantile Hemangiomas

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Purpose: To assess the utility of a near-infrared spectroscopy (NIRS) device in characterizing infantile hemangiomas (IH) during different stages of their natural history and in response to treatment.
Methods: Infants who presented with an IH >2 cm within the first 9 months of life were eligible for enrollment in this prospective pilot study (NCT01673971). A wireless, handheld NIRS probe, able to measure total hemoglobin (HbT) and tissue oxygen saturation (StO2), was developed to prospectively characterize IH through their natural history and in response to treatment. Cross-sectional information was obtained for 1-3 time points. Measurements were obtained from non-lesional skin for most patients. We developed two indices based on HbT and StO2 to obtain a single variable for monitoring IH. Hypoxia Index (HI)=[HbT]/[%StO2] Normalized Hypoxia Index (NHI)=1/2 x [RHbT +(1/RStO2)] RHbT=[HbT IH]/[HbT normal skin] and RStO2 = [StO2 IH]/[StO2 normal skin]. The measurements were grouped into three categories based on the clinical phases of the IH: proliferative, plateau, and involuting. Statistical analysis was performed to demonstrate changes between these phases.
Results: Thirteen patients (ages 1-9 months) were enrolled with a total of 15 IH. Three IH were treated with topical or systemic beta-blockers. The HbT of IH was greater, whereas the oxygen saturation was less, than normal skin, resulting in a significantly increased hypoxia indices for IH compared to normal skin at all time points (Figures 1-2). As the IH stopped proliferating, the indices decreased, trending towards that of normal skin. The hypoxia indices approached normal sooner in the 3 treated patients.
Conclusion: This pilot study demonstrates that this handheld NIRS device is a quick and non-invasive means of characterizing IH. Our data supports the hypothesis that IH are hypoxic despite proliferation of blood vessels and increased HbT. Limitations include small sample size, lack of normal skin measurements for each patient at each time point, non-standardization of time points.

38 Localizing Infantile Hemangiomas: Sites of Predilection

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Purpose: To observe patterns of localized hemangiomas on the face and scalp, determine sites of predilection, and place these patterns in a developmental context.
Methods: Design: Retrospective review of photoarchives at 10 Hemangioma Investigator Group (HIG) pediatric dermatology centers identified localized IH of face and scalp that were mapped to standardized computerized templates using heat map software Participants: 4,153 infants were identified with focal hemangiomas of the face and scalp Methods: Software was developed to qualitatively and quantitatively examine the frequency of infantile hemangioma on the face and scalp. Investigators mapped the central focal point of each hemangioma on standard templates. Main Outcome(s) and Measure(s): Heat map technology was used to qualitatively identify areas of predilection. Dot maps were used to assess frequency of hemangioma location on the face was expressed per facial quadrant. Frequencies of hemangioma location were compared between smaller defined facial units.
Results: Results: 4153 focal hemangiomas were mapped of which 2962 were facial. On the face, approximately 74% (2186/2962) of facial hemangioma occurred either along the midline axis or perpendicularly across the ocular axis in a cross-shaped area of predilection intersecting at the glabella. Eighteen percent of midline facial hemangiomas occur on the nasal tip. The medial cheek is a site of relatively lower frequency for localized hemangiomas. Scalp hemangiomas show predilection for the midline with 149/295 (51%) noted on midline top of the scalp. Localized hemangiomas do not demonstrate preferential laterality.
Conclusion: Conclusions and Relevance: Non-random distribution and areas of predilection exist for localized hemangiomas on the face and scalp. The midline of the scalp and face, perioral region and the horizontal region across the eyes are favored areas. The boundaries between embryonic regions including the maxillary and mandibular metameres did not display increased incidence of hemangioma.

39 Association of infantile hemangioma location with presentation at birth

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Purpose: Although the pathogeny of infantile hemangiomas (IH) remains unknown, the role of hypoxia as a trigger is suspected, as local tissue ischemia is a stimulus for neovascularization. Hypoxia may result from skin pressure during labor and delivery. Since sites of maximal skin pressure differ depending on the type of presentation, we sought to determine whether location of cutaneous IH varied in infants born after cephalic or breach presentation.
Methods: We performed a nine-year retrospective single-center observational study of 230 infants with hemangiomas. The mode of delivery, either vaginal (breech or cephalic presentation) or caesarean section was obtained from children's health record or family interview. IH locations were divided into two main areas: above or below the umbilicus. Comparison of IH locations between cephalic and breech presentation was performed in infants born by vaginal delivery.
Results: A total of 207 infants were included, who had 281 hemangiomas. Vaginal delivery was recorded in164 infants who had 216 IH. Upper hemangiomas (above the umbilicus) were significantly associated with cephalic presentation at birth (OR = 6.47 ; P < 0.0001 ; CI 95% = 2.87 - 14.57) independently from birth weight, sex, prematurity and IH pattern (p>0.05). This association was still present in focal or superficial/mixed IHs, but not in segmental or deep IH.
Conclusion: Our study is the first to report an association between location of hemangiomas and presentation at birth. Our findings are in keeping with the hypothesis that pressure on infant skin during labor and delivery may represent a causal factor for IH.

40 *Quantification of Severity in Infantile Hemangioma*

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Purpose: Haggstrom et al. have reported the validation of a scoring system designated HSS (Hemangioma Severity Scale). We have noted that this system has several significant flaws, and that the study failed to correlate hemangioma scores with clinicians' perception of severity, clinical interventions, and outcomes. The present study was performed to: 1) Confirm the validity of our hemangioma score, termed "QUASH", testing its intra- and inter-rater reliability and reproducibility. 2) Correlate the QUASH score with clinicians' subjective assessment of hemangioma. 3) Determine whether QUASH can be used to predict the probability of and level of intervention. 4) Compare the above data obtained using QUASH with those generated using the HSS of Haggstrom et al.
Methods: Photographs and clinical features of 138 patients with infantile hemangiomas were compiled in a PowerPoint file. Two evaluators scored the cases based on the QUASH and the HSS on two occasions separated by an interval of 4 weeks. A gestalt estimate of severity was also made based on the Hemangioma Grading System.
Results: The temporally separated sets of measurements demonstrated intra-rater reproducibility and reproducibility within and among cases and raters. The second data set demonstrated a high-level of concordance (inter-rater agreement), and correlation between the QUASH scores and the clinician's "gestalt" score of severity based on the Hemangioma Grading System. There was greater variability of scores among cases involving hard-to-measure sites, including the nasal tip and lips. QUASH scores and hemangioma grades were able to predict intervention recommended by the treating clinician. Pre- and post-treatment QUASH scores successfully quantified the clinical changes and were superior to HSS in cases involving color change.
Conclusion: QUASH is a vaild tool for assessment of hemangioma severity and scores can be correlated with hemangioma grade. This tool overcomes some of the drawbacks of other hemangioma scoring systems.

41 *When Do Hemangiomas Need Treatment? A Predictive Scoring System to Screen for Early Referral*

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Purpose: Infantile hemangiomas (IH) are commonly encountered in the primary care setting and most often remain asymptomatic, resolving without sequelae. Certain characteristics are associated with an increased risk of complications, associated anomalies, and disfigurement. The heterogeneous presentation poses a clinical challenge for physicians in determining the need for treatment and subspecialty referral. This study aims to evaluate the utility of the previously-published Hemangioma Severity Scale (HSS) to predict the need for treatment.
Methods: This retrospective study included 106 patients with IH seen in the Indiana University Dermatology Clinic in 2011. Data from electronic medical records and clinical photographs taken at the patients' initial visits were used to score the hemangiomas using the HSS. Treatments employed over a 9-14 month follow up period were recorded.
Results: Four HSS score subgroups were identified. Higher HSS score subgroups correlated with the need for treatment; 98 % of patients with HSS scores of 10 or greater received local or systemic therapy. Higher HSS scores also correlated with an increased frequency of complications and risks for associated structural anomalies and permanent disfigurement. The scores did not correlate with gender, age at initial presentation, history of bleeding or pain, or IH size.
Conclusion: The HSS may be a useful tool for primary care physicians for identifying high-risk IH that may benefit from therapy. This easy-to-use scale can improve clinical outcomes by identifying which patients need intervention to minimize complications. IH with Total HSS scores of 6 or greater should be referred for subspecialty evaluation.

42 Hearing Loss in PHACE Syndrome: Clinical and Radiologic Findings

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Purpose: To characterize the types of hearing loss (HL), associated ear imaging findings and clinical characteristics in patients with PHACE Syndrome and HL.
Methods: Retrospective review of patients presenting to our tertiary care children's hospital between 1994 and 2014 with PHACE with MRI and audiologic evaluations.
Results: 11 patients were identified with hearing and imaging data. 7/11 had normal hearing; 1 had unilateral profound loss; 1 had unilateral severe loss; 1 had unilateral moderate loss; 1 had unilateral mild loss. Of the 4 patients with HL, 3 had internal auditory canal (IAC) lesions (1 involving the cochlea), 2 had dysgenesis of the brainstem and/or cerebellum, 1 had bilateral mastoid opacification, and 1 had a deformed pinna. Of the 7 patients without HL, 4 had IAC lesions (1 bilateral), 3 had deformed pinnas, 1 had dysgenesis of the brainstem and/or cerebellum, and 1 had external compression of the external auditory canal by a parotid hemangioma. Hearing results did not consistently correlate with the radiologic abnormalities. For those children with HL, there did not appear to be improvement with time with or without propranolol. Patients with HL were more likely to have very large surface area, > 150 cm2 (4/4 vs. 2/7, p=.02), and 2 or more extracutaneous findings of PHACE (4/4 vs. 2/7, p=.02). Patients with HL had scalp involvement and more facial segments with hemangioma, but these comparisons were not significant.
Conclusion: Patients with PHACE are at risk for HL and may demonstrate radiologic abnormalities within the ear structures, although the type of HL, imaging findings, and their respective correlation vary. All patients with PHACE should have basic hearing screening (newborn screen). Formal audiology evaluations should be strongly considered for PHACE patients who have multiple extracutaneous systems involved, very large hemangiomas, and IAC hemangiomas or dysgenesis of the brainstem or cerebellum on imaging.

43 Aortic Arch Repair in PHACE Syndrome: Complex Anatomy Requiring Complex Solutions

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Purpose: Forty-one percent of patients with definite PHACE syndrome have intracardiac, aortic arch, or brachiocephalic arterial anomalies. The aortic arch anomalies observed in PHACE syndrome are especially complex and often involve long segments of the transverse aorta arch. Approximately 1/3 of those will require surgical intervention. The majority of patients with PHACE syndrome also have anomalies of the cervical and cerebral arteries. This combination of aortic arch, brachiocephalic, cervical and cerebral vessel malformations leads to increased risk of ischemia and stroke, presenting a unique challenge to the surgical team. The surgical repair, anesthesia, and perioperative care of these patients have not been previously reported.
Methods: We retrospectively reviewed The PHACE Syndrome International Clinical Registry and Genetic Repository to identify children with PHACE that had operative repair of aortic arch obstruction at Children's Hospital of Wisconsin.
Results: Seven patients with PHACE required aortic arch reconstruction from 1996-2015. All needed complex surgical approaches (5 interposition grafts, 2 patch aortoplasties, 1 subclavian flap) because of extensive arch dysplasia that included long-segment areas of stricture with adjacent aneursymal dilatation to relieve the obstruction. Aberrant origin of a subclavian artery was found in 6/7, so that clinical assessment of the gradient by blood pressure measurement was impossible (all arm and leg arteries arose distal to the arch obstruction). The 3 children who had surgery after age 1 showed significant progression of the arch obstruction and/or aneursymal segment dilatation after their initial infant evaluation. No deaths or perioperative complications occurred despite associated cerebrovascular arterial dysplasia in 5/7. Recurrent arch obstruction developed in 3/7 at intermediate F/U (2 had graft replacement at 8 and 11 years due to somatic growth; 1 had repeat patch plasty 11 months after initial repair).
Conclusion: Extensive arch reconstruction is commonly required in PHACE, and careful preoperative assessment is needed to fully characterize the aorta, brachiocephalic, cervical and cerebral arterial anomalies. Standard intraoperative monitoring should include electrocardiogram, pulse oximetry, capnography, noninvasive blood pressure, central venous pressure (CVP), and arterial (right radial and femoral) blood pressure. Advanced neurophysiologic such as Near infrared spectroscopy (NIRS) monitoring is indicated given the increased risk for ischemic brain injury and requirement for cardiopulmonary bypass. Echocardiogram is a good screening tool, but if abnormalities of the aorta are identified further imaging is required to fully delineated the unusual arch anatomy. In PHACE syndrome aortic arch disease maybe progressive and children need to be followed carefully by pediatric cardiologists. Recurrent obstruction is common given the non-native tissue techniques needed to relieve the arch anomaly.

44 Evaluation of maternal infertility as a risk factor for PHACE syndrome

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Purpose: PHACE syndrome is characterized by Posterior fossa anomalies, Hemangioma, Arterial anomalies, Coarctation of the aorta, Eye anomalies, and sternal defects. The etiology of PHACE syndrome is unknown and likely multifactorial and complex. A genetic etiology has been proposed given the syndromic phenotype; however, there are no published reports of heritability in families of children with PHACE. Preliminary X-inactivation studies have not demonstrated significant skewing in affected female patients or their mothers (1). Whole exome sequencing and copy number variation analysis have yet to identify a common pathogenic variant (2). To further delineate the pathogenesis of PHACE, we sought to determine if there is an increased prevalence of infertility and assisted reproductive technologies (ART) in the mothers of children with PHACE. It is known that the incidence of imprinting disorders is increased in individuals conceived through the use of ART. Imprinting disorders occur when either the paternal or maternal normal allele is epigenetically silenced (imprinted) and a mutated allele from the other parent is expressed. Previous studies indicate that ART themselves are not the cause of imprinting disorders, but rather the genetic background of subfertile parents (3). It has been proposed that ART may bypass a natural selection mechanism to allow for an imprinting disorder to occur (4).

Methods: A survey to evaluate the rates of miscarriage, infertility, and ART use was made available to 114 families enrolled in the PHACE syndrome International Clinical Registry and Genetic Repository.

Results: total of 63 responses were gathered from December 14th, 2014 to February 4th, 2015. Twenty-five of 62 survey respondents (40.3%) and 62/218 mothers in the entire registry (28.4%) reported a known or suspected history of miscarriage; this difference likely represents an ascertainment bias. Both rates were statistically significantly higher from the national miscarriage rate of 15-20% in the United States, p=0.002 (5). Sixteen percent of mothers of PHACE children report a history of infertility compared to a national infertility rate of 12% (6). According to the National Survey on Family Growth, 11.9% of women in the United States received infertility services (7). This is comparable to the 14.8% (9/61) in the PHACE registry who reported receiving fertility therapy for the pregnancy related to the child with PHACE.

Conclusion: More mothers in the PHACE registry had miscarriages when comparing to national data. In contrast, rates of infertility and ART use did not differ substantially in the two groups. Limitations to the study include recall and ascertainment biases given the survey based design and low power due to the small sample size.

45 Multidimensional analysis of data: new insights into infantile hemangioma treatment responses

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Purpose: Large randomized clinical trials (RCTs) contain amounts of data which are not systematically used in classical statistical analyseis. Even sub-group analyses explore a limited number of the possible factors and only expected factors of interest are tested. The efficacy of oral propranolol was confirmed in a large RCT. Based on a new approach of multidimensional analysis, we have explored factors associated with greater treatment success or failure.

Methods: Demographic parameters, disease characteristics, intermediate efficacy data, and safety data represent hundreds of factors that could influence patient outcome (success/failure). These factors determine a "n-dimension space" where there are different area of higher or of lower density of success. A multidimensional analysis explores these many factors without setting a priori assumptions. It identifies univariate or multivariate rules (combinations of one or several factors) describing subpopulations with a significant difference in outcome compared to the whole population. Confounding factors were removed and the medical relevance of the rules was evaluated. Rules were further analyzed and thresholds adapted if necessary to make them easier to apply. Only rules easily understandable and clinically applicable were retained.

Results: Early start of treatment (< 70 days) is a strong factor of success. Large IH (≥2.5 cm), and particularly segmental IH, have better results than the treatment group as a whole (69 vs 55%). Success rate can exceed 80% when these patients are of normal body weight. There were no observed conditions of higher success rate with a lower tested dose of propranolol, but there were several subpopulations in which a higher dose gave better results \. IH improvement observed at the three first visits rise the success rate up to 70%.

Conclusion: A statistical multidimensional approach can yield new insights about treatment responses as well allowing for new ways of studying therapeutic management of infantile hemangiomas with propranolol.

46 Validity of centralized photographic assessment of propranolol treatment response in infantile hemangioma

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Purpose: Various tools can be used to assess severity or activity of infantile hemangiomas, but none of them has been used as a primary endpoint in clinical trials. We have developed a centralized photographic method and sought to demonstrate its validity for assessment of clinical response to treatment of infantile hemangiomas.
Methods: Reliability of a centralized photographic method was evaluated through analysis of data from a cohort of 460 patients included in a international randomized controlled trial assessing complete or near complete regression of proliferating infantile hemangiomas in infants on propranolol or placebo. Imaging data were acquired by 56 investigators and transmitted for quality control before evaluation by two blinded trained central observers. Main outcome measures were the rate of successful image acquisition, kappa index for intraobserver agreement, concordance rate for interobserver agreement, and interobserver kappa index at each batch assessment.
Results: During the data acquisition phase, reacquisition of photographs was not needed in 92.7%. During analysis phase, intraobserver kappa indexes were calculated as 0.80 and 0.72, respectively. The interobserver kappa index at each batch assessment remained above 0.6 in 59% of batches without a tendency to decrease or increase over study duration. The overall interobserver concordance rate was 85%.
Conclusion: Centralized photographic assessment of treatment response in patients with infantile hemangiomas is feasible and reliable in the context of a randomized controlled trial. The concordance rate between evaluations remained high, reflecting low impact of observers' subjectivity. This method could be implemented for assessment of treatment response in a number of other skin conditions.

47 Hypothyroidism in the early phase of infantile hemangiomas

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Purpose: Hypothyroidism in infancy can impair psychomotor development. Hypothyroidism resulting from increased triiodothyronine deiodinase activity has been reported in infants with diffuse hepatic or massive infantile hemangiomas (IH) but thyroid hormones have not been routinely screened in infants with IH. We sought to determine the frequency of hypothyroidism in a cohort of hospitalized infants with complicated or threatening IH and report on their management and follow-up.
Methods: Ten-year retrospective study of hospital files in a pediatrics department in a French regional university hospital. A total of 42 infants admitted for prematurity or IH treatment with propranolol or corticosteroids who underwent routine thyroid hormone dosage were studied. The frequency of hypothyroidism was calculated and infants with IH with and without hypothyroidism were compared.
Results: Among 42 infants (35 females, median age 4.7 months), seven (16.6%), aged 2 to 3 months, had altered thyroid function tests. In three infants (7.1%), uncompensated hypothyroidism required L-thyroxine therapy, which was discontinued within 6 to 16 months, after thyroid function had returned to normal and IH had resolved. Four had compensated hypothyroidism which resolved within a few days without hormone therapy. No other causes for hypothyroidism were found. All had normal thyroid function at birth. Prematurity (p=0.008), low gestational age (p=0.009), low birth weight (p=0.02) and multifocal IH (p=0.04) were associated with hypothyroidism, whereas no association was found between hypothyroidism and ulceration or anatomic site of IH.
Conclusion: We found uncompensated hypothyroidism in children with hepatic and massive hemangiomas known to be at risk but also in one small-size facial IH. Routine screening for hypothyroidism might be considered in all infants with IH, especially in preterm and low birth weight infants.

48 Breast hypoplasia as complication of an untreated infantile hemangioma

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Purpose: Infantile hemangiomas (IH) have a characteristic growth pattern of rapid proliferation during infancy followed by slow involution. A minority of cases have significant functional or aesthetic sequelae. We report a case of an untreated IH leading to pronounced hypoplasia of the affected breast.
Methods: Case report
Results: A 14 year old girl presented to our clinic with significant hypoplasia of her right breast. She had a past medical history of an IH that was first noticed at 2 weeks of age and grew to involve the

entire areola and underlying soft-tissue. At that time, no treatment was given and the IH involuted leaving only faint superficial telangiectasias and textural changes. However, at puberty her right breast developed much more slowly than her left leaving her with strikingly asymmetrical breasts. She was referred to plastic surgery for breast augmentation via implant.
Conclusion: This is one of the only reports of breast hypoplasia due to a previously untreated IH. We hypothesize that a bulky or rapidly progressive deep IH may interfere with normal breast gland development. Our case emphasizes the need to consider this potential complication in female infants with mixed or deep IH involving the breast, and consider systemic therapy in this setting in an attempt to prevent this adverse outcome.

49 *Conjunctival infantile hemangiomas – a rare occurrence*

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Purpose: We describe a series of conjunctival IH, their natural course, associated findings and response to treatment.
Methods: Case series
Results: 7 cases of conjunctival IH have been identified. All cases occurred in the first few weeks of life. Two cases had associated cutaneous focal IH (2 and 6 respectively, the latter without evidence for hepatic IH). In one case, the conjunctival IH was accompanied by segmental cutaneous IH and had involvement of the iris as well. The remaining 4 conjunctival IH did not have any extraocular manifestations. No ocular complications requiring treatment occurred in our patients. All conjunctival IH showed significant proliferation during the first months of life and in the cases where follow-up was available spontaneous regression occurred but more slowly than anticipated for cutaneous IH. One case was treated with systemic propranolol, which was effective but nevertheless left the child with significant vascular IH residuum at age 4.5 years. The case with segmental IH was treated with topical timolol on the cutaneous part, which was followed by a regression of the cutaneous as well as the intraocular IH. In a third case, proliferation occurred despite topical treatment with timolol.
Conclusion: Conjunctival IH are a rare finding but nevertheless occur in some infants. Our cases suggest that they may have a slower and maybe incomplete regression phase. Severe ocular complications have not occurred in any of our patients. However, regular controls with an ophthalmologist are mandatory in this situation. For more extensive lesions, topical and systemic beta blocker seem to be effective.

50 *Infantile Haemangiomas with Minimal or Arrested Growth: Clinical and Histologic Features*

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Purpose: To define the clinical features of the insufficiently recognised entity of Infantile Hemangioma with Minimal or Arrested Growth (IH-MAG).
Methods: A retrospective case series of 5 Glut-1 postitive IH-MAG patients were photographed and biopsied for histology and Glut-1 immuno-staining. The clinical appearances were described in detail and all cases were followed up close to resolution
Results: This series of Glut-1 positive, IH-MAG demonstrated a distinctive clinical morphology as compared to Capillary Malformations. The lesions were present at birth and showed areas of lighter and darker erythema, mat erythema, venules, brighter dots at the periphery some of which were tending to Cambell de Morgan like elevation, and the potential for ulceration in macular areas. The histology did not have the distinctive morphology of IH but more closely resembled that of Capillary Malformation.
Conclusion: Based on the morphology, histologic findings and immunostaining patterns of this series of IHMAG , we believe that macular superficial IH can be recognised as a distinct subset of IH with the potential for relatively rapid resolution and without the need for drastic therapeutic intervention.

51 A Prospective Self-Controlled Study of Topical Timolol Cream versus 595nm Pulsed Dye Laser in Treatment of Superficial Infantile Hemangiomas

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Purpose: 595-nm pulsed-dye laser (PDL) and topical Timolol are both extensively used in the clinical treatment of superficial infantile hemangioma (IH). However, there has been no study conducted about the different therapeutic outcomes between the two treatments in IH. We designed the present study to evaluate and compare the efficacy and safety of Timolol cream and PDL treatment in the superficial proliferating infantile hemangiomas.
Methods: We designed the present study to evaluate and compare the efficacy and safety of Timolol cream and PDL treatment in the superficial proliferating infantile hemangiomas. Methods: Twelve patients with superficial infantile hemangioma were included in this study and were treated with both 0.5% topical Timolol cream and PDL. The 0.5% Timolol cream was asked to be used four times daily by patients. The treatment was continued for 2–6 months. Three assessors were asked to judge the changes in both the topical Timolol treated and PDL treated separately by comparing pre- and post-treatmental photographs.
Results: Two months later, the average visual evaluation was 3.83 for PDL treatment and 2.77 for topical Timolol with significant difference (P=0.003). It suggests that superficial proliferating IH respond better to PDL treatment than topical Timolol cream at first 2 months at the settings used in this study. No patients developed scarring or permanent pigmentation change.
Conclusion: Compared with topical Timolol cream, PDL treatment may be more effective in the treatment of superficial proliferating IH in short term (2 months post-treatment). But long-term follow-up to evaluate the efficiency and the side-effects of the two treatments is very required in this continuing study.

52 Beta Blocker Prescribing Practices Among Vascular Anomaly Experts

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Purpose: To describe beta-blocker prescribing practices of experienced vascular anomaly clinicians.
Methods: Attendees of a 2015 advanced vascular anomaly meeting from 46 institutions (13 countries) were invited to complete a 23-question survey describing their beta-blocker initiation for healthy infants with non-airway, non-PHACES infantile hemangiomas, and non-contributory past medical/family histories.
Results: 32 of the 36 participants from 10 countries prescribe beta-blockers: 14-surgical specialists, 10-pediatric specialists (9-hematologists), and 8-dermatologists. 30 were physicians and 2 nurse practitioners. 31 prescribe propranolol and 1 atenolol. 53% of prescribers admit fewer patients now than 2 years ago. 38% start all as outpatients, 22% admit all and 40% admit some based on age, however only ¼ of this latter group use <5 week as cutoff. Among those admitting "all" versus "some", surgeons tend to admit all more than non-surgeons (p=0.06). Initiation practice in North America does not differ from rest of world (p>0.08). 38% treat <20 patients/year; 25% 20-40/year and 38% >50/year. Outpatient therapy is initiated at home in 41%, in clinic in 32%, and either site depending on patient's age in 27%. 75% start below target, usually ½, and increase every 1-2 weeks. Pretreatment evaluation for home-prescribers includes: heart rate:48%, blood pressure:36%, auscultation:36%, echocardiogram:16%, cardiac consult:8%, and blood glucose:4%. 80% of providers see patients every 1-2 months. Medication is "autoweaned" in 28% and over 2-4 weeks in 44%.

Adverse Events	*Frequently*	*Occasionally*	*Rarely*
Bradycardia (Symptomatic/Asympotmatic)	*0/0*	*0/4*	*4/16*
Hypotension(Symptomatic/Asympotmatic)	*0/0*	*0/0*	*3/15*
Hypoglycemia (Symptomatic/Asympotmatic)	*0/0*	*0/3*	*5/9*
Lethargy/Sluggishness	*0*	*9*	*15*
Sleep Disturbance	*6*	*13*	*11*
Sluggishness	*0*	*7*	*14*
Bronchospasm	*0*	*5*	*12*
Cool Extremities	*3*	*9*	*13*
Gastroesphageal Reflux	*1*	*5*	*8*
Rash	*1*	*0*	*7*

Conclusion: Clinicians admit fewer patients now than 2 years prior, however 1/3 still admit patients >8 weeks of age, particularly surgeons. Beta-blocker Initiation should be standardized and recommendations based on current literature are presented.

53 CLINICAL SIGNIFICANCE OF SCREENING ELECTROCARDIOGRAMS FOR THE ADMINISTRATION OF PROPRANOLOL FOR INFANTILE HEMANGIOMAS

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Purpose: Low-dose, nonselective beta blockade is an effective treatment for problematic infantile hemangioma (IH). Screening electrocardiograms (EKG) are performed prior to the institution of propranolol to prevent the risk of exacerbating an undiagnosed heart block. How EKGs affect subsequent propranolol usage and patient management remains unclear. This study examines the value of an EKG prior to propranolol therapy in a quaternary care facility.
Methods: A retrospective chart review was performed on all infants who received propranolol (2mg/kg divided TID) to treat problematic IH at Arkansas Children's Hospital from 2008 to 2015. All available demographic, historical and clinical data were obtained. EKGs and echocardiographic data were reviewed and summarized. All EKGs were read by a pediatric cardiologist.
Results: A total of 339 patients received propranolol therapy. EKG information was available in 320 (94%). Abnormal findings were present on 46/320 (14%) of study EKGs. The most common abnormal finding was "voltage criteria for ventricular hypertophy" (n = 34). Of the 56 patients (17%) who underwent echocardiograms, 39 (70%) were abnormal. Of those patients with abnormal EKGs, 35% (16/46) required ongoing cardiology follow-up. No patient was precluded from taking propranolol due to the findings on screening EKG.
Conclusion: Screening EKGs prior to propranolol therapy are often abnormal in patients with IH, but rarely preclude therapy. Screening EKGs should continue to be performed in this patient population. These data suggest that all patients with IH, regardless of the plan for propranolol therapy, should have a screening EKG.

54 PROPRANOLOL IN COMBINATION WITH INFRARED HIGHINTESITY LASER FOR DIFFERENTIATED TREATMENT OF HEAD AND NECK INFANTILE HEMANGIOMA

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Purpose: Improvement results of treatment for patients with infantile hemangioma (IH) of the head and neck.
Methods: The study comprised 1292 patients with IH of the head and neck treated between 2001 and 2014. Tumors were diagnosed with color Doppler flow mapping. The first group of patients (n=705) was treated before 2010 with non-invasive and intralesional diode laser at 970 and 1060 nm. The second group (n=275) was managed with propranolol since 2010. In 2011 patients with intensive blood flow IH (n=312, group three) underwent propranolol treatment in combination with laser thermotherapy.
Results: Laser thermotherapy in the first group was effective in all cases but in patients with intensive blood flow IH (25,4%) treatment was done iteratively. All patients of the second group were given propranolol 1,3-1,5 mg/kg/day for 8,8±2,6 month. Tumor regress was noted in 46,8% of patients. In other patients of the second group with intensive blood flow this dosage of propranolol was ineffective. Combination of propranolol and intralesional laser thermotherapy in patients with intensive blood flow IH (group three) decreased frequency of iterative laser interventions to 7,9% in compare with first group ($p<0,01$) and duration of propranolol treatment to 4,5 ±2,4 month ($p<0,05$). This method of treatment led to persistent involution of IH in 99,4% patient of the third group with good aesthetic result in 97,5%.
Conclusion: Treatment of head and neck IH must be differentiated. In patients with intensive blood flow IH combination of propranolol and intralesional laser thermotherapy is the method of choice.

55 Propranolol versus Steroids for the Treatment of Ulcerated Hemangiomas

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Purpose: Infantile hemangiomas are the most common tumors of infancy. There has been a recent paradigm shift from steroids to the use of propranolol for treatment. Ulceration of infantile hemangiomas is one of the common indications for medical intervention. This study compares the efficacy of steroids and propranolol for the treatment of ulcerated hemangiomas.
Methods: A retrospective chart review was conducted on 152 patients with ulcerated hemangiomas who presented to a single tertiary care institution between 2007 and 2014. The time to heal was compared between patients treated only with propranolol (n=29) and those treated only with steroids (n=27). For treatment of ulcerations, the propranolol dose was 1mg/kg/day. Multivariate logistic regression and Kaplan Meier survival methods were used for data analysis.
Results: There were no significant differences in the demographics of the two treatment groups including age, gender, size of ulceration, insurance status or location. Patients treated with steroids had mean time to healing of 198 days while those treated with propranolol had a mean healing-time of 105 days ($p<0.05$). 7 patients (26%) treated with steroids and 4 (14%) treated with propranolol did not heal and ultimately underwent surgical resection. 11 (41%) steroid patients and 13 (45%) propranolol patients also underwent laser treatments. Propranolol and steroid treatment groups heal at a comparable rate in patients receiving treatment for less than 125 days. Propranolol shows faster healing rates after 125 days. Fewer adverse effects were seen in the propranolol group, however a propranolol treatment course costs 44% more than a steroids treatment course.
Conclusion: This is the largest study of ulcerated hemangiomas and the first to compare propranolol versus corticosteroids. The overall healing time is lengthy regardless of treatment modality and can cause significant morbidities and quality of life issues for the patient and family. Propranolol appears to be more efficient in the treatment of ulcerated hemangiomas but is significantly more expensive. Adverse effects seen in patients treated with corticosteroids were more frequent and severe. Further studies are required to examine the role of propranolol dose escalation and other therapies for improvement in the significant morbidities in patients with ulcerated hemangiomas.

56 Has Propranolol use eliminated the need for surgical and/or laser intervention in infantile haemangiomas treatment? Over 6,5 years of experience.

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Purpose: Presentation of over 6,5 years of experience in Propranolol use in haemangiomas' treatment. Analysis of the subsequent need for surgical and/or laser intervention.
Methods: The invention of a novel pharmacological therapy with beta-blockers has revolutionized the process of infantile haemangiomas treatment. In Poland it was initiated in Gdansk in March 2009. During more then 6,5 years (III 2009 – XI 2015) we have introduced oral systemic therapy with Propranolol in 278 children, 222 girls (80%) and 56 boys (20%); aged between 4 weeks and 5,5 years. The majority of targeted lesions were in the proliferative phase 265(95,3%); in 10 cases (3,6%) the purpose of the treatment was to accelerate the speed of involution. 3 lesions (1,1%) were not infantile haemangiomas. The response to treatment (growth inhibition, shrinkage in size, healing of ulcerations etc.) was observed in 272 (97,8%). Final assessment was mainly focused on patients' appearance, pointing out the need for subsequent surgery or laser therapy.
Results: The treatment was completed in 235 (84,5%) patients and lasted from 4 months to 28 months (mean 11,7 months); in 2 cases with a wrong diagnosis it was stopped immediately, followed by a surgical approach. Lesions with an unsatisfactory response to pharmacotherapy (3 cases – 1,1%) were removed surgically. 3 patients were lost to follow-up. Rebound effect was observed in 27 patients (9,7%) with a good response to reintroduction of Propranolol in all cases. 11 patients have experienced multiple relapses with a maximum number of 4. 41 patients were operated on with 49 excisional procedures performed; 8 of them had surgery while still on Propranolol. 38 patients had laser therapy (57 procedures), mostly with pulsed dye laser, but also Nd-YAG in some cases. There is also a significant number of patients waiting for surgery (21 patients) and laser treatment (35 patients). In summary, 135 out of 235 patients (57,4%), who had completed the systemic Propranolol treatment for a haemangioma, required or does require additional invasive procedures, such as surgery or laser. There was only one significant adverse reaction notified – a hypoglycemia.
Conclusion: Although, systemic Propranolol seems to be a method of choice among patients with clinically significant infantile haemangiomas, however, there are lesions resistant to the treatment, but, first of all, more then a half (57,4%) still requires an invasive procedure upon completion of therapy. Early introduction of treatment offers the best chances for a good result. Our 6,5 years experience confirms the safety of this form of therapy.

57 Pharmacokinetics of Topical Timolol for Treatment of Infantile Hemangioma

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Purpose: The success of oral propranolol for infantile hemangiomas (IH) treatment has led many practitioners to use commercially available timolol ophthalmic solutions for off-label treatment of IH. Studies in adults with intraocular application of timolol have demonstrated systemic absorption, however, information regarding the pharmacokinetics of timolol applied to cutaneous infantile hemangioma in children is lacking.

Methods: We partnered with the Pediatric Trials Network's Pharmacokinetics of Understudied Drugs Administered to Children per Standard of Care Trial (POPS) to obtain serum pharmacokinetic samples in infants being treated with topical timolol for IH. Children <2 years of age receiving timolol for treatment of IH as prescribed by their treating caregiver were enrolled across 5 sites in the POPS study. The study was designed to gather samples from a range of different clinical scenarios; therefore, enrollees were stratified by post-menstrual age and post-natal age at time of sampling, and by risk for systemic absorption. After enrollment, serum samples were collected and assayed. Demographic data, dosing and route of administration data, clinical photographs, and hemangioma specific data were collected.

Results: A total of 42 children with mean chronological age at sampling of 8.3 months with a range of 35 weeks postmenstrual age to 2 years of age. Dosing ranged from 1-6 drops daily. Forty-five percent (19/42) children enrolled into this study were considered high risk for systemic absorption based on high dose (≥0.3 mg/kg/day), ulcerated IH, applied under occlusion, or applied to eyelid or mucosal surface.

Conclusion: The purpose of this study is to provide important pharmacokinetic data for treatment of IH with topical timolol and correlate that with dose, age of child, application site, condition of the hemangioma, and response to therapy. These results will serve as a tool to better understand drug exposure in children receiving this topical application of timolol for IH.

58 An Update on Effect and Efficacy of Propranolol for Pediatric Growth and Development

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Purpose: Propranolol is widely accepted for treatment of problematic infantile hemangioma (IH). Concerns regarding the effect of propranolol on child growth and development have been raised. The aim of this study is to examine developmental progression in children undergoing propranolol therapy for IH as well as the tolerability and efficacy of therapy.

Methods: 184 patients (47 males, 137 females) undergoing treatment for IH with propranolol were included in the study. Patients were separated into two cohorts: those with (60) and without (124) co-morbidities that affect growth and development. Heights and weights were obtained and guardians completed questionnaires regarding efficacy of treatment, tolerance and satisfaction. Fine and gross motor milestones were assessed at from 4 to 48 months. Anthropomorphic measurements were compared to World Health Organization (WHO) normative data.

Results: 184 patients had heights and weights measured while 97 patients had weight alone. Most patients met fine and gross motor milestones at or before the target age. There was no statistical difference in milestone achievement between the two cohorts ($p>0.06$). Height-for-age was not different than WHO normative data, but BMI-for-age and weight-for-height was significantly higher ($p<0.02$). This observation was pronounced in patients undergoing therapy for greater than 5 months. Overall, therapy was well tolerated: 75.7% respondents were satisfied, 82% reported decrease in size and 70% reported color change. 36.2% of respondents reported side effects. The most common was reflux. 12.4% noted rebound after stopping propranolol.

Conclusion: Propranolol is well tolerated and effective for problematic IH. It is not associated with a delay in achieving developmental milestones however it is associated with a higher weight-for-length and BMI-for-age compared to WHO normative data. These findings should be interpreted cautiously as findings may be characteristic of the patient population in which this study was conducted. Further studies are needed to validate these findings and determine safety.

59 Social Impact of Facial Infantile Hemangiomas on Preteen Children: Treated Versus Untreated.

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Purpose: To assess the social impact of involuted treated and untreated facial infantile hemangiomas (IH) in preteens.
Methods: Observational, cross-sectional study of social anxiety and skills in preteens with history of facial IHs: 1. Social Anxiety Scales for Children-Revised (SASC-R): -FNE: Fear of Negative Evaluation -SAD-New: Social Avoidance/Distress in New Situations 2. Social Competency Inventory (SCI): -Prosocial Behavior -Social Initiative 144/236 parents of eligible preteens were reachable by telephone and 30/144 participated. Main Outcome and Measures: T tests were used to compare survey scores with established normative data and between gender and treatment versus non-treatment groups.
Results: Subjects' mean age was 10.0 years (5.4–12.9) with a 2:1 female:male ratio. 83% had a single IH with the periocular region as the most common site followed by the cheek, nose, lip/perioral, and ear. 18 subjects had prior IH treatment. SASC-R: Social anxiety of subjects was not increased over normative data however subjects that did not receive IH treatment had significantly greater anxiety for new situations compared to those subjects that did receive treatment (SAD-New mean 15.6 vs. 11.5 p=0.0245). SCI: Prosocial Orientation of subjects was similar to normative data (3.96 vs. 3.89, p=0.501) however Social Initiative tended to be poorer in subjects compared to normative controls (mean 3.81 vs. 4.03 p = 0.065). Furthermore Social Initiative was significantly poorer in untreated vs. treated subjects (mean 3.45 vs 4.03 p = 0.006).
Conclusion: Conclusions: Preteen children with involuted, untreated facial IH have higher social anxiety scores in new situations and decreased social initiative scores compared to children who did not receive treatment. This study raises important considerations for whether early treatment of facial IH in cosmetically sensitive areas has a beneficial impact on social skills in preteens.

60 Why patients with infantile hemangioma still require surgical treatment in the propranolol era?

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Purpose: Despite the proven efficacy and safety of beta-blockers in the treatment of infantile hemangiomas (IH), many patients still require surgical treatment. The aim of our study is to analize current indications for surgical treatment of IH in a referral vascular anomalies center
Methods: A retrospective study from 2009 until 2015, including 45 children (38 females and 7 males) referred for surgical treatment of an IH was undertaken (group A). . Epidemiological, clinical and treatment data were collected and variables analysed. In the same period of time a cohort of 42 children aged less than 8 weeks of life and first evaluated at our institution , received propranolol in the context of facial hemangiomas (group B).
Results: Of the 45 patients included in the group A , 22 patients were not offered any treatment as it was not considered necessary, 16 were treated with a systemic b-blocker, 3 patients, refused propranolol administration for fear of potential adverse side effects and the remaining 4 were offered an alternative treatment. The average age of initiation of treatment with propranolol was 10.58 months and the average age at time of surgery was 29.11 months . In comparison, only one patient in the group B receiving systemic beta –blocker in the first 8 weeks of life, needed surgical excision of a lower lip IH.
Conclusion: Not receiving drug treatment or delay in its administration are the main causes of surgical treatment of infantile hemangiomas. Therefore it is important to improve protocols to establish an earlier evaluation and preventive guidelines in order to reduce the need for subsequent surgery.

61 10 yrs follow up of autolog fat injection of severe ulcerating hemangiomas

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Purpose: To investigate whether the patient´s own fatcells could trigger the involution and heal ulceration in proliferating infantile hemangiomas (IH). Ten years ago, before propranolol , the parents of 2 infants with ulcerating hemangiomas (one protruding in front of the neck and one large on a gluttée) refused systemic steroids although their children´s IH was giving a lot of problems like pain, oozing, not thriving or sleeping well.
Methods: During general anesthesia autologous fat injections were made in respectively IH by Prof Syd Coleman plastic surgeon, expert in autologous fat injections. No previous treatment for IH. Case 1: Female infant with large ulcerating IH protruding on her right gluttée preventing her from lying or sitting on that side. Case:2 Male infant with large focal protruding ulcerating IH in front of the throat causing pain and uncomfortness. Lipoaspiration and lipofilling according to the Coleman method. Blunt small tiny canula was used and fat taken from

the lower belly respectively from the inner upper thigh. The fat was centrifuged at 1800 rpm for 3 minutes,isolating the fatty fraction before injection. No post operative problems. Immidiate pain reliefe was noted the day after.
Results: Both IH healed within a week with loss of pain and ulceration. After 3 weeks there was only whitish maculae plus on the neck still some protrusion. The IH did not show any sign of warmth, high bloodflow or swelling. Parents were very satisfied.
Conclusion: Fast result within 1 week with healing of two severe ulcerating IH after only one autologous fatinjection. No relapses were seen. Less residuals after followup at 10 year after in comparison with other large ulcerating IH. More flat and less fibrofatty tissue. Stemcell effect? Further studies are planned.

62 *Surgical management of infantile hemangioma using the purse-string technique: impact on the scar*

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Purpose: To asses scar size reduction (after surgery) using the Purse-String (PS) technique compared to elliptic resection for Infantile Hemangioma (IH).
Methods: Retrospective study of 431 patients with IH or its sequelae, referred to the multidisciplinary Center for Vascular anomalies between 2005 and 2012. Photographs taken before and after management were analyzed. Statistical analyses were conducted considering each tumor independently. The study was accepted by our local ethics committee. 126 patients underwent surgery, 57 were treated using the PS technique. Fourteen patients could not be used for analysis due to lack of information and two patients were operated using a PS for more than one IH. All tumors were measured by estimating the two diameters of an elliptic form covering the majority of the lesion. The scar length of an elliptic resection was estimated using the double of the length of the shortest diameter. The scar lengths of both techniques were compared using a Paired Sample T-Test.
Results: The 48 IH reviewed in our study had a mean surface before surgery of 8.68 cm2 (±7.43 cm2). 41 IH operated by PS presented a mean scar length of 2.57 cm (±1.25 cm) compared to a scar length estimation for an elliptic resection of 5.95 cm (±2.50 cm) (Paired T-test, P-Value < 0,001). Seven scars (n=7/48, 14.58%) suffered from scar widening and the mean scar surface was 3.51 cm2 (±2.72 cm2) opposed to an initial mean surface of 6.26 cm2 (±2.37 cm2) before surgery (Paired T-test, P-Value = 0,019). Four patients needed scar revision and three patients underwent subsequent lipofilling.

63 *Early resection of infantile hemangiomas: short term and long term outcomes*

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Purpose: In 2008 propranolol became the first choice therapy for complicated infantile hemangioma (IH), changing its management significantly. Early resection however, may still be indicated even before the involution-phase. This study evaluates the incidence, patient characteristics and results of early resection of IH. A second objective is to determine possible changes after introduction of propranolol. This will provide information about indications, complications and long term outcomes.
Methods: A retrospective cohort study was performed including all IH patients who underwent surgery before the involution-phase in a tertiary referral centre between 2000 and 2015. Patient, hemangioma and surgical data were retrieved from the EPD. Statistical analysis (Unpaired t-test, Fisher's exact, Fisher-Freeman-Halton) was performed using SPSS 20.0.
Results: Of 494 patients with an IH, 27 patients underwent surgery before the involution-phase (5.5%) with a main age at the time of surgery of 11.6 months (SD 8). The most common location for the resected IH was the head-neck region. Main indications were developmental impairment (37.0%), ulceration (33.3%) and severe cosmetic concerns (22.2%). Complications occurred in seven patients: peri-operative blood loss (4), wound dehiscence (2) and wound-infection (1). Eighty-five percent of the patients were satisfied with the aesthetic outcome without additional surgery. The mean follow-up time was almost eight years (SD 4,5). There was a significant decline in surgical procedures after the introduction of propranolol: 1 every 5 months to 1 every 8 months on average. Furthermore, indications changed significantly: more patients with ulceration; less with developmental impairment or cosmetic concerns.
Conclusion: This study presents a complete overview of early surgery of IH in a tertiary referral center. If patient-selection is done carefully, surgery is safe with good aesthetic outcome. The introduction of propranolol not only resulted in a decline in early surgical resections but also changed indication for surgery towards ulcerated IH.

64 Diagnosis and Treatment of Hepatic Venous Malformations

Wayne Yakes

Vascular Malformation Center

Purpose: To determine the role of ethanol endovascular therapy in the management of liver "hemangioma" (venous malformation of the liver). Currently, only surgical lobectomy with its attendant severe morbidity is the only other treatment option.
Methods: Ten patients underwent thirty-four treatments by direct puncture into the venous malformation involving single and multiple lobes of the liver. Three males and seven females with age range of 30 years – 50 years, mean age, 40 years. Patients underwent arteriography and direct puncture repair of the malformations in the liver; all patients had follow-up performed by CT and MR imaging. Early in the series one patient developed a fever and was placed on antibiotics. Currently all patients are placed on Flagyl and Levoquin for 7 days.
Results: Reduction in the vein malformation within the liver was noted in all patients. More importantly, their pain symptoms resolved. One patient's intractable hiccups resolved. One patient developed a left foot drop due to pressure on the sciatic nerve because she was thin and laying on a hard angiographic table. This completely resolved. One patient developed a fever and was successfully treated with antibiotic therapy. Patients were followed-up by CT and MR imaging documenting the shrinkage of single and multiple lesions (follow-up range: 13 – 52 months; mean: 37 months). Three of ten patients had minor abdominal and right shoulder pain post-procedure.
Conclusion: Reduction in the vein malformation within the liver was noted in all patients. More importantly, their pain symptoms resolved. One patient's intractable hiccups resolved. One patient developed a left foot drop due to pressure on the sciatic nerve because she was thin and laying on a hard angiographic table. This completely resolved. One patient developed a fever and was successfully treated with antibiotic therapy. Patients were followed-up by CT and MR imaging documenting the shrinkage of single and multiple lesions (follow-up range: 13 – 52 months; mean: 37 months). Three of ten patients had minor abdominal and right shoulder pain post-procedure.

65 PNEUMONECTOMY IN A PEDIATRIC PATIENT WITH RENDU OSLER- WEBER SYNDROME. CASE REPORT

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Purpose: Hereditary Hemorrhagic Telangiectasia (HHT) is a rare condition in pediatric population. We report a case of a 7 year-old patient with hemoptysis and evidence of multiple pulmonary arteriovenous fistula who underwent a right pneumonectomy.
Methods: Case report
Results: A 7 year-old girl, with previous diagnosis of HHT, was referred to our institution after 5 days of several episodes of hemoptysis without hemodynamic decompensation which stopped spontaneously. Past medical history includes a first episode of respiratory distress and cianosis, interpreted and treated as pneumonia, but because of being unresponsive to treatment, a chest CT was performed, reaching the diagnosis of arteriovenous (AV) fistula in the right lung. Two consecutive embolization procedures were performed, within 2 years. At the age of five, she arrives to our HHT unit with aggravation of her symptoms, cyanosis, polyglobulia, acropachy, fatigues and headaches, basal pulse oxygen saturation of 84%. An embolization of the pulmonary fistulas was performed in our institution. On physical examination she was stable, with normal breathing and no signs of bleeding. A digital subtraction angiography was performed. Multiple bronchopulmonary AV fistulas along the right lung were observed. Due to the number and localization involved, embolization was not feasible. The patient was discussed, reaching the decision of a right pneumonectomy to avoid further complications. Right pneumonectomy was performed. She recovered well, with peridural catheter for analgesia and 24 hours of suplementary oxygen. A drainage tube was left closed, and was removed on the fifth day. She was discharged and did not present new episodes of hemoptysis after one year follow-up.
Conclusion: In HHT patients with large compromise of the lungs, bleeding can be a serious emergency. Pneumonectomy can be performed without important complications in these patients, but evaluation of surgical indication should be done on a per-patient basis.

66 *Sclerotherapy for the Treatment of Benign Vascular Malformations in the Oral cavity- A Different Approach for Treatment*

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Purpose: Benign vascular malformations (VM) may lead to esthetic complications, pain and spontaneous bleeding in the oral cavity. Sclerotherapy is an expectable and well established treatment method. The purpose of the current study was to assess the effectiveness and morbidity of sclerotherapy by intralesional injection of 5% ethanolamine oleate (EO).
Methods: Twenty patients with a total of 25 VM lesions treated with 5% EO were retrospectively assessed. A descriptive statistical analysis was performed.
Results: Lesions' diameter ranged from 3-30 mm. All lesions showed total clinical regression with excellent aesthetic results. No recurrence occurred after an average of 18 month follow-up. In most of the cases, the dosage required for complete resolution was 0.04 ml/mm (18, 72%), and a single application was sufficient (19, 76%). One patient needed further intervention for debridement of necrotic tissue, after which complete healing occurred. A single injection up to 0.5 ml of 5% EO found to be well tolerable by the patients, with minimal side effects. Complete resolution achieved after 8-12 weeks.
Conclusion: Sclerotherapy by 5% EO is an effective treatment with minimal morbidity when applied in limited dosage. It seems that the total effective dosage and the number of applications necessary are lower than stated in previous publications. On the other hand, the waiting time required for complete healing is usually longer than previously reported; therefore prolonged interval between treatment sessions should be considered as well.

67 *Intralesional lidocaine anesthesia: a novel local anesthesia technique facilitating ethanol sclerotherapy of venous malformation*

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Purpose: To describe a novel anesthesia, intralesional lidocaine anesthesia (ILA), for ethanol sclerotherapy of venous malformation and evaluate the efficacy and safety. Actually, It has been originally used by our team for more than 10 years in more than 1500 sessions of alcohol sclerotherapy annually for the cases with venous malformations.
Methods: A prospective study of 100 patients with venous malformations undergoing 100 sclerotherapy procedures with intralesional lidocaine anesthesia (ILA) was conducted. We adopted concentration of lidocaine as low as 0.25% . Pain was evaluated by numeric rating scale (NRS) immediately following the procedure. The grade of pain was classified by the NRS as no pain (0), mild (1-3), moderate (4-6), and severe (7-10). Local and systemic complications caused by lidocaine were recorded.
Results: The median injected volume of absolute ethanol and 0.25% lidocaine was 5.9 mL and 17.0 mL. In ILA group, 13 patients had no pain during the procedure, 42 patients had mild pain, 38 patients had moderate pain and 7 patients had severe pain. No local or systemic complications attributed to lidocaine were reported.
Conclusion: In a limited series, intralesional lidocaine anethesia seems to be efficient and safe in pain management for ethanol sclerotherapy of venous malformation. This innovative anesthesia technique may be a promising first approach for the ethanol sclerotherapy of VMs, as it is easy to handle and has minimal sequelae.

68 *PERCUTANEOUS SCLEROTHERAPHY OF EXTENSIVE FACIAL VENOUS MALFORMATION INVOLVING THE SCLERA OF EYE. CASE REPORT*

Galli Eduardo

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Purpose: to show the results of the follow up after 2 years of percutaneous treatment of a left facial venous malformation involving the sclera and superior eyelid.
Methods: a 32 year female patient was treated for palpebral and scleral venous malformation in one single session using bleomycin sclerosis.
Results: Significative reduction of the lesions was observed after 2 years follow-up, without complications.
Conclusion: Percutaneous sclerotheraphy was a safe and effective treatment for venous malformation involving the sclera.

69 How to combine alcohol embolization and surgical therapy to preserve the facial nerves in managing challenging AVM at head neck region?

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Purpose: Arteriovenous malformations (AVMs) are congenital vascular anomalies, that tend to behave aggressively with unpredictable growth and tissue destruction. It can be found at any part of body, but the most common regions are head and neck. Facial AVM are cosmetically and psychologically significant. Treatments of complicated AVMs are still challenge to plastic surgeons utilizing conventional preoperational embolization and surgical resection therapies because the lesion may be surgical inaccessible and facial nerves are often involved. For these cases with huge AVM, multiple sessions of alcohol embolization can not achieve immediately relieve large blood loss because of ulcertaition, or be too difficult to performed because of patient's lesion. Hence, we have to combine surgical approaches with alcohol embolization together to preserve facial nerves and cosmetically reconstruct the facial defect.
Methods: A total of 8 cases with AVM of head neck region were enrolled in this series. We preserved deeper part of facial AVM as well as facial nerves by multiple sessions of alcohol embolization followed by facial skin reconstruction with expanded flaps in 4 cases. For other 4 cases with extremely large and dangerous auricular and facial AVM, we resected the major AVM lesion and preserved the facial nerve at mastoid process area, followed by alcohol embolization of residual lesion at second stage.
Results: Facial nerves and function were well preserved in all these cases without recurrence symptomatically and radiologically.
Conclusion: Alcohol embolization is now independent therapy of AVM, not an adjunctive one. The goal of the alcohol embolization is to achieve symptom control with better aesthetic results, limited morbidity and less recurrence than traditional interventional or surgical therapies. However, not all cases with AVM can be cured by ethanol embolization such as substantial lesion with infiltrating microfistulas, which is the better candidate of surgical approach. For some emergent cases with bleeding ulceration, surgical management can also be a choice to save the life. Therefore, the issue about which is better between surgery and alcohol embolization should not spark more controversy, we need to widely and flexibly combine them together for better quality of patients' life if each of them can not achieve alone.

70 Ethanol Embolotherapy Management of Pelvic Arteriovenous Malformations

Wayne Yakes

Vascular Malformation Center

Purpose: To determine the curative role of ethanol endovascular and/or ethanol coils in the treatment of large pelvic arteriovenous malformations (AVMs).
Methods: Forty-eight patients (25 females; 23 males; age range: 4 - 86 years; mean age: 37 years) underwent 315 endovascular procedures (6.5 procedure/patient) to treat their pelvic AVMs. Two patients had bilateral pelvic AVMs (1 male; 1 female). Two patients had traumatic lesions (2 males). Patients underwent transarterial, retro-grade transvenous, and direct puncture embolization procedures. Embolic agents included absolute ethanol (Dehydrated alcohol injection, USP; American Regent, Inc.; Shirley, NY); Cook stainless steel and Nester fibered coils (Cook Inc.; Bloomington, IN), and Terumo Azur Hydrocoils (Terumo Europe; Leuven, Belgium).
Results: Thirty-six patients are cured of their pelvic AVM (mean follow-up: 43 months) and 12 patients' treatments are on-going. Pelvic AVMs were cured by using ethanol, coils, or ethanol with coils. The addition of coils was particularly useful in those AVMs with enlarged venous outflows and in those AVMs with giant venous aneurysms. Three patients suffered transient sciatic nerve injuries. One patient suffered an ipsilateral perineal numbness that also completely resolved. Four instances of perineal blistering and tissue injury with one injection, was treated uneventfully. One patient had a rectal wall injury requiring bowel diversion, and after healing, underwent re-anastamosis. One elderly patient died within 30 days of a 4th procedure from pulmonary embolus (PE).
Conclusion: Endovascular approaches to manage pelvic AVM have proven to be curative at long-term follow-up. In our cases, surgery adjunctively to remove the AVM has not been required. Despite previous embolizations with coils, glue, and surgical ligations prior to being referred to our institution, endovascular and direct puncture approaches using ethanol, ethanol and coils, has proven to curatively manage pelvic AVMs involving soft tissue and bone with low complication rates and no recurrences.

71 The Abernathy Malformation: current requirements from invasive angiography

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Purpose: To describe the catheter angiographic techniques required when children with the Abernathy malformation / congenital extrahepatic porto-systemic shunt (CEPSS) are being considered for closure (surgical / radiological / combined) of the malformation.
Methods: A 4-year restrospective review (ending 2015) was undertaken on 5 consecutive patients undergoing catheter angiographic assessment of the Abernathy malformation. Patient records, imaging and angiographic procedures were analysed.
Results: Practical tips at angiography:- 1. Shunt venograms and pressure measurements (with and without balloon occlusion testing of the shunt) are routinely performed on all patients. 2. Inflation of the shunt occlusion balloon should not obstruct the hepatic vein outflow. 3. SMAP is not routinely required, however coincidental intrahepatic porto-systemic shunts were shown in one case. 4. Wedge hepatic venography has not previously been described in the Abernathy malformation assessment and can demonstrate patency of the intrahepatic portal veins.
Conclusion: The angiographic findings of the Abernathy malformation are illustrated in this poster presentation. This rare type of major named vessel vascular malformation demands an understanding of the shunt anatomy and the requirements from invasive angiography. The interventional radiologist has an important role in assessing these features prior to shunt closure. Wedge hepatic venography has not previously been described in the assessment of the Abernathy malformation and can demonstrate patency of the intrahepatic portal veins. This poster highlights the important features during the angiographic assessment of the Abernathy malformation.

72 Indications for puncture method of treatment of children with lymphatic and lymphovenous malformations of head and neck area.

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Purpose: To determine the indications for sclerotherapy of children with lymphatic (LM) and lymphovenous (LVM) malformations of head and neck area.
Methods: The results of treatment of 48 children aged from 8 months to 16 years were analyzed. There were 29 patients with LM (60.4%), 19 of children (39.6%) had LVM, 36 of patients (75%) had macrocystic form, 12 of patients (25%) had a mixed form. Ultrasound, MRI, fiberoptic laryngoscopy were used for patients' examination. 2% aqueous solution of doxycycline (31 patients) and 0.15% aqueous solution of bleomycin (17 children) were used as sclerosants.
Results: The results were evaluated after a single injection of sclerosant. The result was defined as excellent if formation volume decreased for more than 90%, good result - from 50 to 90%, satisfactory - 30% to 50%, unsatisfactory - less than 30%. Local inflammatory reactions, dyspepsia, pain were evaluated. The following results were obtained after application of doxycycline: excellent in 20 children (64.5%), good in 5 patients (16.1%), satisfactory in 4 patients (12.9%) and negative in 2 patients (6.5%). After using of bleomycin excellent results were not obtained, good results were achieved in 11 children (64.7%), satisfactory in 2 children (11.8%), unsatisfactory in 4 patients (23.5%). The pain after doxycycline, hyperthermia within 2-3 days and dyspepsia after bleomycin were observed. One patient, 3 months of life, with an extensive macrocystic form of LM died from fulminant form of viral infection in the postoperative period.
Conclusion: Sclerotherapy of doxycycline and bleomycin solutions is the most effective treatment in case of macrocystic form of LM and LVM. Satisfactory and unsatisfactory outcomes were obtained in cases of mixed LM and LVM. In case of good result after single injection of sclerosant the continuation of treatment of children with macrocystic form of malformation might be used. Doxycycline is more effective as sclerosant.

73 TREATMENT OF TONGUE LYMPHATIC MALFORMATIONS USING PERCUTANEOUS APPROACH IN 6 PEDIATRIC PATIENTS

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Purpose: To describe our experience in percutaneous sclerotherapy in tongue lymphatic malformations.
Methods: 6 male patients (from 3 to 13 years) with symptomatic microcysts lymphatic malformation of the tongue were treated with percutaneous sclerosis using Bleomycin. One of them also received endovascular arterial embolization for severe bleeding.
Results: All patients had successful reduction of clinical symptoms and tongue size. 2 patients had acute inflamatory reaction needing prolonged hospitalization.
Conclusion: Percutaneous sclerotherapy was safe and effective treatment for lymphatic malformation of the tongue.

74 Effectiveness and safety of balloon-assisted scleroembolotherapy for subcutaneous arteriovenous malformation, AVM: A novel technique for controlling blood flow in AVM

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Purpose: Controlling of blood flow is extremely important in treatment of AVM. Without it, the more sclero-embolic agent would be used bringing about more complications and the efficacy would be less. Manual compression might be effective but insufficient. Here, we have developed a novel technique, balloon-assisted sclero-embolotherapy (BAST), using a micro balloon catheter to control blood flow. By controlling blood flow, the sclero-embolic agent is able to remain within the lesion longer, exerting more powerful sclero-embolic effect. In addition, because we do not use N-butyl cyanoacrylate (NBCA) in BAST, BAST is free from the risks associated with NBCA such as cast migration through accompanying high-flow arteriovenous shunting, sticking of casts to the catheter and unexpected embolization of normal vessels. The purpose of this study was to evaluate the effects and safety of BAST.
Methods: Thirty-four patients with AVM were enrolled in this study and 36 BAST sessions were performed. The micro balloon catheter (2.7 Fr) was inserted and advanced as close as possible to the lesion and arteriography was performed both before and after balloon inflation to confirm blood flow control. After confirming blood flow control, absolute ethanol, polidocanol or monoethanolamine oleate foam was injected. Decreased contrast enhancement on arteriography, changes in clinical symptoms (pain, skin ulceration, cosmetic problems) and complications were assessed.
Results: Adequately decreased contrast enhancement on arteriography after treatment was confirmed in all patients. Thirty-one patients (91%) experienced clinical symptom improvement. In 34 lesions, 12 lesions were 5cm or less in size. In this 12 lesions, 4 lesions disappeared after treatment and had complete remission on follow up CTA. No major complications requiring surgical treatment occurred. Minor complications, blistering and skin necrosis occurred in only one patient, and healed within a month.
Conclusion: BAST for high-flow AVMs was effective in this cohort and might be safer than conventional procedures.

75 Transcutaneous Glue Extrusion Following Embolization of Arteriovenous Malformations

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Purpose: To describe extrusion of glue following embolization of arteriovenous malformation (AVM) in four patients.
Methods: We reviewed the clinical and imaging findings in patients who developed glue extrusion following embolization. Glue (N-butyl cyanoacrylate, Histoacryl, B. Braun) was used as an embolic agent for AVM.
Results: Four patients with AVM of the lower extremity developed post- embolization glue extrusion. One patient had PTEN hamartoma tumor syndrome and large AVM of the left thigh (22-year-old male), one had AVM of the calf (18- year-old female) and two AVM of the foot (6-year-old female and 20-year-old male). In addition, there was a history of ulceration prior to embolization (n=3) and severe bleeding (n=1). The number of embolization procedures was 2-6 with total glue volume of 2.9-29.1 mL. The treated vessels were primarily located in the subcutis. The tissue reaction was evident by 3-8 weeks. In 2 patients, glue extrusion was associated with local infection. Treatment included glue extraction via small incisions, wound care including serial debridement, excision of glue-containing vessels and surrounding granulomatous tissue, partial closure and antibiotics. Except for one foot AVM, wound eventually healed. Histopathologic findings in patient # 1 demonstrated acute and chronic inflammation and foreign body giant cell reaction to foreign material.
Conclusion: The risk of transcutaneous extrusion of glue following embolization of arteriovenous malformation is likely increased with subcutaneous location, large volume of glue and preexisting ulceration. Extraction of glue casts is necessary for wound healing.

76 Intralesional Bleomycin Injections for Vascular Malformations: A Systematic Review and Meta-Analysis

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Purpose: Vascular malformations are congenital anomalies of the vascular system. Intralesional injections with the chemotherapeutic and sclerosing agent bleomycin are commonly used to treat vascular malformations. However, pulmonary fibrosis could potentially be a severe complication, known from systemic bleomycin therapy for malignancies. In this study, we investigate the effectiveness and safety

of bleomycin (A2, B2 and A5) injections for vascular malformations, when possible relative to other sclerosants.

Methods: A PubMed,EMBASE, CENTRAL and grey literature search for studies (1995-now), reporting outcome of intralesional bleomycin in patients with vascular malformations (n≥10). Predefined outcome measures of interest were size reduction, symptom relief, Quality of Life, adverse events (including pulmonary fibrosis) and patient satisfaction.

Results: 27 studies enrolling 1325 patients were included, 4 were eligible for meta-analysis. Quality of evidence was generally low. Good to excellent size reduction was reported in 84% of lymphatic and 87% of venous malformations. Pulmonary fibrosis did not occur in the included studies. Meta-analysis of venous malformations treated with bleomycin versus other sclerosants, showed similar size reduction (OR 0.67, 95%CI [0.24-1.88]), but a significant lower adverse event rate (OR 0.1, 95%CI [0.03-0.39]) and less severe complications after bleomycin. Symptom relief, QoL and patient satisfaction were inadequately reported.

Conclusion: Our data suggest that bleomycin injections are effective in reducing the size of lymphatic and venous malformations, and lead to a lower adverse event rate and less severe complications than other sclerosants. The included literature does not provide evidence that pulmonary fibrosis is a complication of intralesional bleomycin injections.

77 ROLE OF PERCUTANEOUS DIRECT PUNCTURE SCLEROTHERAPY WITH BLEOMYCIN IN THE MULTIMODALITY TREATMENT OF PEDIATRIC HEAD AND NECK ARTERIOVENOUS MALFORMATIONS

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Purpose: Introduction: Arteriovenous malformations (AVMs) of the head and neck (HN) are challenging lesions to treat. Percutaneous direct puncture sclerotherapy (PDPS) for treatment of AVMs has been reported, but the use of bleomycin has not been described. Objectives: To examine the role of bleomycin PDPS in the treatment of pediatric HN AVMs.

Methods: Methods: Retrospective chart review was performed of all pediatric patients with HN AVMs treated at our institution with PDPS using bleomycin. Clinical data including patient demographics, other treatment modalities, complications, and outcomes were recorded.

Results: Results: Six children received bleomycin PDPS. The average age at presentation was 7.8 years (1.6 to 18.4 years). All except one patient had diffuse HN disease. All patients were managed with multimodality treatment including various combinations of laser therapy, sclerotherapy, embolization, or surgical excision. Average length of follow-up was 1.4 ± 0.8 years (0.3 to 2.3 years). Four of the five diffuse HN AVMs received two treatments of bleomycin PDPS. The final patient received only one treatment to date. Each patient demonstrated decreased AVM size following the bleomycin injection(s) with 83% experiencing decreased skin/mucosal discoloration (likely a benefit from laser therapy). A focal upper lip AVM experienced complete clinical resolution after 4 multimodality treatment sessions; bleomycin provided her the best result. There were no major complications. Hyperpigmentation occurred in one patient.

Conclusion: Conclusion: PDPS using bleomycin has a role in the multimodality treatment of pediatric HN AVMs as evidenced by this small cohort. Precautions should be followed according to institutional chemotherapeutic protocols for bleomycin use while drug dosages are closely monitored.

78 MRI-ROI (Region of Interest) Imaging Reconstruction and Regression Measurement in Venous Malformation after Sclerotherapy

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Purpose: This study introduces the application of MRI (Magnetic Resonance Image) - ROI (region of interest) imaging reconstruction to evaluate the efficacy and clinical research of the sclerotherapy based on the 18 patients on the head and neck of venous malformations(VMs).

Methods: In this study, a total of 147 patients with peripheral venous malformations were treated by our research team. A retrospective analysis was conducted, compised of 18 patients with venous malformation and with fully qualified MRI data, from October 2012 to March 2015 in our clinic. All patients treated either once or twice in our clinic were divided into two groups. Percutaneous sclerotherapy was performed by direct injection of Ethanol (group A) or Polidocanol foam sclerosants (group B). Patients underwent MRI before and after sclerotherapy. We then imported MRI data into Mimics18.0 software. We have followed up these patients for 30 months after treatment. The threshold ranges of venous malformations in ROI MRI were selected. The regression rates of lesions were compared before and after sclerotherapy.

Results: By MRI-ROI volume assessment, the three dimensional reconstruction of volume can be used for regression measurement in venous malformations after sclerothearpy. The effects of VMs load percentage ranges in this study were divided into 4 levels, with Level I being poor(0%~25%) and level II primary(26%~50%) and level III as well(51%~75%) and level IV excellent (76%~100%). Level III and Level IV percentage are considered as valid. Group A had 10 out of 11 effective cases (45%). Group B had 6 out of 7 effective cases (86%).

Conclusion: MRI-ROI (region of interest) imaging reconstruction and regression measurement can reflect and evaluate the regression rates of the lesion after percutaneous sclerotherapy, of the 18 patients on the head and neck of limited Vms. Our experiences demonstrate that it is highly potential for the evaluation and prediction of treatment outcome for patients with VM after sclerotherapy.

79 THE ROLE OF TRANSARTERIAL LUNG PERFUSION SCINTIGRAPHY (TLPS) IN DIFFERENTIAL DIAGNOSIS HIGHFLOW AND LOW –FLOW VASCULAR MALFORMATIONS

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Purpose: Clinical behavior and management of high-flow and low-flow vascular malformations (VM) differs, therefore accurate diagnosis is important in treatment planning. Traditional diagnostic methods can be inadequate in distinguishing complicated VM forms. The aim of our study was to assess the role of transarterial lung perfusion scintigraphy(TLPS) in differential diagnosis of high-flow and low-flow VMs.
Methods: 40 patients with expected arteriovenous malformations (AVMs) or other congenital VM containing arteriovenous(A-V) fistulas were studied with TLPS and analyzed retrospectively. The results of A-V shunt on TLPS were compared with clinical data, ultrasonography, magnetic resonance, computed tomography, angiography, histology studies and assessed against final clinical diagnosis. TLPS results were classified based on A-V shunting into insignificant(0%-10%) or significant(10%-100%). The test was evaluated for accuracy, sensitivity, specificity, positive and negative predictive values.
Results: 45 TLPS tests in 40 patients aged 12-65 years (mean 25.23 years) were performed. Lesions were located in: lower extremities - 24, gluteal/pelvic region - 9, upper extremities - 5, trunk - 2. 5 lesions were localized, others were diffuse. Significant A-V shunting was in 19 cases and insignificant in 26. TLPS test helped confirm diagnosis in 18 high-flow AVMs and 15 mixed VMs. In 8 VMs the test correctly rejected diagnosis of high-flow lesion, in 3 high-flow and 1 mixed VM the study did not aid in making a definitive diagnosis. Those 3 high-flow lesions were small and localized. TPLS was able to differentiate lesions in 41 cases, with an accuracy rate of 91.1%, sensitivity 85.7%, specificity 95.8%, positive predictive value 94.7%, negative predictive value 88.5%.
Conclusion: TLPS diagnostic test plays an important role in differentia sl diagnosis of high-flow and low-flow VMs, especially in complicated cases. TLPS has high accuracy, specificity and sensitivity for most lesions except for small-localized forms. It can aid in making accurate diagnosis and help select appropriate management strategy.

80 ENDOSCOPIC SCLEROSIS IN A BLADDER VENOUS MALFORMATION

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Introduction: Vascular malformations (VM) are a heterogeneous group of disorders with different strategies of treatment depending on the type, size, location and other variables. Venous Malformations are the most common type of VM. The sodium tetradecyl sulfate sclerosis constitutes the firstline treatment in most cases and is a safe and effective strategy.
Methodology: It was made a retrospective revision of a venous vascular malformation (VVM) case, located in the bladder that was treated by endoscopic sclerosis at Hospital Italiano de Buenos Aires.
Description: Female patient, 16 years old with diagnosis of complex pelvic VVM and episodes of massive bleeding including hematuria. The patient was evaluated at the Clinic of Vascular Anomalies (CAV) and studied by images (CTAngiography, Magnetic resonance imaging, Phlebography) that shows in bladder an heterogeneous image of 36 x 41 x 40 mm protruding on roof. The bladder lesion was treated by cystoscopy under general anesthesia: It was used a 14 French cystoscope. The VVM was visualised in bladder roof, with tortuous vessels of varicose appearance and blood clots, vestiges of bleeding. It jabbed under cystoscopic vision and inject sodium tetradecyl sulfate with fluoroscopic control. The outcome was favorable, without perioperative complications or new episodes of hematuria.
Conclusions: The Cystoscopy constitutes a helpful tool in patients with hematuria and suspicion of VM, not only for the diagnosis and characterization of the defect , but also for sclerotherapy.

81 Clinical spectrum of Klippel-Trenaunay syndrome in a third level pediatric hospital in Argentina

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Purpose: To describe the clinical spectrum of pediatric patients with Klippel-Trenaunay Syndrome (KTS). According to 2014 ISSVA classification, KTS is characterized by these clinical features: cutaneous capillary malformations (CM), venous malformations (VM) and/or lymphatic malformations (LM), and soft tissue and/or bony hypertrophy of the extremities.
Methods: Forty-five patients with KTS were assessed at our vascular anomalies clinic between November 2003 and September 2015, and included in this restrospective study. Twenty-one patients (46%) were males. The mean age at first consultation was 8.9 years. The mean follow up was 2.2 years [1 to 9.6 years]. Ultrasound (US) and US-Doppler scanning were the most frequent imaging methods for assessing vascular and intra-abdominal compromise. Long bones X-ray were performed to assess limb length discrepancies and MRI for lesions extent and anatomic relationships assessment. Venograms were obtained when percutaneous treatment was considered. Schlerotherapy, was indicated in presence of associated painful focal lesions and performed under general anesthesia.
Results: Twenty-seven patients (60%) had VM, CM and hypertrophy. CM were found in 40 (89%). Venous malformations were found in 31 (69%). Twelve patients (26.6%) presented with localized LM. Vascular lesions become more apparent with increasing age. Limb hypertrophy, was found in 27 (60%). Upper limb involvement was found in one patient (2%), who also had one lower limb affected. Involvement of one of the lower limbs was found in all patients, being the right leg affection more frequent 29 (63%). One patient had both lower limbs affected. Four patients suffering from pain and/or discomfort underwent percutaneous treatment of focal venous malformations with good clinical outcome.
Conclusion: KTS is a multifactorial disorder that generates a wide variety of clinical manifestations. It requires a multi-disciplinary approach for comprehensive management. Most of the patients with KTS should be managed conservatively. Percutaneous treatment of vascular anomalies when pain is found yield good clinical results.

82 Klippel-Trenaunay Syndrome: study of 160 cases and protocol for Ultrasound Doppler diagnosis

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Purpose: Klippel-Trenaunay Syndrome (KTS) is a rare congenital disease. The clinical diagnostic criteria consist of the classic triad: capillary malformations in the skin, bone or soft tissue hypertrophy and vascular malformations. Complex vascular anomalies (venous, arterial, lymphatic) may occur, as well as arteriovenous fistulas (AVFs) which frequently cause pain. The purpose of this study is to report clinical and sonographic findings encountered in KTWS.
Methods: Between June 2009 and November 2015, 160 patients (ages ranging from 18 days to 48 years; 62% women) with a clinical diagnosis of KTS were examined. Clinical evaluation and usual Ultrasound (US) Doppler techniques were used with an exam protocol developed for KTWS.High-frequency linear transducers (5-12Mhz) were used to identify anomalous arterial branches (AAB) and AVFs located in the region in which the patients reported pain.
Results: Main clinical findings: port-wine skin patches (80%); lesions on lower limb (78%), on upper limb(18%), bilateral(10%), on all limbs(5%); increase in limb length (50%) and increase in limb volume (72%). Main sonographic findings: deep venous malformations (53%); lateral marginal vein (36%); anomalous arterial branches (86%); AVFs (70%); venous aneurysms (16%, among which 35% with AVFs); thrombosis (15%) and lymphatic cysts (18%).The AAB are tortuous and form angles of approximately 90 degrees with the trunk branch, extending from the muscle to the fat and presenting low resistance flow (spectral biphasic pattern). These signs allowed the identification of the origin of the AAB, as well as the location of AVFs, along its path. These findings were confirmed by angiography in 100% of 15 treated cases.
Conclusion: When US-Doppler is performed with the appropriate protocol,it enables morphologic and hemodynamic evaluation of complex vascular malformations, especially AVFs. These evaluations are indispensable in the therapeutic planning and treatment of KTS.

83 Near-Infrared Fluorescence Lymphatic Imaging in a Subject with Klippel-Trenaunay Syndrome

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Purpose: Vascular anomalies frequently consist of both hemo- and lympho-vascular malformations. While the hemovasculature can be readily observed clinically, the lymphatics are not typically examined, owing to their small size and lack of endogenous contrast. As such, lymphatic contribution to disease is often not well understood. As part of an FDA-approved clinical investigation of lymphatic disorders, we recently used near-infrared fluorescence lymphatic imaging (NIRFLI) to assess the lymphatic architecture and contractile function of a 32 year old male diagnosed with Klippel-Trenaunay syndrome (KTS), who presented with a large port wine stain, boney overgrowth, and swelling in the right leg.
Methods: After informed consent, the subject received a total of twelve intradermal injections, each containing 0.25µg indocyanine green (ICG) in 0.1mL of 0.9% saline, in the lower extremities. Immediately after injection, NIRFLI was performed by illuminating the lower limbs with excitation light and collecting the resultant fluorescent signal using a custom imaging system. Sequences of images were analyzed to assess lymphatic architecture and lymphatic propulsion from the injection sites to the inguinal nodal basins.
Results: Imaging revealed well-defined lymphatic vessels in both legs. While the lymphatics in the affected leg were less numerous than in the unaffected leg and several appeared to be dilated, they were linear and intact, with active contractile propulsion (see attached video) comparable to that seen in normal subjects.
Conclusion: The lack of lymphatic anomalies in the affected, right leg suggests that there is no direct lymphatic involvement with the malformed hemovasculature in this KTS subject. Additional studies are needed, however, to determine whether lack of lymphatic involvement is typical in KTS patients and/or whether unresolved swelling in the affected limb could result in future lymphatic degradation. Supported in parts by the National Institutes of Health (R01 HL092923 and U54 CA136404).

85 Cytologic Evaluation of Clinically Suspected Lymphatic Malformations as a Guide to Sclerotherapy

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Purpose: The purpose of the study is to determine the value of cytologic evaluation of fluid from clinically suspected lymphatic lesions prior to or during sclerotherapy treatments in order to identify non-lymphatic lesions and maximize therapy.
Methods: Fluid is collected at the time of sclerotherapy and submitted for cytologic evaluation. Two cytospin preparations are stained with Wright-Giemsa and one cell block is stained with hematoxylin and eosin. The typical cellular components of lymphatic fluid are first defined. Cases in which the appearance of the fluid is characteristic of lymphatic fluid and those that are suggestive of non-lymphatic lesions are quantitated. When subsequent surgical resections are performed, cytologic and surgical diagnoses are correlated.
Results: Twenty eight cytology specimens from lesions presumed to be lymphatic malformations based on imaging and clinical features were examined between January 2013 and November 2015. The characteristic appearance of lymphatic fluid is an admixture of lymphocytes, blood and macrophages, typically with a predominance of lymphocytes. In 23/28 cases, cytology fluid showed features consistent with lymphatic fluid, but in 4/28 cases, features were diagnostic or suggestive of non-lymphatic lesions. Three of these four cases showed significant numbers of epithelial cells. The forth was paucicelluar and devoid of lymphocytes and given the site was characteristic of a bursal cyst. Based on cytologic findings, the three cases suggestive of epithelial-lined cysts were surgically excised rather than continuing with sclerotherapy. All three were confirmed to be non-lymphatic; one a foregut duplication cyst and two branchial cleft cysts. Overall, 14% of cases in which cytologic evaluation was performed revealed features of non-lymphatic lesions and redirected treatment.
Conclusion: Cytology is a simple and valuable tool that can help identify cases misclassified as lymphatic malformations prior to sclerotherapy, thereby optimizing treatment for non-lymphatic lesions while focusing sclerotherapy on lesions most likely to respond.

86 Is surgery a triggering factor for clinical worsening of lymphatic malformations?

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Purpose: To figure out whether surgery might be a triggering factor for clinical worsening in lymphatic malformations (LM) in children.
Methods: Retrospective analysis of the records of children seen in our department, who previously underwent surgery or a skin biopsy for a LM.
Results: 15 females, 11 males (mean age at the time of the study: 11.6 y); Mean age at last surgery was 5.5 y (0-13 y), mean follow-up was 5.86 years (1-18 y). The LM was located to the limb (n=16), the trunk (n=7), head and neck (n=5). Two adjacent areas were involved (n=2). Seven patients displayed a complex vascular malformation. Two children (8 and 13 years-old) had a skin punch biopsy, without clinical worsening. Surgery was always followed by long-lasting lymph oozing and delayed healing. Surgery led to mass reduction (n=19/22). Seventeen/22 children had further inflammatory manifestations. Functional impairment was due to scars on joint areas (n=5), or hypertrophic scars (n=2). Superficial skin lymphangiectasia (SSL) were observed in 14 children: present before surgery, without worsening afterwards (n=5); SSL occurred during the first year after surgery (n=3); For 3 children SSL occurred respectively 2, 2.5 and 5 years after surgery. For 2 patients, SSL were removed surgically without recurrence. SSL were not observed before or after surgery in 9 patients. In a group of 56 LM patients (mean age 6.86y), 29 (mean age: 9.5 y) experienced SSL spontaneously or after sclerotherapy.
Conclusion: SSL were equally observed in patients with LM, after surgery or not. In only 3 patients SSL occurred after surgery. Spontaneous SSL were observed in older patients probably because of the natural history of the disease. Functional impairment seems to be due to the area of surgery.

87 OUTCOMES OF SUBMUCOSAL REDUCTION TECHNIQUE IN PEDIATRIC CASE SERIES OF MICROCYSTIC LYMPHATIC MALFORMATIONS OF THE TONGUE

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Purpose: Introduction: Microcystic lymphatic malformations (LM) involving the tongue are complex lesions to treat. Multimodality approach to treatment is usually required. Sclerotherapy and laser ablation result in inadequate tongue reduction in many cases, leading to subsequent need for tongue reduction surgery. We report a series of three pediatric patients with microcystic LM involving the tongue who were treated with tongue reduction surgery using a submucosal technique.
Methods: Study design: Retrospective case series. Setting: Tertiary care pediatric hospital. Methods: Three pediatric patients with microcystic LM involving the tongue who underwent tongue reduction surgery using a submucosal technique were reviewed. Patient outcomes and **complications were compared.**
Results: All three patients had previous sclerotherapy treatments using doxycycline and/or bleomycin, which resulted in inadequate tongue reduction. Subsequent tongue reduction surgery using a submucosal technique was performed (average age at time of surgery: 3.3 years). Average length of postoperative hospitalization was 2 days (range: 1-3 days). All three patients demonstrated adequate tongue reduction (average length of follow up: 7 months). There was no postoperative airway emergency, intensive care unit admission, hemorrhage, or dehydration/uncontrolled pain. The only complication was tongue wound dehiscence in one patient, requiring wound debridement/closure and hospital readmission for one day.
Conclusion: Microcystic lymphatic malformations involving the tongue frequently require multimodality treatment. When tongue reduction surgery is required, a submucosal technique results in excellent outcomes with few complications.

88 A single center experience of prenatal diagnosed lymphatic malformation

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Purpose: Lymphatic malformations (LM) can be detected in utero, but there is no clear treatment pathway. With the recent use of sirolimus in complex LMs, the treatment paradigm of these patients has shifted. The purpose of this study is to review the prenatal diagnosis of complex LM and their treatments.
Methods: A single center IRB approved retrospective review of all patients diagnosed with LM prenatally between 2010-15 was performed. Demographics, pre and postnatal images, and the treatments were obtained.
Results: A total of 22 patients were diagnosed with LM on prenatal imaging – simple cysts in 6 patients, and complex cysts or diffuse soft tissue thickening in 16 patients. The finding of complex cysts or diffuse soft tissue thickening on prenatal imaging was correct in predicting LMs in 15/16 patients, but only 4/6 in the simple cysts. Postnatal course for the 3 patients with simple lymphatic macrocyts was uncomplicated with surgical excision or sclerotherapy. In contrast, survival

rates in the complex lymphatic malformation group was 56% (9/16) - 3 in utero fetal deaths, 3 neonatal deaths (respiratory distress, sepsis), and 1 infant death (sepsis). These patients had complicated LMs located in the neck, and had extensive disseminated disease. In the surviving 9 patients, all were managed by our multidisciplinary team. Treatment depended on the site of the lesion and the symptoms, but all required debulking, sirolimus, multiple sclerotherapy and surgical excision. All patients have good functional outcomes.

Conclusion: Prenatal diagnosis of lymphatic malformations is usually accurate in the complex, extensive malformations; however, a finding of a simple cyst on prenatal imaging is not always accurate. Perinatal and postnatal course for patients with complicated lymphatic malformation are challenging and require a long term multidisciplinary approach. With the use of sirolimus in these patients, surgery can often be delayed out of the neonatal period with good functional outcomes.

89 *Efficacy of treating large/giant cystic lymphatic malformations (LMs) in the neonatal period*

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Purpose: To report on the efficacy and safety of sclerotherapy initiated in the neonatal period to treat large/giant cystic lymphatic malformations.
Methods: Retrospective review on 7 term consecutive neonates (4 female) over a 5yr period (ending Nov 2015) undergoing intralesional sclerotherapy. Clinical, photographic & radiological records were analysed. Pt demographics, pre & post-procedural clinical & imaging findings, treatment details including complications and length of follow-up were documented. Outcomes were measured qualitatively as 1) change in lesion size (clinically and imaging) and 2) disease residue post sclerotherapy.
Results: LMs involved the chest wall (in 6), neck (in 6), mediastinum (in 1), tongue (in 3), axilla (in 4) and upper extremity (in 2). All had mixed cystic LMs with predominant macrocysts in 6/7 pts. 3 pts had an EXIT procedure at delivery as airway threatening was evident on prenatal imaging. 1 pt had minimal surgical debulking to allow for interval tracheotomy. Doxycycline sclerotherapy was used in all, 3% sodium tetradecyl sulphate in 5 and Bleomycin in 3 pts. Drainage catheters were used in all. 3 pts completed treatment in the neonatal period, 2 continued treatment into early infancy and 2 neonates are currently undergoing treatment. All treatments were well tolerated. Significant reduction in lesion size has been documented in 6/7 pts, with an excellent response in 4. In 1 neonate, currently undergoing treatment, sudden lesion expansion has necessitated further airway support. In 5 pts only small residues of microcysts remain, in 1 pt there has been complete imaging clearance of disease and in 1 current pt, recent sudden cyst expansion has occurred. Total treatments performed to date = 31. One treatment-related minor complication was seen with a small facial abscess associated with a temporary inability to close the ipsilateral eye (with no facial palsy). Length of clinical follow-up= 0-48 months.
Conclusion: Intralesional sclerotherapy is a satisfactory treatment option in the neonatal period for large / giant cystic LMs. The treatments are well-tolerated, low risk and durable. This provides a useful treatment option for such complex and extensive mixed cystic / macrocystic LMs when alternative invasive treatments may be associated with high risk. Persistent residual microcystic disease however may require interval sclerotherapy.

90 *Beta-adrenergic receptor expression and mast cells in lymphatic anomalies (Kaposi´s sarcoma and Lymphatic Malformations)*

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Purpose: To evaluate the correlation between beta-adrenergic receptor expression and mast cells in vascular anomalies. The beta adrenergic receptor inhibitor propranolol is the gold standard treatment in infantile hemangioma, and recent data suggest that β-blockade alone substantially reduce angiosarcoma proliferation in patients with this tumor. On the other hand it has been postulated mast cells as posible target of propranolol therapy.
Methods: Mast cell counts and β-adrenergic receptor expression were performed in the following vascular anomalies: 24 classic Kaposi´s sarcoma (KS); and 30 Lymphatic malformations (LM). Using the immunohistochemical stain tryptase mast cells were expressed as cells per 10 high-power fields. Expression of β -1, β -2, β -3 adrenergic receptors were evaluated for each lesion, and the results scored for the of cell expression as negative, weak positive, or strong positive. The primary antibodies used were rabbit anti-ADBR1, rabbit anti-ADBR2, and rabbit anti-ADBR3 (Abbiotec). Control tissue were infantile hemangiomas and arterio-venous vascular malformations.
Results: Results revealing strong signals for ADRB1(19 of 24 (79%) KS and 21 of 30 (70%) LM) and ADRB2 (21 of 24 (87%) KS and 24 of 30 (80%) LM), and weaker sample-dependent signals for ADRB3. Most LM did not express ADRB3 (negative). Most KS lesions were weak positive for ADRB3. Compared to LM, we found that KS and infantile hemangiomas seemed to harbor a significantly higher number of mast cells. A positive correlation between mast cell numbers and microvascular density was found. We found no correlation between the presence of mast cells and the expression of β-adrenergic receptors.
Conclusion: Beta-adrenergic receptor inhibitors could be an effective alternative for symptomatic Kaposi´s sarcoma lesions compared with the treatments currently available. Although mast cell density is significantly higher in areas of microvascular proliferation, its value is uncertain.

91 Bone and Joint Traumas in Vascular malformations are a Case of Emergency: Peculiarities in Management

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Purpose: Fractures in vascular malformation patients are always a situation of exceptional urgency. Standard emergency centers are not familiar with such emergency procedures. There is the problem of severe hemorrhage and the challenge of conservative or surgical treatment
Methods: A retrospective analysis of the clinical course of 10 cases and the long follow up results were studied. In 4 patients(2 femoral neck, 2 femoral) orthopedic surgery was performed. One patient with an extensive AVM and a fracture of the femoral neck declined the proposed orthopedic surgery. 5 additional patients with forearm fractures(2), lower limb fractures(2) and tibial plateau fracture(1) were treated conservatively.
Results: It is mandatory first to apply all techniques of conservative treatment. However hereby some fractures do not heal and have to be treated by surgery, as for a fracture of the femoral neck or a femoral fracture. As in vascular malformations there exists the risk of severe hemorrhage only a small incision should be performed. In addition a bleeding complication can appear opening up the bone. A good practice approach is the ESIN for femoral fractures and the traction screw for femoral neck fractures. The pathologic bones are only at the limb which is affected by the vascular malformation. There is a markedly prolonged bone healing process. Finally however the regular check up demonstrated normal sequences of movement. One patient with a fracture of the femoral neck declined treatment. One year after his accident he is severely physically handicapped.
Conclusion: The orthopedic surgeon and the vascular surgeon cooperatively have to rule out the optimal possible concept of treatment dependent on the type and the location of each fracture individually adapted for each patient. There is no routine standard method of treatment. A less invasive fixation method should be used when possible.

92 Contracture by vascular malformations: causes and treatment

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Purpose: Vascular malformations have a variety of functional and esthetical symptoms, and tend to get worse gradually throughout life. In vascular malformations of the extremities, there are cases that have a swelling and pain, leading to functional disorders such as joint contracture. The authors review the clinical courses, symptoms and treatments of limb vascular malformation patients with arthrogryposis in our hospital, and discuss about causes and treatments.
Methods: In the cases of intramuscular vascular malformation treated in our department from July 2008 to May 2013, 16 cases showed the joint contracture. Of these, four cases (one case of upper limb, lower limb three cases) were arteriovenous malformations, and venous malformations were 12 cases (one case of upper limb, lower limb 11 cases). As the treatments, the 16 cases of all patients underwent sclerotherapy, and then resection followed in eight cases.
Results: Patients who underwent resection followed by range of motion exercise resulted in improvement of joint range of motion and there was no muscle weakness due to lesion resection.
Conclusion: Vascular malformations of the limbs often result in arthrogryposis by fibrotic changes and muscle pain that spans a long period of time. Cases with dysfunctions which are the harmful effect of everyday life are not a few. Degeneration of intramuscular lesion itself, disuse atrophy of muscle, deformation of the joint itself by intra-articular pathology and so on can be considered as the cause of joint contracture. Treatment for these can not be solved by only the control of blood flow in the lesion, so that surgical resection is also a choice. However, many cases have the state of the blood coagulopathy especially in huge venous malformations, which can be complicated by persistent bleeding after surgery. It should be considered a sufficient removal of fibrotic lesions causing contracture following endovascular treatments.

93 Subsequent Management and Outcomes After Primary Surgical Excision of Venous Malformations of the Head and Neck

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Purpose: Objectives: Discuss outcomes of primary surgical excision of head and neck (H&N) venous malformations (VMs) and possible need for subsequent therapy.
Methods: Study Design: Retrospective chart review. Setting: Academic tertiary care pediatric hospital with a vascular anomalies center. Subjects and Methods: A retrospective chart review was performed on the 142 patients with H&N VMs who presented between 1996 and 2012. 73% (103 patients) received primary treatment at our institution, 25% of whom were treated with primary surgical excision (n = 26). We conducted a retrospective chart review on these 26 patients treated with primary surgical excision.
Results: Mean age at initial presentation was 8.4 years. The most common anatomical subsites were the face/cheek (15%), neck (15%), and scalp (12%). 92% of the patients had focal lesions, while only 8% had diffuse disease of the H&N. Average length of follow up was 1.9 years. A majority of patients (77%) experienced significant improvement (significantly decreased size/resolution of VM and decreased pain) after the initial excision, though 23% of patients ultimately required subsequent treatments (repeat excision and/or laser therapy) to obtain overall disease control. The majority of patients (77%) required only the initial surgical excision for adequate treatment. Anatomical location of the lesions was not predictive of need for subsequent treatment after primary surgical excision.
Conclusion: Venous malformations of the head and neck are uncommon. However, when appropriately selected for primary surgical excision based on focal lesions and not necessarily on anatomical location alone, 77% do not require subsequent treatment for disease control.

94 INTRACRANIAL VS EXTRACRANIAL (CERVICO-FACIAL) –ARE THEY DIFFERENT: CASE REPORT

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Purpose: NEUROSURGEONS SAY THAT INTRACRANIAL AVM ARE MOSTLY LOCALIZED AND MANY ARE RESECTABLE. THIS PAPER PRESENTS A YOUNG WOMAN WITH EXTENSIVE MULTIFOCAL CERVICAL-FACIAL AVM WHO ALSO HAD AN INTRACRANIAL AVM. THIS PATIENT'S INTRACRANIAL AVM WAS FELT TO BE LOCALIZED AND RESECTABLE BY THE NEUROSURGEONS BUT TURNED OUT TO BE MULTIFOCAL AND UNRESECTABLE. WE WANTED TO REPORT THIS CASE TO MAKE VASCULAR ANOMALY PROGRAMS AWARE THAT PATIENTS WITH CERVICAL-FACIAL AVM AND INTRACRANIAL AVM, THAT THE INTRACRANIAL AVM MAY BE DIFFUSE AND UNRESECTABLE. THIS PATIENT DIED AS A RESULT OF HER SURGERY.
Methods: THE MEDICAL RECORDS AND IMAGING STUDIES OF THIS PATIENT WERE REVIEWED BOTH PRE-OPERATIVE AND POST-OPERATIVE. THE OPINIONS OF THE NEUROSURGEONS AS TO RESECTABILITY ARE PRESENTED. THE SURGICAL FINDINGS, THE FOLLOWUP COURSE AND THE IMAGING STUDIES ARE PRESENTED.
Results: THIS PATIENT WAS FELT TO HAVE A LOCALIZED INTRACRANIAL AVM BY THE NEUROSURGEONS. DURING SURGERY, AFTER THE AVM WAS THOUGHT TO HAVE BEEN RESECTED, THE PATIENT HAD SEVERE, UNCONTROLLABLE BLEEDING. AFTER 15 UNITS OF BLOOD TRANSFUSIONS, THE WOUND WAS PACKED OFF AND THE PROCEDURE TERMINATED. SHE NEVER WOKE UP AND DIED 30 DAYS LATER. THE POST OP IMAGING STUDIES SHOWED PERSISTANCE OF MOST OF THE INTRACRANIAL AVM INDICATING THAT THIS WAS A DIFFUSE LESION SIMILAR TO HER CERVICAL-FACIAL AVM LESIONS.
Conclusion: MOST INTRACRANIAL AVMS ARE CONSIDERED LOCALIZED AND POTENTIALLY RESECTABLE. THIS CASE REPORT SHOULD MAKE VASCULAR ANOMALIES TEAMS AWARE THAT IF A PATIENT HAS MULTIFOCAL AVMS IN THE CERVICAL-FACIAL AREA, THAT AN AVM IN THE BRAIN CAN BE DIFFUSE RATHER THAN FOCAL OR LOCALIZED AND IS PROBABLY UNRESECTABLE. IT IS IMPORTANT THAT THIS BE KNOWN TO AVOID UNNECESSARY SURGERY WHICH CAN BE FATAL.

95 Expression of Components of the Renin-Angiotensin System in Venous Malformation

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Purpose: Venous malformation (VM) is the most common form of vascular malformation. It consists of a network of thin-walled ectatic venous channels. There is an increasing role for the renin-angiotensin system (RAS) in vascular biology. This study investigates the expression of components of the RAS, namely angiotensin converting enzyme (ACE), angiotensin II receptor 1 (ATIIR1) and angiotensin II receptor 2 (AIITR2), in VM.
Methods: Subcutaneous (SC, n=7) and intra-muscular (IM, n=7) VMs were analysed for the expression of ACE, ATIIR1 and ATIIR2 using NanoString gene expression

analyses, immunohistochemical (IHC) staining and Western blotting (WB).
Results: SC and IM VMs displayed similar profiles. The expression of ACE was demonstrated at both the IHC and transcriptional levels. The expression of ATIIR1 was detected at the IHC, transcriptional and WB levels. ATIIR2 was not detected using any of the three methods. The IHC localised the expression for both ACE and ATIIR1 to the endothelium of VMs.
Conclusion: The results of this study indicate a potential role for RAS signalling in the biology of VM. The presence of ACE and ATIIR1 coupled with the absence of ATIIR2, would suggest that the RAS signalling in VM is predominantly via ATIIR1. This study demonstrates the novel expression of ACE and ATIIR1 in SC and IM VMs, and highlights ATIIR1 as a potential therapeutic target for these lesions.

96 *Electrochemotherapy (EChT): A Unique Technique for Treating Low Flow Vascular Malformations (LFVMs)*

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Purpose: To introduce a unique technique (EChT) for treating LFVMs
Methods: 875 cases of LFVMs treated with EChT were evaluated retrospectively from May 2005 to July 2013. 670 cases were followed up for half to 6 years (M: 293, F:377, 3-62 ys and means 15.5 ys. 56.4% (378/670) were recurrent patients after surgical resection in other hospital before they were treated by EChT. Table.1 Confirming the diseased region by MRI, 18G trocar was used to insert into diseased region from 2cm beyond the margin of tumor under anesthesia. Pulled out the needle core of trocar and replaced by the electrode. They were allocated so as to cover the whole tumor with a space of 1-1.5cm between one another and the ratio between anode and cathode used was 1:1. The electrodes were connected to anodes and cathodes of EChT instrument respectively. The electricity was then set up to begin the EChT with the current of 100-180mA and the voltage of 6-12V. The total electricity used was in general 80-100 coulombs per 1cm diseased tissue. Figure.1&2.
Results: The effect was evaluated as 4 grades. Grade 1: clinical obliteration, functional impairment recover to normal; Grade 2: most clinical symptoms disappear and/or functional impairment improve significantly; Grade 3: clinical symptoms and functional impairment improve; Grade 4: poor, little or no improvement of symptoms and functional impairment. The final effective rate was 96.4%. (Table 2 and 3).
Conclusion: EChT has a confirmed therapeutic effect on treating LFVMs (venous malformations and lymphatic malformations). It has the advantages of fewer traumas, quick recovery, less complication, being handled simply and being easily accepted by patients. It offers a completely new effective method for treating low flow vascular malformations.

97 *Ultrasound-guided sclerotherapy with polidocanol microfoam in symptomatic venous malformations: treatment and followup of 160 patients.*

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Purpose: To evaluate the efficacy, safety, and long-term outcomes of ultrasound-guided sclerotherapy with polidocanol microfoam in symptomatic vascular venous malformations (VVM)
Methods: Retrospective fifteen year review (Jan 01-016) of patients with VVM treated at our centre with polidocanol microfoam. Of the 160 patients identified (65 male and 95 female patients; mean age, 26.1 years; age range, 8-59 years), 86 (53%) had lower limb VVM, 36 (21%) had upper limb VVM, 29 (18%) facial VVM, 14 (8%) genital VVM, and 17 (10%) had truncal VVM. Forty two of the 160 patients (26%) had Klippel-Trenaunay syndrome. Sixty two of the patients had limited (subcutaneous) VVM, and 98 had infiltrating (intramuscular) VVM. Most of the patients refered pain as the most important symptom. Treatment response was assessed clinically and by means of lesion size measurement with color echo-Doppler ultrasonography imaging.
Results: Microfoam was injected under ultrasound guidance (associated with fluoroscopic guidance since 2013 in intramuscular VVM) every three months for the first two years and every six months or yearly as a maintainance. The concentrations of polidocanol used ranged from 1% to 3% (volume per session ranged from 4-80 cc). The average number of sessions was 7.1 (1-36). After a median follow-up at 12 months after the last session 98% of patients reported a decrease in pain. In 97 cases (60%) over 75% reduction in size was observed, and in 62 cases (40%), a reduction between 50-75% of the original size was obtained. Tolerance was excellent. Complications in 11 patients included: photopsia (2pt), headache (3pt), hemoglobinuria (1pt), superficial cutaneous ulceration (2pt), and transient neuropathy(3pt).
Conclusion: VVM are chronic diseases requiring continuous and regular treatment. Ultrasound-guided sclerosis using polidocanol microfoam seems to be well tolerated and can improve the symptoms of low-flow malformations without the risks of more aggressive sclerosing agents, such as ethanol.

98 Sclerotherapy for venous malformations of the glans penis in children.

Dmitry Romanov, Junior members

Purpose: Venous malformation of the glans penis is a rare pathology in children. This article provides a retrospective evaluation of safety and efficacy of percutaneous sclerotherapy with Bleomicin in two (2) children suffering from venous malformations glans penis. Vascular malformations of the external genitalia may not only lead to aesthetic damages but also to functional disability. Also, there is a risk of traumatizing abnormal vessels and venous bleeding. Venous malformations Penis glans are rare and their treatment is still controversial.
Methods: Two patients at the age of 2 and 15 were diagnosed with venous malformations glans penis in St.Vladimir Children's Municipal Clinical Hospital in 2014 and 2015. These lesions proceeded with no obvious symptoms but had a tendency for enlargement with age. The parents brought their children to the hospital, primarily, for cosmetic reasons. Both patients were evaluated with the use of Doppler ultrasound scanning and MRI of the pelvic area. Direct intralesional injection of Bleomicin was chosen as treatment for both patients. The concentration of the sclerosant was 15 mg of Bleomicin in 5 ml NaCl 9% solution, and the volume of the solution varied from 2 to 5 mL per injection. After the sclerotherapy, the urethral catheter was installed and the superimposed compression bandage was applied to the designated area for 3 days.
Results: Both patients experienced hyperemia and mild swelling on the injection site. After the surgery, the patients did not have pain, cutaneous necrosis and other complications on the injection site. The effectiveness of this treatment was assessed after 3, 6 and 12 months. After 12 months, no signs of venous malformations were found in glans penis of both patients. The results of the sclerotherapy were considered successful.
Conclusion: Sclerotherapy with Bleomicin is a well-tolerated, safe and effective treatment of venous malformations glans penis in children. We consider sclerotherapy with Bleomicin to be our treatment of choice for this pathology.

99 Combining Interventional radiology and surgery in the treatment of Venous Malformations: Experience with 50 cases.

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Purpose: Large venous malformations (VM) are difficult to manage. Combined endovascular and surgical techniques are useful in many cases. The purpose of this report is to highlight the advantages and disadvantages of the combined method.
Methods: Retrospective analysis of 50 cases treated between 2008 and 2015 in our Interdisciplinary Center for Vascular Malformations.
Results: 47 patients with a VM in the head and neck region and 7 patients with a VM of the trunk or extremity were treated with endovascular sclerotherapy followed by surgical resection 24-48 hours later. Two patients had blood loss of more than 200 ml (500 and 1000 ml). One patient with post-operative bleeding required blood transfusions. Two patients experienced severe tissue necrosis, one post-operative bleeding requiring reoperation, and one wound dehiscence. Two patients had recurrence of cheek VM. 12 operations benefited from intraoperative neuromonitoring of the facial nerve.
Conclusion: The combination of endovascular methods and surgical resection allows more complete removal of venous malformations because of reduced intraoperative bleeding and better visibility of tissues and planes. Despite extensive experience, significant complications can occur.

100 Pregnancy in patients with Klippel-Trenaunay Syndrome

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Purpose: Klippel-Trenaunay Syndrome (KTS) is a congenital disorder associated with limb overgrowth or hypotrophy and the presence of vascular malformations. Pregnancy and childbirth can possibly expose KTS patients to important health risks, such as bleedings from vascular malformations involving the pelvic and vulvar regions and thromboembolic events. However, to date, there are no evidence-based guidelines for the management of KTS patients in the preconceptional phase and during the course of pregnancy (antepartum, peripartum and postpartum). Due to the low prevalence of KTS (1:100.000), only small case series and expert-opinion reviews about obstetric complications and management have been published so far. The purpose of this study is to investigate reproductive health and pregnancy course in a Dutch cohort of female KTS patients, in order to provide evidence for

clinical decision-making.
Methods: In this cross-sectional cohort study, 86 female patients with KTS of 18 years and older, who visited the academic hospitals of Amsterdam and Maastricht in the Netherlands, will be invited to complete an online questionnaire about KTS presentation, reproductive health and possible pregnancy course(s). Additional medical data will be acquired through the hospital's patient files.
Results: We will present patient characteristics, KTS presentation and the prevalence of pregnancy and childbirth. Abnormalities in reproductive health will be categorized in KTS-related and not KTS-related. We will give an overview of complications encountered in this cohort during the pregnancy course(s), categorized into antepartum, peripartum and postpartum complications. These data will be compared to a healthy population-based cohort from the literature, in order to calculate relative risks. In addition, we will report obstetric management strategies and effects in the included patients.
Conclusion: This study will describe the reproductive health and pregnancy course in female patients with KTS, providing a basis for evidence based guidelines for preconceptional and obstetric management of KTS patients.

101 *Revisiting Classic MRI Findings of Venous Malformations: Changes Found with Contemporary Techniques*

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USCF

Purpose: Classically, venous malformations (VM) demonstrate central enhancement on magnetic resonance imaging (MRI). Additionally, presence of phleboliths is suggestive of a VM while the presence of fluid-fluid levels (FFL) suggests a lesion is a lymphatic malformation (LM) rather than a VM. MRI technology has advanced considerably since the first description of these classic findings, so this study reexamines these to see if technical changes have affected their specificity for the diagnosis of VMs by MRI.
Methods: Data queries were performed of a prospectively maintained database from the multidisciplinary birthmarks and vascular anomalies clinic at a major academic medical center to identify patients with a final diagnosis of VM. Patients with reviewable contrast-enhanced MRIs were identified. Patients were selected by identifying the oldest MRI studies in the database against the newest MRI studies to identify equal numbers of patients from the temporal extremes. Imaging was reviewed to assess for presence of FFL, phleboliths, and enhancement. Enhancement was quantified by measuring signal in the same location of the lesion on both pre- and post-contrast sequences. Such comparison was made with the same MRI sequences performed before and after contrast administration. The most avidly enhancing segment of the lesion was targeted for measurement of signal. Percent enhancement was calculated by the formula (post-contrast signal – pre-contrast signal)/pre-contrast signal. The time elapsed between contrast injection and image acquisition was noted. Chi-square analysis was performed to compare rates of visualization of FFL, phleboliths, and enhancement between the older and newer cohorts. Independent sample t-test was performed to compare percent enhancement between the older and newer cohorts. Pearson's coefficient was performed to evaluate the correlation between percent enhancement, time to contrast, and date of imaging.
Results: 40 patients were identified with 20 studies performed between 1995 and 2006. 20 studies were performed between 2011 and 2012. The new cohort had higher rates of FFL visualization, $\chi 2$ (1, n=40) = 11.91, p=0.001. No difference was found in rates of phlebolith visualization, $\chi 2$ (1, n=40) = 0.10, p=0.500. Correlation was found between time to contrast and enhancement, r=0.600, n=40, p<0.001. Inverse correlation was found between scan date and time to contrast, r=-0.502, n=40, p=0.001, and scan date and enhancement, r=-0.364, n=40, p=0.021. Studies in the older cohort were more likely to demonstrate enhancement, t(38)=10.62, p=0.002.
Conclusion: Changes in MRI techniques have changed the specificity of classic findings of VMs. With contemporary techniques, FFLs can frequently be seen and thus cannot reliably exclude VMs. FFLs appears to be a less useful distinguishing feature between VMs and LMs than previously believed. Current techniques demonstrate less pronounced enhancement of VMs, which is a result of less temporal delay in post-contrast imaging. The low-flow nature of these lesions leads to their progressive enhancement. Allowing for longer time to post-contrast imaging after administration of contrast. Central enhancement of VMs helps distinguish them from LMs, which demonstrate only peripheral enhancement and do not enhance centrally. To better demonstrate this central enhancement, protocols should seek to maximize the time to contrast for post-contrast MRI sequences. Visualization of phleboliths has not changed with current techniques and maintains specificity for VMs. Changes in MRI techniques have changed the reliability of classic findings of VMs. FFLs should no longer be exclusionary for the diagnosis of VMs. Timing following contrast administration should be maximized to increase likelihood of enhancement to confirm the diagnosis of VMs.

102 Comprehensive Surgical Correction of Serious Soft Tissue or Bone Deformities for Complicated Venous Malformation Cases after Sclerotherapy

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Purpose: Sclerotherapy is the mainstream treatment for venous malformation(VM). However, soft tissue or bone deformities could be still evident in complicated VM cases though most of the lesions were removed by sclerotherapy. The patients were usually not satisfied with the sclerotherapy outcomes, so the surgery is the final and indispensable choice for them. This study is going to investigate the indications and methods of surgical correction for serious soft tissue or bone deformities.
Methods: 14 cases with giant VM lesions in head and neck region were included from Jun 2012 to Oct 2015. All cases received 12 to150 sessions of absolute alcohol sclerotherapy until the lesions were dramatically shrunk or nearly disappeared, which ensured low risk of recurrence and controllable bleeding during operation. Soft tissue or bone deformities were evaluated by MR and CT before surgery. Surgical plans were made according to the features of the deformities.
Results: All cases had obvious appearance or function improvements after surgery. The deformities including serious zygoma or mandible overgrowth(n=5, obvious facial depression or hypertrophy(n=6), lower eyelid ectropion(n=2), extensive scar@n=1). Comprehensive surgical methods were performed for those cases, including zygomatic and mandible osteotomy, pedicled axial flap and free adipofascial flap transplantation and prefabricated expanded skin flap transplantation. With 6 to 24 months follow-up, no obvious residual lesions re-expanded and post-op outcomes were stable.
Conclusion: The main indication of surgery for venous malformation is not to remove the lesions, but to enhance the good results, or alter the unsatisfactory results of sclerotherapy. It is necessary but challenging because of both skillful sclerotherapy and comprehensive surgery techniques are required.

103 Combined Lymphedema and Capillary Malformation of the Lower Extremity

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Background: Primary lymphedema and capillary malformation are independent vascular malformations that can cause overgrowth of the lower extremity. We report a series of patients who had both types of malformations affecting the same leg. The condition is unique, but may be confused with other types of vascular malformation overgrowth conditions (e.g., CLOVES, Klippel-Trenaunay, Parkes Weber).
Methods: Our Vascular Anomalies Center and Lymphedema Program databases were searched for patients with both capillary malformation and lymphedema. Diagnosis of lymphedema-capillary malformation was made by history, physical examination, and imaging studies. Because lymphedema-capillary malformation has phenotypical overlap with other conditions, only patients who had imaging confirming their diagnosis were included in the analysis. Clinical and radiological features, morbidity, and treatment were recorded.
Results: Eight patients (4 female, 4 male) had confirmed lymphedema-capillary malformation (Figure 1). Referring diagnosis was Klippel-Treaunay syndrome (n=4), diffuse capillary malformation with overgrowth (n=3), or lymphatic malformation (n=1). The condition was unilateral (n=6) or bilateral (n=2). Morbidity included: infection (n=6), problems fitting clothing (n=6), bleeding or leaking vesicles (n=5), leg length discrepancy (n=4), and difficulty with ambulation (n=3). All patients were managed with compression regimens. Operative management was: liposuction (n=3), treatment of phlebectatic veins (n=3), staged skin/subcutaneous excision (n=1), and/or epiphysiodesis (n=1).
Conclusions: Lymphedema and capillary malformation can occur together in the same extremity. Both conditions independently cause limb overgrowth primarily because of subcutaneous adipose deposition. Compression garments and suction-assisted lipectomy can improve the condition. Lymphedema-capillary malformation should not be confused with other vascular malformation overgrowth diseases that have different morbidities and treatments.

104 Management of Primary and Secondary Lymphedema: Analysis of 375 Referrals to a Center

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Background: Lymphedema is the progressive swelling of tissue due to inadequate lymphatic function. Although lymphedema is a specific condition, patients with a large extremity are often labeled as having "lymphedema", regardless of the underlying cause. The purpose of this study was to characterize referrals to a center to determine if lymphedema should be managed by specialists.

Methods: Patients treated in our Lymphedema Program between 2009 and 2015 were reviewed. Diagnosis was determined based on history, physical examination, photographs, and imaging studies. Lymphedema type (primary, secondary), location of swelling, age, gender, previous management, accuracy of referral diagnosis and the geographic origin were documented.

Results: Three hundred-seventy-five patients were referred with a diagnosis of "lymphedema"; 70% were female and 30% were children. Lymphedema was confirmed in 73% of the cohort: primary (56%) and secondary (44%). Twenty-seven percent of patients labeled with "lymphedema" had another condition. Before referral, only 4% of the cohort underwent lymphoscintigraphy (the gold standard diagnostic test for lymphedema), whereas 31% of patients with lymphedema received nondiagnostic tests for lymphedema. Eight percent were given a diuretic which does not improve the condition. One-third of patients resided outside of our local referral area. The average time between onset of lymphedema and referral to our Lymphedema Program was 10 years (range, <1–62 years).

Conclusions: Patients presenting to a center with "lymphedema" often have another condition, and may be suboptimally managed prior to their referral. Patients with suspected lymphedema should be referred to specialists focused on this disease.

105 Near-Infrared Fluorescence Lymphatic Imaging in a Toddler with Congenital Lymphedema

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Purpose: Vascular anomalies frequently consist of both hemo- and lympho-vascular malformations. While the hemovasculature can be readily observed clinically, the lymphatics are not typically examined, owing to their small size and lack of endogenous contrast. As such, lymphatic contribution to disease is often not well understood. As part of an FDA-approved clinical investigation of lymphatic disorders, we recently used near-infrared fluorescence lymphatic imaging (NIRFLI) to assess the lymphatic architecture and contractile function of a 32 year old male diagnosed with Klippel-Trenaunay syndrome (KTS), who presented with a large port wine stain, boney overgrowth, and swelling in the right leg.

Methods: After informed consent, the subject received a total of twelve intradermal injections, each containing 0.25µg indocyanine green (ICG) in 0.1mL of 0.9% saline, in the lower extremities. Immediately after injection, NIRFLI was performed by illuminating the lower limbs with excitation light and collecting the resultant fluorescent signal using a custom imaging system. Sequences of images were analyzed to assess lymphatic architecture and lymphatic propulsion from the injection sites to the inguinal nodal basins.

Results: Imaging revealed well-defined lymphatic vessels in both legs. While the lymphatics in the affected leg were less numerous than in the unaffected leg and several appeared to be dilated, they were linear and intact, with active contractile propulsion (see attached video) comparable to that seen in normal subjects.

Conclusion: The lack of lymphatic anomalies in the affected, right leg suggests that there is no direct lymphatic involvement with the malformed hemovasculature in this KTS subject. Additional studies are needed, however, to determine whether lack of lymphatic involvement is typical in KTS patients and/or whether unresolved swelling in the affected limb could result in future lymphatic degradation. Supported in parts by the National Institutes of Health (R01 HL092923 and U54 CA136404).

106 Prenatal diagnosis of cerebral and extra-cerebral high-flow lesion revealing familial CM-AVM syndrome related to RASA1 mutation

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Purpose: To report 2 cases of prenatal diagnosis of cerebral and extra-cerebral high-flow lesion which led to further diagnosis of unknown familial CM-AVM syndrome related to RASA1 mutation.
Methods: Observational study of 2 prenatal cases referred in the third trimester due to cerebral high-flow lesion in one, and unilateral hypertrophy of the left arm, associated with increased vascularization of the soft tissue and unexplained polyhydramnios, in the second.
Results: Prenatal imaging was suggestive of A-V pial fistula in the first case and of Parkes Weber syndrome in the second. Physical maternal examination showed small multifocal capillary malformation in the two patients. The maternal medical history included termination of pregnancy for aneurysm of Galien for a previous pregnancy in the first patient and a surgical excision of nasal AVM in the mother of the second patient. The prenatal imaging findings, as well as maternal multifocal CMs associated with a familial history of high-flow lesion, were highly suggestive of CM-AVM syndrome, which was confirmed by genetic testing (RASA 1 mutation).
Conclusion: Prenatal diagnosis of cerebral/soft tissue high-flow lesion is extremely rare and should thus prompt careful maternal dermatological examination as well as familial history-taking in order to consider a diagnosis of unknown CM-AVM syndrome.

107 Prenatal Diagnosis of Vascular Anomalies and Correlation with Postnatal Imaging

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Purpose: Vascular anomalies and associated syndromes are detected prenatally with increasing frequency. Accurate imaging assessment and characterization are important to ensure appropriate diagnosis, prenatal counseling, and postnatal management.
Methods: The medical records and imaging studies of patients who underwent prenatal and postnatal imaging for a suspected vascular anomaly between 1999-2015 were reviewed retrospectively to document diagnosis and characterize imaging features. Lesions were assessed for the present of solid and cystic tissue, abnormal vessels, and cerebral, truncal and/or limb overgrowth. Agreement between pre- and postnatal diagnoses was determined, and pitfalls in lesion characterization were analyzed.
Results: 55 patients (28 males, 27 females) with a suspected vascular anomaly had prenatal imaging (US and/or MRI) and immediate postnatal imaging (radiographs, US, MRI, CT, angiography). Lymphatic malformations (LM; 35) were characterized pre- and postnatally as macrocystic, septated lesions, usually in the head/neck region. A duplication cyst without septa (1) was mistaken prenatally for an LM. Complex syndromes, including Klippel-Trenaunay (KTS; 6) and CLOVES (3) were diagnosed pre- and postnatally with limb overgrowth in KTS; truncal overgrowth in CLOVES; and lymphatic cysts/ectatic veins in both. Megalencephaly- capillary malformation (2) and PHACES syndrome (2)were suspected prenatally due to macrosomia/macrocephaly and multiple posterior fossa abnormalities, respectively. Two rapidly involuting hemangiomas were identified prenatally as focal liver lesions that spontaneously resolved. Kaposiform hemangioendothelioma manifested as a high flow lesion of the upper trunk was misdiagnosed prenatally as an arteriovenous malformation. A low flow portovenous shunt was correctly identified with Doppler US pre- and postnatally. A venous malformation presented pre- and postnatally as a slow flow craniocervical lesion. Prenatal chylous ascities diagnosed via in utero tap was suspected postnatally to be due to a central conducting anomaly.
Conclusion: Prenatal imaging identifies critical differential diagnostic features of vascular anomalies that influence pre- and postnatal management and parental counseling.

108 A Decade experience with personalized therapy for Bannayan-Riley Ruvalcaba

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Purpose: Bannayan Riley Ruvalcaba Syndrome (BRR) is a cancer predisposition syndrome characterized by macrocephaly, pseudopapiledema, hamartomas and intertriginous freckling. It is caused by a germinal mutation in PTEN gene (10q23.31) and can manifest in childhood (BRR) or adulthood (Cowden Syndrome). PTEN associated vascular malformations require repeated surgical and endovascular interventions accounting for significant morbidity. Four children were started on a combination of thalidomide and Celebrex to minimize the need for surgical and endovascular interventions or to minimize blood loss associated with GI lesions.
Methods: The initial dose was thalidomide 3-23 mg/

kg (max 1000 mg daily) and Celebrex 100 mg PO BID (200 mg PO BID if over 20 kg) for minimum of six months with a gradual wean of the therapy to a minimal maintenance dose (on average 50 mg daily for the past 7 years). All patients were seen monthly by the treating oncologist, and clinical and radiological re-evaluation was done using serial angiography and/or non-invasive imaging such as MRI every 6 months for first 2 years and as needed thereafter.
Results: None of the four patients treated with thalidomide/ celebrex has required intervention since beginning therapy (5- 10 years). All patients responded with lesional regression, improved angiography, and improvement in pain and physical activity. One child, after being stable for four years, had moved back to her country of origin and now requires 2-3 embolizations/ surgeries per year.
Conclusion: For 4/4 children with unmanageable PTEN-associated vascular anomalies initiation of thalidomide/ celebrex reduced the number of needed interventions.Thalidomide and Celebrex can be used as adjuvant medical therapy to endovascular management of PTEN-associated vascular anomalies, or in cases, where diagnosis is made early, initiation of this therapy avoids the need for endovascular or surgical intervention(s) altogether.

109 *Seven-year-old male with a PTEN hamartoma of soft tissue (PHOST) arising in the stomach*

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Purpose: Germline mutations of the tumor suppressor phosphate and tensin homolog (PTEN) gene result in increased risk for certain malignant and benign tumors, hamartomas, and vascular malformations which manifest in a spectrum of disorders known as the PTEN hamartoma tumor syndrome (PHTS). A subset of PTEN related lesions with distinctive clinical presentation and histopatologic findings has recently been termed PTEN hamartoma of soft tissue (PHOST) (1). Fifty percent of PHOST have associated vascular malformations. PHOST are not known to involve the abdominal viscera. We describe a case of PHOST arising within the wall of the stomach with diffuse involvement of the omentum in a previously healthy seven-year-old male.
Methods: Retrospective review of medical records, imaging, and histopathology.
Results: 7-year-old patient presented with abdominal pain and hematemesis. On initial workup, including an abdominal ultrasound, a large high flow epigastric mass was identified. Cross sectional MRI confirmed a predominantly large gastric vascular tumor with abnormal fatty epigastric, abdominal and posterior mediastinum tissue. Biopsy suggested PHOST, which then led to clinical correlation with macrocephaly and penile freckling. Because of ongoing bleeding, surgical resection was performed. A partial gastrectomy and omentectomy were done with a Bilroth 1 reconstruction. A 358gm stomach resection showed a 13 cm oval fatty mass in the submucosa and muscularis propria, which on histology was composed of excessive mature fibroadipose tissue, foci of small concentrically thick walled arteries, and foci of alveolar-like lymphatic channels consistent with PHOST. In addition, there was a vascular malformation predominantly composed of large distorted veins and lymphatic channels associated with an angioproliferative capillary component. The 7cm omentum resection also demonstrated a venous-lymphatic malformation. Subsequent genetic testing confirmed heterozygous PTEN mutation.
Conclusion: PHOST are hamartomatous masses with distinctive clinical and histopathologic findings and can rarely present with primary visceral involvement, prompting clinical investigation for PHTS.

110 *Pathological Alterations in the Skin of Infantile and Early Childhood Port Wine Stain*

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Purpose: Port wine stain (PWS) is a congenital, progressive vascular malformation that early in its course involves mainly the superficial venular plexus. The histopathology of infantile PWS skin remains incompletely understood.
Methods: Biopsy samples were taken from one 9 month old female infant and a 22 month old male with PWS. Semi- or ultra-thin sections were prepared and examined under light or transmission electron microscopy. Four structures within PWS lesional skin, namely, blood vessels, epidermis, hair follicles/glands and connective tissues, were dissected on formalin-fixed paraffin embedded (FFPE) sections by laser capture microscopy (LCM). GNAQ exon 4 fragment was amplified by a nesting polymerase chain reaction (PCR) after genomic DNA was extracted from LCM collected samples. The GNAQ mutation (R183Q) was confirmed by next generation sequencing (NGS).
Results: We found an increase in the number of layers of both pericytes and basement membranes, bridged fenestrations between endothelial cells, ectasia of superficial venule-like blood vessels, and hypertrophy and anisotropic orientations of collagen fibers. Lymphatic vessels were noted to be normal. The GNAQ mutation (R183Q) was identified within hair follicles/glands with a frequency of 6.19% in the PWS lesions from the 9 month old female; While the same mutation was harbored within blood vessels and connective tissues with frequencies of 12.37% and 22.17%, respectively, in the PWS lesions from the other infantile subject.
Conclusion: Our findings show that there are indeed multiple pathological abnormalities present very early in infantile skin with PWS, suggesting that

early alterations in extracellular matrix components contribute to the pathogenesis and development of PWS. The GNAQ mutation (R183Q) is distributed in various structures, suggesting that pluripotent cells with the GNAQ (R183Q) may give rise to multilineages in PWS. Our results indicate PWS is not only a vascular malformation, but also with abnormalities present in the entire physiological milieu of human skin.

111 Vascular anomalies, Pediatric anesthesia, and Neurodevelopment: What is the best practice?

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Purpose: Children suffering from vascular anomalies will frequently require anesthesia in early life, as they undergo multiple examinations, procedures and surgeries. Over the last fifteen years, experimental data from animal models with developing brains exposed to various types of anesthesia show neuroapoptosis and neurodevelopmental changes with long term neurocognitive effects. The results of observational studies in children on possible iatrogenic effects of anesthesia seem less conclusive, making decisions about optimal care unclear.
Methods: To attempt to clarify these findings, we conducted a systematic review of recent publications on this subject, to search for relevant data on the relationship between pediatric exposure to anesthesia and neurocognitive outcomes.
Results: None of the retrospective studies identified involved patients with vascular anomalies, although many of the examinations and procedures these patients receive were included. Although clinical evidence suggests a modestly elevated risk of adverse neurodevelopmental outcomes (mostly learning difficulties and language developmental delay), no firm conclusion regarding causality can be drawn on the basis of these studies. Many questions arise with respect to methodology and confounding factors. Some children appear to be at greater risk of neurotoxicity: younger age (< 3 years), higher dose of anesthesia received (> 1 MAC), and longer duration of anesthesia (> 1 hour). Many of these risk factors apply to children with vascular anomalies.
Conclusion: There is no evidence to guide best practice regarding anesthesia administration in this population. The ultimate recommendation as to choice of modality should be made by the multidisciplinary team and shared with the patients and their families. References 1. Defining safe use of anesthesia in children. N Engl J Med 2015, 364(15); 1387-90. 2. Anaesthetics, infants, and neurodevelopment: case closed? The Lancet Oct 2015. http://dx.doi.org/10.1016/ S0140-6736(15)00669-8 3. SmartsTots (http://smarttots.org/). Consesnsus Statement on the Use of Anesthetic and Sedative Drugs in Infants and Toddlers, Oct 2015.

112 An innovative surgical method to alleviate refractory cutaneous pain

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Purpose: Many cutaneous or subcutaneous disease can lead to refractory and persistent cutaneous pain, such as eccrine angiomatous hamartoma (EAH). It is a rare benign disease that comprises vascular and eccrine malformations. Pain is one of the most common symptoms and surgical resection was required if needed. We report a novel surgical approach that can reduce severe pain caused by a large EAH lesion.
Methods: The patient was an 18-year-old male who was born with a red purple plaque (approximately 11*15cm in size) on the right iliolumbar region. The physical examination revealed pain with palpation and slightly high skin temperature. Chronic pain had an impact on the hip joint movement and gradually led to pelvic tilt showed on the X-ray. MRI found subcutaneous abnormal signal on the right hip and groin area. During the operation, the lesion was carefully elevated from the normal tissue above plane of the deep fascia and was sutured in situ.
Results: The visual analog scores (VAS) of his pain decreased from 9 points to 2 points one week after surgery, then dropped to 0 point another week later. The only complication was local numbness. Three months after surgery, the numbness disappeared with no recurrence of pain. One year after surgery, the pain severity still remained 0 point without complication. Histological findings demonstrated that the numbers of eccrine sweat glands and abnormal vessels decreased. X-ray of the hip joint showed the pelvic plane was normal.
Conclusion: The surgery procedure in our case present effective surgical option for large EAH with severe pain. It is also a novel method, invasive but effective, for refractory pain because of many cutaneous and subcutaneous disease.

113 RASA1 mutations associated with capillary malformation - arteriovenous malformation: A true AVM?

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Patients with RASA1 mutations demonstrate multiple capillary malformations and may have high-flow lesions also. An arteriovenous malformation is a high-flow lesion related to an abnormal communication between arteries and veins resulting in arteriovenous shunting. The diagnosis is performed by color Doppler ultrasound characterized by multiple feeding arteries with increased diastolic flow and high-velocity venous flow with a low-resistive index.

We sought to study the specific pattern of radiologic findings in high-flow lesions that are unique to patients with RASA1 mutations. We reviewed seven cases of RASA1-positive CM-AVM patients (6F, 1M) with high-flow lesions (Buttock: n=3, inferior limb: n=1, superior limb: n=1, face: n=2). None of our patients had cerebral AVM. The following criteria were analyzed on color Doppler ultrasound: 1. number of vessels; 2. the presence of high-diastolic flow with low-resistive index indicating the presence of arteriovenous shunting (< 0.4); 3. a resistive index > 0.4 (no arteriovenous shunting). MR criteria were the presence or not of an increased thickness of the fat and/or muscle in the area of the vascular lesion. Angiography criteria were the presence of arteriovenous shunting between arteries and veins demonstrated by an early venous return.

High-vessel density (> 5 cm) was seen in two and moderate vessel density (2-5) in five lesions. Arteriovenous shunting was observed in two patients whereas high-resistive index was observed in five. The presence of increased fat and/or muscle was observed in all patients. An angiogram was performed in only two patients and demonstrated a hypervascularization of the muscle without arteriovenous shunting.

In conclusion, the peripheral high-flow lesions diagnosed clinically in patients with RASA1 mutations can be associated with arteriovenous shunting like classical AVM but most of our patients have a hypervascularization of the hypertrophic area without arteriovenous shunting.
Are these lesions vascular malformations or vascular tumors?

114 Serum Angiopoietins Are Biomarkers For Kaposiform Lymphangiomatosis And Kaposiform Hemangioendothelioma And Respond To Sirolimus Treatment

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Purpose: Prediction of disease diagnosis, progression and response to therapies for vascular anomalies will be improved if biomarkers can be identified. The goal of this study was to identify biomarkers in the serum of patients with varied vascular anomalies pre- and post sirolimus treatment.
Methods: Groups of patients included: 1) generalized lymphatic anomaly (GLA)(n=7); 2) kaposiform lymphangiomatosis (KLA)(n=7); 3) kaposiform hemangioendothelioma (KHE) with Kasabach-Merritt phenomenon (KMP)(n=8), and other vascular anomalies (n=32). Serum was obtained at baseline, then 6 and 12 months after sirolimus initiation on our recent phase II study. Control serum was also obtained from age– and sex–matched healthy children and young adults (21 days - 28.5 years; 42% males 58% females; n=55). A panel of 8 angiogenic factors was measured in the serum samples using ELISA.
Results: Baseline levels of VEGF-A, -C, –D, IGF-1, ET-1 and TSP-1 were not different in the patient groups compared to controls. Ang-1 levels were lower (65%) in the serum of KHE with KMP patients compared to controls. Ang-2 was elevated in GLA (1.5-fold), KLA (10-fold) and KHE (14-fold) patients compared to healthy controls. Multivariable analysis and receiver operating characteristic curves showed that Ang-2 and Ang-1 levels discriminate between KLA and KHE+KMP patients with high sensitivity and specificity. After 12 months of sirolimus treatment, serum levels of Ang-2 were lower in KLA (4-fold) and KHE+KMP (10.5-fold) patients, whereas Ang-1 levels were higher in most KHE patients and similar to controls.
Conclusion: Serum Ang-2 was highly elevated in KLA patients and KHE patients with KMP and decreased with sirolimus therapy. Ang-1 was reduced in KHE patients with KMP. Serum levels of Ang-2 and Ang-1 deserve further study to discriminate between these diagnoses and as possible biomarkers of response to sirolimus therapy.

115 *Lymphangiomatosis involving the mandible and the spleen treated with sirolimus and bevacizumab*

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Purpose: To present a case of Diffuse lymphangiomatosis,nowadays, known as generalized lymphatic anomaly (GLA), which is a rare disorder characterized by the proliferation of lymphatic vessels in different organs, most commonly the lungs, bone, soft tissue, and spleen.
Methods: A case report
Results: We present a girl with congenital diffuse lymphangiomatosis limited to a mixed solid-micro cystic tumour in mandible bone and involvement of spleen with multiple tiny lesions. The diagnosis was confirmed on histhopatological studies. Recurrent transient worsening of the tumour with involvement of neck, bilateral sternocleidomastoid muscles, parotid glands, oropharynx and tongue, were associated with viral infection. Moreover, these episodes were associated with mild thrombocytopenia and coagulation disorder. The patient received multiple scheme of treatment with initial partial response which included propanolol (ov), sildenafil, corticosteroid (ev), sirolimus and bevacizumab (4 doses ev) and repair of the mandible with an iliac crest bone graft. During these treatments the patient had recurrent episodes of worsening, some associated with bleeding and mild thrombocytopenia. Currently, the patient is 4 years of age and tumour relapse free.
Conclusion: This was a rare case of Diffuse lymphangiomatosis involving both soft tissue and osseous mandible and spleen. The mandible fracture required bone graft and the disease was treated following multiple schemes, including sirolimus and bevacizumab. After two years follow-up the patient remains disease relapse free.

116 *Rapamycin-associated lymphoedema in an infant with Kasabach-Merritt phenomenon*

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Purpose: To describe a case of rapamycin-associated lymphoedema during the treatment of a Kaposiform hemangioendothelioma (KHE) with Kasabach-Merritt Phenomenon (KMP).
Methods: Case report
Results: Observation: A healthy 3.5 month-old male infant was referred for KMP associated with a KHE located on his left thigh. At presentation, a massive purple firm tumor encompassing the whole thigh coupled with swelling of the leg was noted. Blood count showed profound thrombocytopenia (1000/mm3). Rapamycin was implemented orally at the dose of 0.1 mg/kg/day, once a day. At day 8, the platelet count increased and 3 weeks later reached 50000/mm3. A dramatic shrinkage of the tumor and upstream lymphatic stasis resolution were noted without adverse side effects. Nine months under rapamycin therapy, the left inferior limb dramatically swelled. Clinical examination was consistent with lymphoedema showing a firm, painless, non inflammatory left limb. There was neither clinical sign, nor biological abnormality supporting KMP recurrence. We hypothesize that the lymphoedema was induced by rapamycin.
Conclusion: Given its anti-angiogenic effects and good safety profile, beneficial rapamycin use has been reported in the treatment of KHE associated with KMP. Rapamycin-associated lymphoedema is a rare side effect in solid organ transplant occurring 2 to 10 months after rapamycin initiation. Its location is anatomically related to the site of surgery or haemodialysis access. In vitro, mTOR inhibitors are able to inhibit lymphangiogenesis; then rapamycin may inhibit postsurgical lymphangiogenesis leading clinically to lymphoedema, in patients with mechanical or compressive pre-existing lymphatic «weakness». Upstream lymphostasis is frequently observed in the context of voluminous obstructive KHE of the limbs; KHE which displays a lymphatic component, may locally disrupt the integrity of the lymphatic network, which may be especially sensitive to mTOR inhibitors in the postnatal period. Close monitoring of children treated with rapamycin for KMP is mandatory in order to measure the frequency and duration of rapamycin-associated lymphoedema.

117 *Safety and efficacy of a 2mg/m2/day dose of rapamycin as treatment of superficial vascular anomalies in Algeria*

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Purpose: Vascular anomalies are a heterogeneous group of diseases which include infantile hemangiomas, other vascular tumors, and vascular malformations. A lot of new discoveries have allowed us to assume a more prominent role in clinical care relating to these diagnoses. Recent publications reported effectiveness of sirolimus 2mg/m2/day in cases of aretrio venous malformations, lymphatic, venous and capillary malformations. It has been proved as well to be effective in vascular tumors like kaposiforme hemangioendotheliomas complicated or not with consumptive coagulopathy as well as in aggressive infantile hemangiomas. We present here our results treating vascular anomalies with this new molecule

Methods: The objective of this study is to assess the safety and efficacy of a first line treatment with rapamycin 2 mg/m2/day in superficial vascular anomalies patients, namely in terms of: rate of disease control and one year survival. Type of study: observational non interventional study for a period of one year

Results: 15 patients were treated with rapamycin 2 mg/m2/day: 7 females and 8 males representing: 3 cases of Kasabach Merritt phenomenon 2 cases responded biologicaly and clinicaly and the third did not respond biologicaly, 4 cases with arterio-venous malformations all the cases responded very well with decrease of the arterial flow, 2 cases with thickened port wine stain, only one case showed clear collapse, 2 cases of venous malformations showed improvement, 3 cases with lymphatic malformations with improvement in only one case, 1 case of ressistant infantile hemangioma to betablockers, loosing angioumatous aspect. Side effects were, fever in 2 cases, aphtous ulcers in three cases, asthenia in one case.

Conclusion: Responses often occur slowly compared to those seen with propranolol in treating hemangiomas, and often are not noted for 2–9 months. Length of treatment is not defined. Anti-angiogenesis is one likely mechanism of action of these agents, as mTOR intersects with several angiogenesis pathways. Apoptosis may be another yet unexplored mechanism of action in this setting, as endothelial cells of vascular malformations actually appear to disappear in some situations.More studies are needed to identify prognostic factors of treatment succes, (i.e., combination of high efficacy and minimal side effects) in order to define the main characteristics of superficial vascular anomalies patients who could mostly benefit from this treatment, (in terms of age and general condition for the safety, and disease extent for the efficacy) .

118 *Treatment of Kaposiform hemangioendothelioma and Tufted angioma with Sirolimus. A case clinical series*

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Purpose: Kaposiform hemangioendothelioma (KHE) and Tufted angioma (TA) are locally aggressive vascular tumours. KHE, and to a lesser extent, TA can cause a coagulopathy called Kasabach-Merritt phenomenon (KMP). Both entities can cause significant morbidity and mortality, including hemodynamic instability, local invasion, and compression of vital structures. Treatment is particularly difficult for those who had no response to conventional therapies. This clinical series want to share experience of mammalian target of Rapamycin (mTOR) inhibitor Sirolimus in the treatment of KHE and TA.

Methods: Nine cases of KHE and TA with histopathologic diagnosis were treated with Sirolimus in our institution from December 2012 – November 2015.

Results: We identified nine patients, six male and three female children. Seven with diagnosis of KHE and two of TA. All the patients presented KMP except for two. Patients had been pretreated with corticoesteroids except for one. Six out of nine received vincristine concomitantly. The goal was to increase the serum Sirolimus level from 5 to 10 ng/mL, which was achieved at a dose lower than 0,1 mg/kg per day in most of the patients. All of them showed improvement in clinical status. The average response time was 6 days. Patients who presented KMP, except for two, have stabilizations of the platelet count during 2 weeks of treatment. The average time for Sirolimus as single therapy was 5,6 months. Two patients showed recurrence of the KMP and Sirolimus was reintroduced with good response. Only one patient showed mild oral apthosis and transient leukopenia. One patient died after discontinuing the treatment. Five patients kept taking Sirolimus.

Conclusion: Sirolimus appears to be effective and safe in patients with KHE and TA and represents a promising tool in treating refractory KHE/TA but also as first line treatment. It should be noted that most patients required a lower dose than recommended in the bibliography.

119 Sirolimus for the Treatment of Vascular Anomalies in Children

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Purpose: Management of complex vascular malformations can be challenging. Although surgical interventions can be beneficial, recurrence is common and some cases may not be amendable for surgeries. Successful treatment with sirolimus has been reported, but clinical trials to date are limited to adults. The purpose of this study was to (i) evaluate the clinical outcomes of vascular anomalies in children treated with sirolimus; (ii) explore the benefit of sirolimus as an adjuvant therapy.
Methods: Retrospective chart review was performed on 8 children treated with sirolimus for vascular anomalies in our institution for the past three years. The patients have various anomalies including lymphatic malformations (x3), mixed venolymphatic malformations (x4), and arteriovenous malformations [AVM(x1)]. All subjects were refractory to previous surgical and medical therapies prior to systemic sirolimus treatment.
Results: The subjects' ages range from 3 to 17 years old. Median duration of treatment was 12 (6-31) months. One patient with AVM of the head and neck also had embolization two months after sirolimus was initiated and had marked improvement. Seven of the remaining patients (7/8) had notable clinical response evident by reduced swelling or pain. One patient demonstrated clear radiologic improvement. Sirolimus was well-tolerated by all patients with no significant adverse events. All 8 patients are still on treatment. The most common side effect observed was oral ulceration, which occurred in 3/8 patients. Only one patient requested dose adjustment because of the oral ulcer.
Conclusion: Sirolimus can be used alone or as an adjuvant therapy for effective treatment of complex vascular anomalies, especially in children. There is no clear correlation between the diagnosis and extent of response to sirolimus. Further molecular and genetic characterization of these patients may improve our understanding in the management of vascular anomalies using mTOR inhibitors.

120 Sirolimus for the Treatment of Juvenile Nasopharyngeal Angiofibroma

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Purpose: Juvenile nasopharyngeal angiofibroma (JNA) is a pathologically benign yet locally aggressive and destructive vascular tumor typically affecting adolescent boys. Embolization and/or surgery are considered the standard treatment approach. Postoperative radiotherapy has been considered an effective adjuvant. We present 3 patients with JNA that received treatment with sirolimus, an m-TOR inhibitor with antiangiogenic properties.
Methods: Retrospective multisite case series of JNA treated with sirolimus for a minimum of 3 months between January 2007 and June 2014.
Results: Three patients with JNA were included in the above retrospective study. These patients were started on sirolimus for significant bleeding, continued growth and/or recurrence after resection. All experienced a partial reduction of tumor size, improved clinical symptoms, with less bleeding and resolution of anemia in 2 of the boys, with no or manageable side effects. Please see table in abstract file.
Conclusion: The use of sirolimus in patients with JNA is safe and effective. Sirolimus should be considered as a potential neoadjuvant treatment for JNA prior to definitive resection to reduce tumor size, or as maintenance therapy to control symptoms and prevent recurrence.

121 Phase II Study Follow Up: Efficacy and Safety of Sirolimus in the Treatment of Complicated Vascular Anomalies

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PURPOSE: Complicated vascular anomalies have limited therapeutic options and cause significant morbidity and mortality. We previously conducted a Phase II trial, enrolling 61 patients with complicated vascular anomalies, in order to determine efficacy and safety of treatment with the mTOR inhibitor Sirolimus (Rapamycin). Here we present follow up data on 43 of the 46 patients who completed all 12 courses of the Phase II safety and efficacy study.
METHODS: We prospectively followed 46 patients who chose to remain on off-label sirolimus. Patients were
evaluated every 6 months for disease evaluation and any toxicity attributable to sirolimus. Serum drug levels were obtained to titrate dosage to either low dose (serum level less than 6 ng/mL at 12 hours) or standard dose (serum level 10-13 ng/mL) depending on disease status and drug tolerance.
RESULTS: The range of follow up was 6 – 54 months with mean of 26.7 months and median 24 months.

Sirolimus was discontinued in 20 patients sometime after the 12-month study period, of those 20, eight patients remained off and 12 required restarting. Low dose sirolimus was administered in 22 patients while 13 required standard dose, six of which needed additional therapy (medical or surgical). Three patients were lost to follow up.
CONCLUSIONS: Sirolimus is effective and safe in patients with complicated vascular anomalies specific to this study and represents an important tool in treating these diseases. Low dose sirolimus was required in the majority of patients in order to maintain stable disease. There were no long term toxicities or complications observed in any of these patients.

123 *Sirolimus for Cervicofacial Lymphatic Malformation*

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Purpose: Lymphatic malformations (LMs) are challenging to manage, particularly those involving the cervicofacial region and airway. Primary therapy is sclerotherapy and/or resection, while the role of sirolimus is evolving for the treatment of cervicofacial LMs.
Methods: An IRB-approved retrospective review of 19 patients treated with sirolimus for cervicofacial LMs from November 2012 to October 2015.
Results: Five patients have completed therapy (duration 5, 9, 17, 25, and 26 months) and 14 remain on sirolimus (range 4-35 months). Age at initiation ranged from 2 months to 34 years. Nine patients had microcystic LM and ten had mixed macrocystic-microcystic LMs. All patients have serial photographs and 10 patients have serial imaging to gauge response. All patients demonstrated some reduction in LM bulk, ranging from dramatic to visually modest. Younger patients with mixed macrocystic-microcystic disease with less prior therapy demonstrated more siginificant responses. 94.7% (18) patients reported subjective improvement on sirolimus including decreased LM bulk, softening tissue, decreased bleeding/leaking related to mucosal vesicles, and decreased rates of cellulitis. All patients (n=13) with mucosal vesicles present at initiation of sirolimus resolved or improved. Median time to initial response was 1 month (range 5 days to 4 months). Of six patients with tracheostomies, one was decannulated after maxillofacial surgery and two are tolerating capping while on sirolimus. Six patients developed cellulitis within the LM during treatment; none progressed to sepsis or had more cellulitis on sirolimus. No opportunistic infections occurred. Two patients have undergone surgical debulking following sirolimus treatment to decrease residual remaining tissue with wound healing issues.
Conclusion: The use of sirolimus in the management of cervicofacial LMs appears to be efficacious, especially in younger patients and for mucosal disease, with limited adverse events. Long-term follow-up, durability of response, and coordination of sirolimus around procedural therapies need further evaluation.

124 *Sirolimus for microcystic lymphangioma in the head and neck region of children with tracheostoma and/or gastrostoma*

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Purpose: Microcystic lymphangioma in the head and neck region can cause respiratory and alimentary problems. Tracheostoma and/or gastrostoma can be necessary to ensure breathing and nutrition. Sirolimus could help reversal of tracheostoma and/or gastrostoma.
Methods: Five children with microcystic lymphangioma of the tongue, mandibular, neck and mediastinum region needed tracheostoma (n=3), gastrostoma (n=1) or both (n=1). Tracheostoma was operated at the age of 2, 7, 17 and 150 days. Gastrostoma was placed at the age of 3 and 5 months. Further therapy was surgery (n=5), sclero- (n=3) and lasertherapy (n=1), radiofrequence ablation (n=1) as well as steroids and propranolol (n=2). Sirolimus was initiated at the age of 2, 3, 5, 8 and 18 years. Treatment was stopped after 6 months in two patients and is ongoing in three patients for 7, 13 and 31 months.
Results: Gastrostoma in one child could be reversed after 22 months of sirolimus at the age of 4 years. Four children still need their tracheostoma. In three children mouth closure was improved and number of infections diminished. In an 18-year-old girl sirolimus caused several episodes of fever of unknown origin and had to be stopped regularly with no clinical and radiological effect. Another 6-year-old boy without side effects also showed no effect with sirolimus. In both patients sirolimus was stopped after 6 months.
Conclusion: These preliminary results of a small case series from two centers show that sirolimus helped to take off gastrostoma in one child after nearly two years of therapy but could not support reversal of tracheostoma in four children. Importantly, mouth closure ameliorated and infection rate was decreased by sirolimus in three patients. Eventually age at initiation and duration of sirolimus as well as pre-treatment seems to play a role for the effect of sirolimus on microcystic lymphangioma.

125 *Sirolimus is highly effective for bleeding and lymph leakage in vascular anomalies*

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Purpose: Bleeding and lymph leakage in vascular anomalies can lead to anemia and infections. Supportive care consists of lymph drainage, compression stockings, iron supplement and prophylactic oral antibiotics. Compression dressings, i.v. antibiotics and red blood cell transfusions are emergency measures.
Methods: Eight patients were treated with sirolimus as an individual "ultima ratio" therapeutic approach for bleeding and/or lymph leakage. The vascular anomalies were localized at the flank and pelvic region (1), the axillary region (1), the leg and gluteal region (4) and the genital region (2). Patients had multiple pre-treatments such as surgery, laser- and sclerotherapy. First bleeding and/or lymph leakage episodes started at the age of 2 months, 8 years, 12 years (2), 14 years (2), 20 years and 31 years. Duration was 10, 16 and 18 months, 2 years (2), 4 years, 6 years, and 28 years before sirolimus was introduced.
Results: Sirolimus was effective after one day (1), ten days (1), four weeks (5) and after four months (1). Especially in a 20 month old boy and a 12 year old girl, both with bleeding of venous-lymphatic malformations of the leg necessitating blood transfusions and iron substitution, sirolimus stopped bleeding after one and ten days. A female patient with vaginal lymphorrhea of 4-6 liters/day for more than 20 years showed complete remission 4 months after sirolimus was started. She relapsed after another 4 months but with significant minor volumes. Two patients relapsed after sirolimus was stopped and showed again response when treatment was re-started. Importantly, no toxicities were observed. Five patients are still on sirolimus for up to 3 years.
Conclusion: All patients showed response on sirolimus with a fast and long lasting effect also observed when reintroduced after therapy breaks. Sirolimus could be an emergency treatment for bleeding and lymph leakage in vascular anomalies.

126 *Denosumab for lymphatic malformation in Gorham Disease of the cervical spine*

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Purpose: Gorham-Stout Disease (GSD) is characterized by lymphatic malformation affecting a single or multiple bones and adjacent soft tissues. In contrast to Generalized Lymphatic Anomaly (GLA), which does not progress with time and in which the bone cortex is spared, GSD invades the bone cortex, and causes progressive osteolysis. GSD has no known effective medical management, and we have used individualized therapy for an otherwise untreatable case of GSD.
Methods: A 28-year-old male was diagnosed with cervical spine Gorham disease following a hockey injury in 2005 at the age of 18. Despite posterior cervical fusions, he had progressive bone destruction, and required anterior fusion in 2008. He was treated with low dose interferon alpha 2B (1.5 mill units/m2) and alendronate 15 mg daily, and while the therapy was associated with no further progression of the local disease, he had continued loss of bone density, abdominal pain, nausea and weight loss. In February 2012, he was started on denosumab (Xgeva) 120 mg subcutaneously every four weeks, vitamin D 2000 i.u daily, calcium 1600 mg daily, and Interferon alpha 2B 1.5 million i.u.sc daily with excellent resolution of the symptoms
Results: The treatment with denosumab, interferon alpha 2B, Vitamin D and Calcium has led to improvement of bone density, daily function and pain. The therapy is not associated with nausea, abdominal pain or weight loss, enabling the young man to return to school, non-contact sports, and work.
Conclusion: Denosumab has been approved for the treatment of osteoporosis and giant cell tumor of the mandible in 2010. It is a monoclonal antibody inhibiting RANKL and TNF pathway signaling, the main contributors to osteoclast differentiation. Its mechanism of action suggests an important role in bone destruction associated with GSD, and we present the first case where its use led to stabilization, possibly improvement in the disease.

127 *Intraoperative Talc Administration Decreases Rate of Wound Complications in the Surgical Treatment of Lymphatic Malformations*

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Purpose: Surgical management of lymphatic malformations (LM) is associated with a significant complication rate , including recurrence, postoperative seroma and infection. Current treatment modalities include sclerotherapy, surgical and medical therapies with no standard protocol defined. We hypothesized that intraoperative administration of a sclerosant would result in a decreased rate of wound complications, particularly seroma. The purpose of this study is to evaluate the effectiveness of intraoperative application of dry talc prior to surgical closure in preventing postoperative complications at a multidisciplinary vascular anomalies center.

Methods: With IRB approval, a retrospective chart review was completed on all patients diagnosed with extraabdominal lymphatic malformations at CHLA between April 2004-June 2015. Exclusion criteria included intra-abdominal LM patients. Complications included postoperative seroma, wound separation, wound infection or persistent wound drainage. Statistical analysis was not completed due to the study being under-powered with limited number of patients receiving intra-operative talc administration.

Results: One hundred-twenty three patients were found to have an extra-abdominal LM and 48 patients underwent surgical intervention. Of the 48 patients, 25 were treated with sclerotherapy prior to surgery and 23 had surgery alone. During surgery, 6 patients received talc administration to the wound bed prior to closure. The post-operative seroma rate for surgery alone was 44%, 36% for pre-operative sclerotherapy and 17% for surgical talc administration. Post-operative wound infections for surgery alone was 13%, 40% for pre-operative sclerotherapy and 17% for surgical talc administration (Table 1).

Conclusion: In our preliminary study, the application of talc during surgical resection of LMs prior to wound closure results in a trend towards a decreased rate of postoperative wound complications, including seromas and wound infections. Further studies are needed to clarify the role of intra-operative talc during surgical resection in LM patients.

128 *Comparative study of recurrence after resection and reconstruction of arteriovenous malformation*

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Purpose: The treatment of arteriovenous malformation(AVM) is challenging yet good prognosis can be anticipated after complete extirpation of a localized AVM. Wide resection of large diffuse AVMs tends to be avoided, because of the potential risks of devastating blood loss and functional impairments following wide resection. Cosmetic results are often suboptimal. In addition, it may be impossible to attain complete cure in large AVMs which involve a critical anatomical area. In these patients, long term follow up is required to observe for recurrence. Taking into account these risks and problems, we have chosen an aggressive approach to AVM resection, developing new operative techniques while prioritizing safety and effectiveness. We report our results, focusing on the incidence and type of recurrence in patients who were reconstructed by skin grafts or free flaps after extensive resection of large AVMs.

Methods: Between 2006-2014, 20 patients underwent reconstruction after AVM resection. There were 14 male and 6 female patients, with an average age of 36.5 years old. There were 12 AVMs of the trunk and extremities and 8 of the head and neck region. 17 patients underwent free flap reconstruction with the rectus flap (n=6), latissimus dorsi flap (n=6), anterolateral flap (n=4) or 2 free flaps (n=3). Defects in the remaining 3 patients were covered with skin grafts. Only partial resection was achieved in two patients with head and neck lesions and they were excluded from the subsequent analysis.

Results: After an average follow up of 3 years 4 months (range 6 months to 7 years), recurrence was observed in 2 of the remaining 18 patients. Both patients had been reconstructed with free flaps and the recurrence could be observed as a red stain around the flap. These could be classified as Schobinger stage I lesions and and the patients remained asymptomatic on long term follow up of 6 years and 4 years respectively.

Conclusion: DesPrez, et al. have suggested that well-vascularized tissue such as free flaps could suppress AVM recurrence. Our results seem to concur with their report in that the two patients with recurrence after free flap reconstruction, had suppression of their disease which did not progress beyond simple skin staining (Schobinger 1). However, no recurrence was noted in two patients in whom skin grafting had been chosen for defect coverage. Complete resection of the lesion had been achieved in each case. We postulate that the mode of resection (partial vs complete) is more important than the type of reconstruction, in influencing AVM recurrence.

129 MANAGEMENT OF PEDIATRIC INTRAMUSCULAR VENOUS MALFORMATIONS

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Purpose: Although venous malformations (VMs) are common vascular anomalies, intramuscular VMs are rare and can be highly symptomatic. Few reports have documented management outcomes, particularly with regards to intramuscular contractures. Our goal was to compare the results of observation, sclerotherapy, and surgical resection of intramuscular VMs at a single vascular anomalies center.
Methods: In our retrospective review, the medical records of 121 patients with a diagnosis of VM of an extremity or trunk between June 2005-June 2015 were reviewed. 61 were intramuscular and of these, 45 patients had adequate follow-up (2 months-10 years). Patients were grouped into cohorts based on initial treatment modality. Outcomes were compared with the chi-squared test; p-values < 0.05 were considered significant.
Results: The most common presenting complaints were pain (80%), enlarging mass (44%), and functional limitation (37%), but only 20% of patients presented with muscle contracture. The most common initial treatment was sclerotherapy (70%), followed by observation (17%) and surgery (11%). 75% of patients who were initially observed had symptomatic improvement without any subsequent procedures. A course of sclerotherapy effectively decreased pain in 72% of patients. Of the patients who presented with muscle contracture, 33% resolved with sclerotherapy combined with physical therapy and aspirin, 22% resolved with surgery, and 45% had persistent contracture even after physical therapy and bracing. 40% of patients treated with sclerotherapy then surgery developed new muscle contractures, compared to 4% of sclerotherapy only patients and 0% of the surgery only patients (p=0.04).
Conclusion: VMs often cause functional limitations secondary to pain, mass effect, and muscle contracture. They can effectively be treated by surgery and sclerotherapy. Sclerotherapy is more effective for treating pain than contractures and when used alone, rarely causes a new muscle contracture. Observation and supportive care should be considered as a primary treatment for patients with minimal symptomatology and no functional limitations.

130 SURGICAL TREATMENT RESULTS OF INTRAMUSCULAR VASCULAR MALFORMATIONS

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Purpose: Intramuscular vascular malformations (IMVM) are rare and their treatment is challenging due to functional muscle involvement. Surgical treatment is often considered not feasible due to location and uncertain outcome. The goal of our study was to evaluate surgical treatment results of IMVMs and provide an update on outcomes.
Methods: A retrospective analysis of 72 patients with IMVMs was performed. Lesions were classified into high-flow or low-flow, localized or infiltrative forms. Surgical techniques included either muscle oversewing or extirpation of muscle with entire malformation or combination of both. A positive result included cure, improvement or remission, a good result - cure or improvement.
Results: 14 high-flow and 58 low-flow IMVMs in patients aged 1-70 years (mean 21.8 years) were treated surgically.9(64.3%) arteriovenous high-flow malformations underwent prior embolization. 32 lesions were localized, 40 – infiltrative and located in: head/neck 6, upper extremities 15, trunk 11, gluteus 4, lower extremities 36. Majority lesions were treated with combination of oversewing/ extirpation 65(90.3%), 3(4.2%) with oversewing, 4(5.5%) with extirpation. Cure was achieved in 33(45.8%), good result in 59(81.9%), positive in 69(95.8%) patients.The best results were achieved in gluteus and calf compared to other locations:cure 76.9% and 39.0% respectively(p=0.013).There was no difference between high-flow and low-flow lesions: cure in 50.0% and 44.8%,good result in 92.9% and 79.3% respectively(p>0.005). Significant difference was observed between localized and infiltrative forms: cure in 84.4% and 15.0%,good result in 100% and 67.5% respectively(p<0.001).In 32(80.0%) infiltrative IMVMs multi-stage operation was need for complete lesion excision.No patients reported functional impairment post-operatively.
Conclusion: Here we report a first large case series of surgical treatment results for IMVMs. We recommend that IMVMs including high-flow lesions can be treated with radical surgical muscle excision. Excellent outcomes can be achieved in localized IMVMs of gluteus and calf muscle groups. Surgical treatment of IMVMs is a safe and effective treatment strategy that might require several procedures and needs great surgical expertise.

131 Angiosarcoma arising in a patient with a 27-year-old lymphatic-venous malformation: a case report

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Purpose: Malignant change in benign vascular tumor is exceedingly rare, and there have been only 10 previously reported convincing cases in literature. Herein, we report the first case of angiosarcoma spontaneously arising in a lymphatic-venous malformation (LVM).
Methods: We performed a retrospective review of medical records, radiologic studies, pathology and laboratory results of a single patient.
Results: A 27-year-old woman presented with a huge Red-to-violet papule involving the left side of her trunk at birth, associated with a 1-year history of discomfort and pain. The lesion was a pale-pink flat birthmark initially and expanded slowly in proportion to the body. She received three courses of sclerotherapy using pingyangmycin when she was 7 years old, and a local resection without pathological examination 2 years later. In July 2015, when she was presented to our hospital, we aspirated normal venous blood and lymph from different parts of the lesion. It was supportive for the diagnosis of LVM. MRI and CT disclosed obviously heterogeneous enhancement. The "no enhancement" part indicated the lymphatic component of the lesion. Laboratory evaluation showed profound thrombocytopaenia, with platelets 38,000/μL, which might occur in low-flow vascular malformation. However, biopsy specimen showed high grade epithelioid angiosarcoma. The distinctive histopathological feature was the epithelioid tumor cells observed filling the lumen of the normal vascular. The epithelioid cells characterized by intracytoplasmic vacuoles with red cells inside were in keeping with a diagnosis of angiosarcoma. Immunohistochemical staining showed that the tumor cells were positive for CD31, CD34, D2-40, factor VIII. Further examination revealed no evidence of metastases. The patient is undergoing adjuvant radiotherapy.
Conclusion: We describe a unique case which differs from those reported previously in some clinical and morphologic aspects. The case highlights the potential that benign vascular malformation can transform into malignant tumors.

132 Clinical Case Series of Angiosarcoma in the Liver

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Purpose: Angiosarcoma is a rare (2% of sarcomas), aggressive, malignant soft tissue neoplasm of the vascular endothelium with a very poor prognosis.
Methods: We report a systematic retrospective multisite case series of 8 pediatric patients with liver angiosarcoma. Patients were from five international institutions.
Results:

Patient	Age of AS DX	Initial presentation	Diagnosis'	Time to Diagnosis of Angiosarcoma	Treatment	Response	Outcome
1	3 yrs.	Abdominal Distention, Poor Feeding	Infantile Hemangioma	1 year 9 months	Propranolol, Sirolimus/Vcr Sorafenib Avastin/Gemcitabine/Docetaxel Sirolimus/Trametinib	relapse	Died
2	Birth	Multiple cutaneous lesions, brain, liver, bone lesions	Vascular Tumor	17 days	Vincristine, Steroids, Sirolimus	No response	Died (60 days)
3	3 yrs.	Abdominal distention At birth cutaneous infantile hemangiomas	Angiosarcoma Second biopsy Glut-1 positive hemangiomas Final Glut 1 + hemangioma with islands of angiosarcoma	At presentation	Gross Total resection Sorafenib Ifos/Dox/VCR Avastin/Gemcitabine/Docetaxel Radiofrequency ablation Propranolol Avastin/Gemcitabine/Docetaxel	relapse	Died
4	4 yrs.	Abdominal Distention, Pain	Infantile Hemangioenothelioma Glut- 1 + High proliferation	15 days	Transplant	none	Alive 3 years from diagnosis

Patient	Age of AS DX	Initial presentation	Diagnosis'	Time to Diagnosis of Angiosarcoma	Treatment	Response	Outcome
5	2 yrs.	Skin and liver lesions after birth, Hypothyroid 2 years later liver lesion, increased abdominal girth	Transformation of a infantile hemangioma with high grade angiosarcoma	2 years	Propranolol Gross Total Resection Intra-arterial therapy	relapse	Died
6	4 yrs.	Initially skin lesions. 2 years of age liver lesion DX are hemangioma 4 year of age increasing lesion	Hemangioma Bony lesion angiosarcoma	4 years	Steroids Embolization Interferon Radiation Cytoxan Liver transplant Radiation Cisplatin/Doxo	relapse	Died
7	3 yrs.	Abdominal Distention	Angiosarcoma arising from an infantile hemangioma	1 year	Transplant Lung mets Ifos/Dox/VCR sirolimus	remission	Alive
8	3 yrs.	Abdominal pain and Distention	Initial Diagnosis Hemangioma Angiosarcoma	4 months	VCR/Cisplatin/Cytoxan Doxo/Etop/Ifos	Partial response initially	Died

Conclusion: Liver angiosarcoma is a rare tumor in children with a high mortality rate. The pathology of these liver lesions is confusing. Transformation from benign to malignant pathology seems to occur.

133 WT-1- expression in angiokeratoma and verrucous hemangioma; a positive marker for malformation when negative?

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Purpose: To further clarify and understand the origin and characteristics in a clinical and histopathologic context of both lesions to enable better diagnosis, prognosis, and treatment.
Methods: 12 patients (7 male, median age 48 range 6-89) with solitary angiokeratoma have been sorted from a list of cases diagnosed as hemangioma (SNOMED m91200). Keywords from the diagnos such as "thinwalled vessels","hyperkeratosis" and "acanthosis" were used to question the hemangioma diagnosis. Others were diagnosed as angiokeratoma primarily. Concerning verrucous hemangioma, 7 cases (5 male, median age 19, range 2-41) discussed in multidisciplinary conferences were sampled. All were patients registered in our database 2012-2015. Immunostaining with WT-1 was performed in order to classify the lesions as tumour vs malformation; WT-1 negativity indicating malformation. Angiokeratoma was defined as a superficial vascular lesion in the papillary dermis, with a mixture of lymphatic and hematic vessels. Verrucous hemangioma was defined as a vascular lesion comprising both superficial and deep dermis and underlying tissues, with more extensive growth and exclusively hematic vessels.
Results: More male patients were identified (c:a 70%). Angiokeratoma patients were older. Verrucous hemangioma patients were predominantly children and young adults. Most lesions regardless diagnosis were located to the lower extremity. WT-1 was negative in all angiokeratomas. However, a focal positivity in WT-1 was expressed in 2 cases of verrucous hemangiomas, a previously reported in other series.
Conclusion: Angiokeratomas and verrucous hemangiomas are still controversial entities regarding their nosological classification. Although WT-1 expression seems to vary for verrucous hemangiomas, we think that the distinction should not only be done with the immunostaining profile but also according to their clinical course which favors a malformation diagnosis. We therefore suggest to name the lesions superficial and combined/deep angiokeratotic malformation, respectively.

134 Congenital smooth muscle hamartoma mimicking cutis marmorata telangiectatica congenita

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Purpose: To present an interesting case of congenital smooth muscle hamartoma mimicking cutis marmorata telangiectatica congenita.
Methods: case report
Results: A two-month old boy was referred for the evaluation of a congenital vascular lesion on his leg. At first sight – before palpation of the lesion – he seemed to have CMTC in a band-like distribution along the lateral aspect of his right leg including the dorsum of the foot with characteristic partial atrophy of the involved area (Fig 1a and b). However, even without touching the skin we observed vermiform movement of the affected skin and sudden marked patchy whitening within the band-like lesion which spontaneously resolved within 30-40 seconds (Fig 1c). On palpation there was a firm indurated linear plaque in association with the livedo-like, partially atrophic skin. A skin biopsy was performed at the age of 3 months and the histology was consistent with a smooth muscle hamartoma with fascicles of spindle cells and positive immunohistochemical staining for smooth-muscle-actin. At the last follow-up at the age of 10 months the child continued to be asymptomatic with a similar presentation of his SMH with CMTC-like feature, however the periodic spontaneous smooth muscle contractions were less visible (Fig 2a and b).
Conclusion: We were intrigued by the unusual presentation of this case with CMTC- like features on top of a congenital SMH. However, we were able to find a single, strikingly similar case in the literature. Vivehanantha et al. had recently described a congenital smooth muscle hamartoma masquerading as a reticulate vascular nevus on the leg. The clinical picture as well as the histology strongly resembles our patient. It remains unclear, whether the vascular component is fully caused by the SMH or if the CMTC-like aspect occurs superimposed on the SMH. We advised for a conservative approach because of the benign nature and rather large extension of this lesion. This case is another example that vascular appearing lesions at birth do by no means have to be vascular in nature.

135 Unusual Vascular Anomaly in Infantile Boy

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Purpose: Vascular anomalies are divided into malformations and tumors. While malformations are usually slow growing, vascular tumors proliferate rapidly and are characterized by endothelial turnover. It is often difficult to provide definitive diagnoses, as lesions may not conform ideally to existing classifications. Here we present the case of a newborn with an unusual growth in the inferomedial aspect of the left eye.
Methods: Otherwise healthy Hispanic infant boy born with a pedunculated bright red, vascular-appearing nodule involving the medial aspect of the left lower eyelid (Fig 1). DOL 4: Mass continued growing and started on 3mg/kg/day prednisolone and ranitidine prophylaxis. DOL 9: Decreased vertical lid fissure. DOL 10: Prednisolone increased to 5mg/kg/day, slight bleeding and mild superficial ulceration noted. Mass continued to enlarge and bleed. Patient was admitted and started on propranolol 1.4 mg p.o. qid. Mass was removed at DOL 23 and sent to pathology (Fig 2).
Results: The patient presented with a growing mass that was unresponsive to steroids and propranolol. The mass was interfering with his field of vision and causing astigmatic change, and emergency resection was ordered. The lesion was immunoreactive to CD31 stain and negative for GLUT1 and D240 stains. Additionally, sections showed epidermal hyperplasia with acanthosis and focal parakeratosis. Mild inflammatory infiltrate and areas of fibrosis, scarring, and necrosis were noted within the dermis, which resulted in its designation as an unusual vascular malformation. Following whole exome sequencing, a heterozygous NRAS c.181C>A, pQ61K mutation was found and confirmed by Sanger sequencing. Interestingly, the mass was negative for previously identified vascular mutations in TEK, RASA1, VEGRF3, FOXC2, SOX18, ACVRLK1, MADH4 and ENG.
Conclusion: Although the case was initially perceived as infantile hemangioma, after reviewing the excised mass and histological slides, it was determined to be a vascular neoplasm that was not indicative of hemangioma.

136 *Angiokeratoma Corporis Diffusum. One Phenotype, Different Ethiologies*

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Purpose: Angiokeratomas are a type of vasculr lesion classified as Provisionally unclassified vascular anomalies. The term Angiokeratoma Corporis Diffusum (AKD) is used to describe the presence of multiple angiokeratomas distributed predominantly over the bathing suit area (from the umbilicus to the knees). Although in the past it was considered a sinonym of Fabrys disease, today, several other ethiologies have been also shown to manifest with this phenotypic expression. To date, AKD has been described in Fabry´s disease, Galactosialidosis, beta Mannosidosis, Aspartilglucosaminuria, Shidler/Kanzaki disease, GM1 Galactosialidosis and in a group of patients with not known lysosomal alterations named Idiopathic AKD
Methods: We describe 4 patients with AKD and different underlying conditions.
Results: Four different patients with the AKD phenotype seen at our department are described. One of the patients, a 20 year old male, with Fabry disease. Patient 2, a 29 year old male with beta mannosidosis. Patient 3 a 26 year old female with galactosialydosis. The last patient is 16 year old girl in whom known lysosolmal deficiencies were ruled out, so she is considere an idiopathic AKD.
Conclusion: AKD is a phenotypic expression of several diseases. Undubtedly Fabry´s disease should be the first disease to rule out in this patients, not only because it is the most frequent, but also because it has a specific replacement therapy. Once this disease is shown not to be the cause, further studies should be performed to study all the other possible etiologies.

137 *Congenital Disseminated Pyogenic Granuloma: Characterization of a Rare Multisystemic Disorder*

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Purpose: To characterize the clinical and imaging findings of congenital disseminated pyogenic granuloma, a rare, potentially lethal disorder with aggressive natural history.
Methods: Retrospective review of the medical records, photographs and imaging studies of the databases at Boston Children's Hospital from 1999 to 2015 for patients with congenital hemangiomatosis or pyogenic granuloma. Only patients with histological proven patterns of pyogenic granuloma were included.
Results: Six patients were found to have histologically-proven congenital disseminated pyogenic granuloma (5 male, 1 female). Multiple reddish pedunculated papules were evident at birth. The most serious manifestation was brain involvement (n=4) presented as multifocal large hemorrhages and neurologic deficit. Multiple pyogenic granulomas were noted in the liver (n=3), muscles (n=2), bone (n=1), spleen (n=1), lungs (n=1), mesentery (n=1), pancreas (n=1) and adrenal gland (n=1).
Conclusion: Congenital disseminated pyogenic granuloma is an aggressive multisystemic disorder which affects the skin, brain, viscera and musculoskeletal system. This disorder , which was referred to as "diffuse neonatal hemangiomatosis" in the literature, can be differentiated from multiple infantile hemangiomas by the predilection to the brain and musculoskeletal system, among others.

138 ERUPTIVE, MULTIPLE, AGMINATED PYOGENIC GRANULOMAS, SUCCESFULLY TREATED WITH TOPICAL TIMOLOL: CASE REPORT

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Purpose: Pyogenic granulomas are common benign vascular tumors, but they are usually solitary. Eruptive, multiple pyogenic granulomas are rarely described. We report a case arising on a congenital capillary malformation, successfully treated with topical timolol.

Methods: A five year-old boy presented with a pink vascular stain on the right cervical area that had been present since birth. At the age of four, he developed five red papules on the stain. Doppler ultrasound was performed and arteriovenous (AV) malformation was ruled out. One of the papules was surgically excised, and the biopsy confirmed the diagnosis of pyogenic granuloma. An attempt to excise multiple lesions resulted in recurrence of all of them. Shortly after the procedure, new lesions continued to develop, some of them grouped.

Results: The patient was treated initially with propranolol 1.5mg/kg/day for 6 weeks with mild changes in color. Afterwards, the patient received topical 1% timolol cream twice daily for two months, showing significant changes of EMAPGs in color and size. No adverse events were reported.

Conclusion: Reports of eruptive, multiple, agminated pyogenic granulomas (EMAPGs) over a congenital vascular malformation are uncommon and surgical excision has been the treatment of choice.1 The use of β-blockers, including topical timolol, has been described for isolated pyogenic granulomas, with good response, although the exact mechanism of action is still unknown.2-4 To our knowledge, there are no previous reports of EMAPGs being treated with β-blockers. Our case suggests that therapy with topical timolol may induce at least partial regression of EMAPGs over congenital capillary malformations. Further studies and longer periods of treatment are needed to assess the true efficacy and outcome of topical β-blockers in the treatment of this condition.

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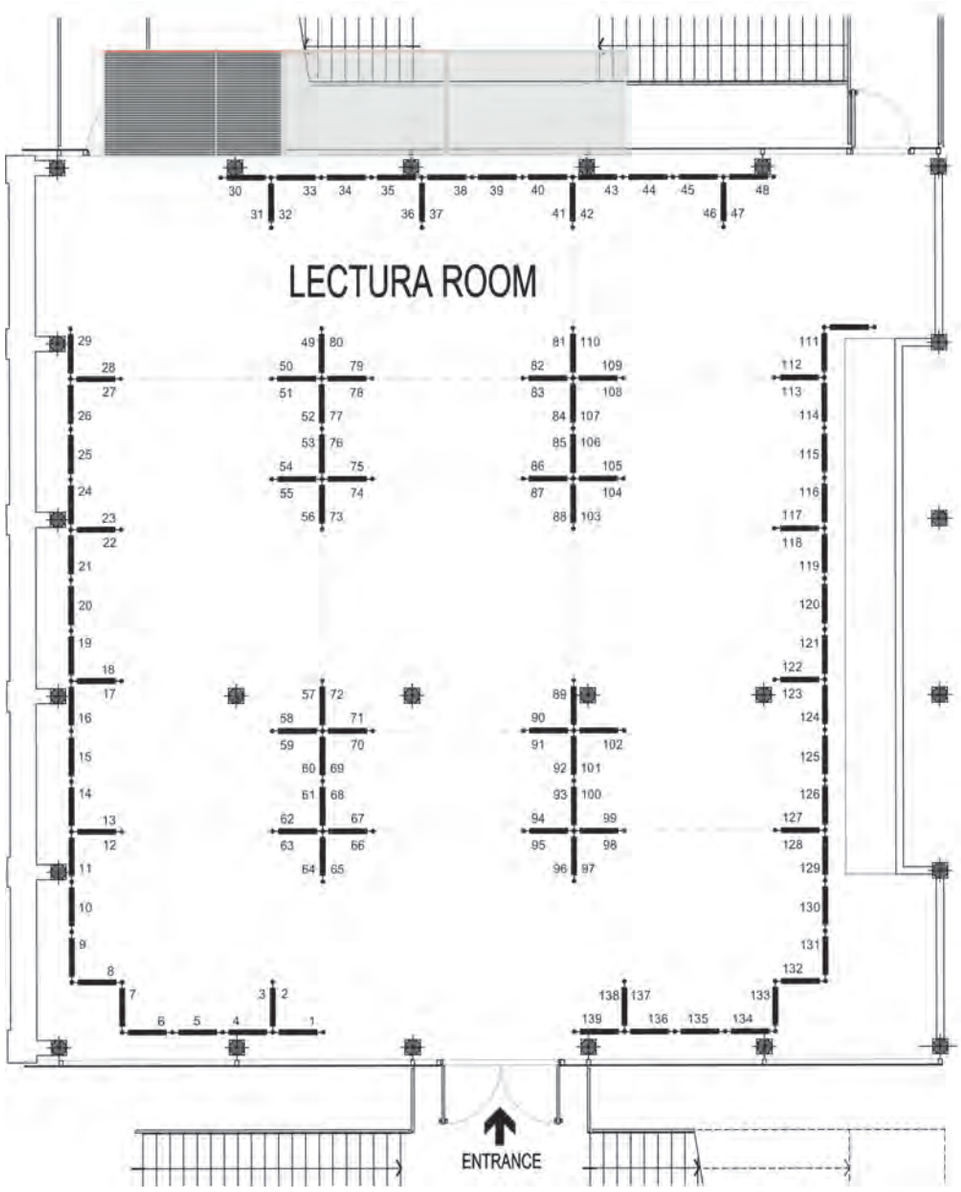

ABSTRACT #	PANEL #
5	59
12	7
14	96
16	24
17	114
28	102
29	115
33	76
35	25
38	91
40	116
48	60
56	101
57	66
58	85
61	117
62	100
65	43
66	21
67	29
68	2
69	86
77	52

ABSTRACT #	PANEL #
80	12
82	67
92	31
94	72
95	32
96	81
97	133
100	129
105	130
112	13
115	82
117	53
120	15
123	33
124	99
126	131
132	51
135	8
136	78
138	34
139	9
145	97
148	90

ABSTRACT #	PANEL #
150	22
154	113
160	111
162	127
163	16
165	137
166	136
167	35
174	95
175	28
180	118
190	132
198	37
201	98
202	38
203	112
206	40
208	41
212	110
216	74
217	128
219	3
221	63

ABSTRACT #	PANEL #
226	54
227	138
232	79
245	42
246	119
247	57
249	120
250	61
255	19
258	65
259	108
262	44
264	30
266	83
273	20
274	73
275	45
278	103
279	27
280	104
284	105
286	68
287	106

ABSTRACT #	PANEL #
291	126
292	134
295	135
296	36
300	46
303	47
304	121
305	48
306	4
308	49
309	107
310	39
316	62
318	75
320	17
323	23
324	123
325	26
326	5
327	69
330	55
331	11
332	18

ABSTRACT #	PANEL #
333	64
336	70
338	1
339	6
343	109
349	87
350	80
351	93
352	94
353	77
357	71
358	56
360	58
362	88
364	89
365	92
368	50
369	124
370	125

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