International Society for the Study of Vascular Anomalies
Newsletter Vol 1 - No 2 | November 2017

President's Message

Dear ISSVA members and friends,

We are pleased to launch the second ISSVA newsletter, to keep you informed about all the newest developments regarding our Society. The first newsletter was very welcomed by many of you as an important new avenue for ISSVA communication, and thus we will try to make this a regular newsletter.

First of all, I would like to **welcome all new ISSVA members**. I was thrilled to see that our Society has been joined by **44 new members** that show enthusiasm and passion for our field. Additionally, we had **5 Junior ISSVA Members upgrade their status to Active Status!** We need your input and we need to keep on extending our knowledge in our field for the benefit of patient management in many new big and small centers all around the world.

I would like to **Remind All ISSVA Members to Complete Your Online Information for the Membership Directory**. Do not forget that if you want to be visible towards patients, you need to go to the public directory, opt in and fill in your information. If not, you will only be visible to ISSVA members. I was sadden to see that this is the case for many of you. When I opened our website without connecting as an ISSVA member, our Society has only 54 members that are visible, although 284 members have filled in the user profile. If you wish to have some of your contact info visible (such as name of your center, address, website, secretary phone number, etc.) please take a few minutes to modify this.

Online Member Directory

Please Complete Your Online Information for the Public Membership Directory.

Please take a few minutes to modify this (Directions Here)

We are approaching our **22nd ISSVA Workshop**, which will be held in the beautiful city of Amsterdam, the Netherlands. The Scientific Committee, in conjunction with the Board and the Local Hosts, are working hard to offer you a great meeting. Several modifications have been made to this workshop in response to the remarks we received from our membership.

First, the **primer course** will be organized by the ISSVA Board and Scientific Committee so it will be kept truly basic. This course is dedicated to beginners in the field of vascular anomalies with the aim that after this one-day course, they will be able to diagnosis and manage the most common vascular anomalies. Moreover, they will be able to follow more easily and effectively our meeting the following days.

Second, we have started **advanced specialty workshops** dedicated to specific specialties or areas of expertise. These will be run concurrently with the basic course in the afternoon of Tuesday, 29 May 2018. These Advanced Specialty Workshops will enable discussion of very specific questions in selected specialties.

However, to maximize interdisciplinarity of our meeting, each Advanced Specialty Workshop will be summarized during the ISSVA meeting by one of the chairpersons; this will replace the parallel sessions. We will start with four Advanced Specialty Workshops: 1) pathology, 2) interventional radiology, 3) surgery, and 4) genetic and medical management.

Are you a Published Junior Member?

If you're an ISSVA Junior member and have recently been published in the field of Vascular Anomalies, you might be eligible to upgrade your status to Active membership with ISSVA. Simply e-mail your updated CV, with your publication(s) on Vascular Anomalies included, to the ISSVA Secretariat at: jdodge@issva.org.

The meeting itself will also be slightly modified, as a full day will no longer be dedicated to infantile hemangioma. The program will be completely determined by the submitted abstracts.

We hope, and foresee, that even more people will be attending our 22nd ISSVA meeting, and thus the latest record of 550 attendees will be surpassed!

I am looking forward to meeting all of you in Amsterdam.

Laurence M Boon
ISSVA President

Call for ISSVA Applications

ISSVA is accepting applications for membership. **Please encourage your colleagues to apply to become a Junior, Active, or Associate member.** New Junior Members don't need experience in Vascular Anomalies, just an interest to learn more. Encourage your young physician colleagues to apply today!

Start Your ISSVA Application Today! If you have questions, please don't hesitate to contact the ISSVA Secretariat at: jdodge@issva.org

22nd International Workshop of the International Society for the Study of Vascular Anomalies

29 May - 1 June 2018

www.issva2018.org

Meeting Schedule

Tuesday, 31 May 2018:	Primer Course, Advanced Specialty Workshops & Welcome Reception
Wednesday, 1 June 2018:	Workshop (day 1), ISSVA General Assembly & Amsterdam City Tour
Thursday, 2 June 2018:	Workshop (day 2) & Gala Dinner
Friday, 3 June 2018:	Workshop (day 3)

Primer & Advanced Specialty Workshops

The agenda for the Primer Course is now online; please look at the program and sign up or encourage your colleagues to register.

If you are looking for an Advanced Specialty Workshop, ISSVA will be offering four (4) Advanced Specialty Workshops with details coming soon.

Visit the ISSVA 2018 Website for updates: www.issva2018.org

Receive Workshop Updates & Other Important Information through ISSVA's Social Media

Twitter:
https://twitter.com/ISSVA1992

Facebook:
https://www.facebook.com/issva1992

LinkedIn:
https://www.linkedin.com/company/issva/

Keynote Speaker

ISSVA is excited and proud to announce that the Keynote Speaker at ISSVA 2018 will be **Dr. Steven Fishman**, who will speak on the topic of **"Lessons learned from our patients".**

Important Dates & Deadlines

05 December 2017:	Online registration opens
05 December 2017:	Abstracts open
05 January 2018:	Abstracts close
16 March 2018:	Early registration closes
01 May 2018:	Regular registration closes

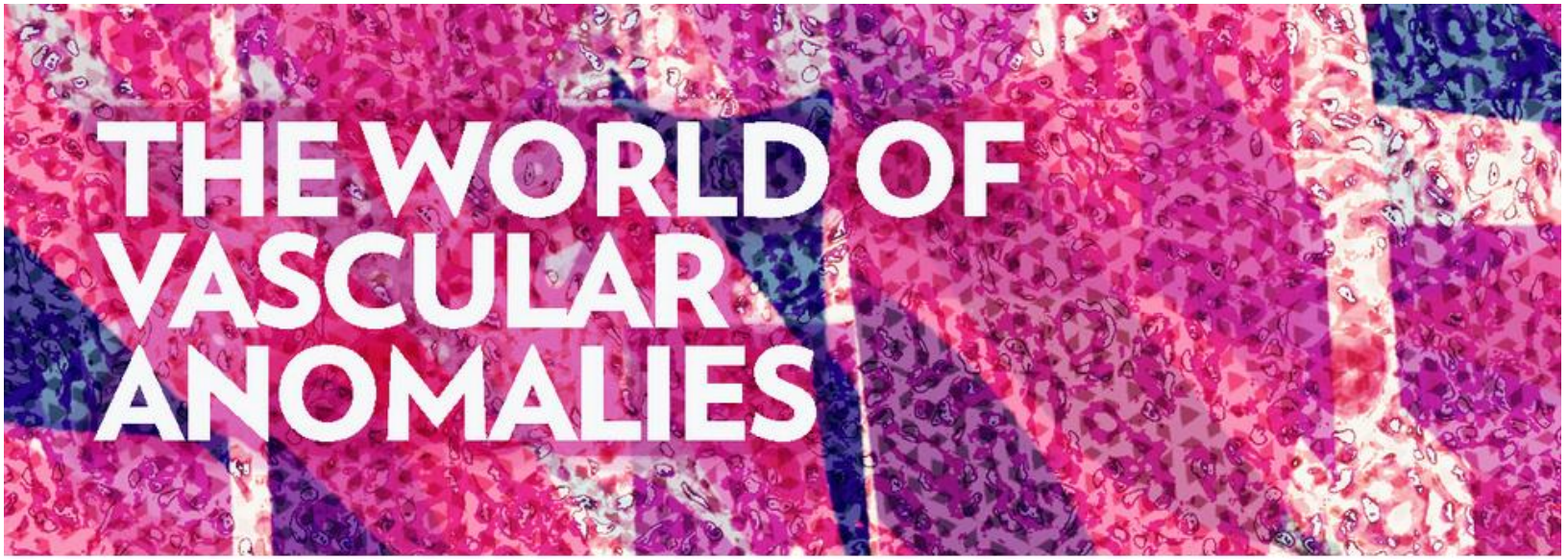
Explore Amsterdam

Learn more about the incredible city of Amsterdam.

Official Website of Amsterdam

Is your city interested in hosting ISSVA 2022?

If so, ISSVA will be accepting proposals for a host city at the ISSVA 2018 meeting in Amsterdam. For details, contact the ISSVA Secretariat: jdodge@issva.org.



Review of the Vascular Anomaly Literature

(Published January-August 2017)

Editor: Francine Blei, MD
Contributors:

- Maria Gnarra, MD, PhD* / Francine Blei, MD – Basic Science
- Morgane Barreau, MD / Anne Dompmartin, MD – Dermatology
- Israel Fernandez-Pineda, MD* / Juan Carlos Lopez Guttierez, MD, PhD – Surgery
- Taizo Nakano, MD* / Denise Adams, MD – Pediatric Hematology Oncology
- Rush Chewning, MD* / Gulraiz Chaudry, MD – Interventional Radiology

Junior ISSVA Member/Scientific Committee Member*

Our contributors have scanned the literature by discipline and provided a short synopsis. Click on the topics below to access their review.

Volunteers needed for literature review

We are seeking senior ISSVA members to assist with the literature review in their fields. The literature review will be published in the newsletter bi-annually. We suggest working with a junior member.

For details, reach out to the ISSVA Secretariat (jdodge@issva.org) or Dr. Francine Blei (Fblei@northwell.edu), ISSVA Scientific Committee Chair.

GENETICS & BASIC SCIENCE

Return to Scientific Article Reviews

Amyere M, Revencu N, Helaers R, Pairet E, Baselga E, Cordisco M, Chung W, Dubois J, Lacour JP, Martorell L, Mazereeuw-Hautier J, Pyeritz RE, Amor DJ, Bisdorff A, Blei F, Bombei H, Dompmartin A, Brooks D, Dupont J, González-Enseñat MA, Frieden I, Gérard M, Kvarnung M, Hanson-Kahn AK, Hudgins L, Léauté-Labrèze C, McCuaig C, Metry D, Parent P, Paul C, Petit F, Phan A, Quere I, Salhi A, Turner A, Vabres P, Vicente A, Wargon O, Watanabe S, Weibel L, Wilson A, Willing M, Mulliken JB, Boon LM, Vikkula M. "Germline Loss-of-Function Mutations in EPHB4 Cause a Second Form of Capillary Malformation-Arteriovenous Malformation (CM-AVM2) Deregulating RAS-MAPK Signaling." Circulation 2017 Sep 12;136(11):1037-1048.

Background - Most AVMs are localized and occur sporadically; however they also can be multifocal in autosomal dominant disorders, such as Hereditary Hemorrhagic Telangiectasia (HHT) and Capillary Malformation-Arteriovenous Malformation (CM-AVM). Previously, we identified RASA1 mutations in 50% of patients with CM-AVM. Herein we studied non-RASA1 patients to further elucidate the pathogenicity of CMs and AVMs. Methods - We conducted a genome-wide linkage study on a CM-AVM family. Whole exome sequencing was also performed on 9 unrelated CM-AVM families. We identified a candidate-gene and screened it in a large series of patients. The influence of several missense variants on protein function was also studied in vitro. Results - We found evidence for linkage in two loci. Whole-exome sequencing data unraveled four distinct damaging variants in EPHB4 in five families that co-segregated with CM-AVM. Overall, screening

How to Subscribe to NCBI Alerts

Did you know that you can create alerts in PubMed - NCBI? The procedure is quite simple:

1. Go to: https://www.ncbi.nlm.nih.gov/pubmed/
2. Select MeSH* (Medical Subject Headings) in the drop-down menu located in the upper-left upper corner of the screen.
3. Enter search terms in the dialog box (Ex. Vascular Malformations).
4. Click “Create Alert” to create an email alert for this search.
5. Sign in to NCBI (with NCBI Username and password) or Register for an NCBI account if you do not have an account.
6. Specify your search parameters and click “Save”.

*MeSH (Medical Subject Headings) is the NLM controlled vocabulary thesaurus used for indexing articles for PubMed.

of EPHB4 detected 47 distinct mutations in 54 index patients: 27 lead to a premature stop codon or splice-site alteration, suggesting loss of function. The other 20 are non-synonymous variants that result in amino-acid substitutions. In vitro expression of several mutations confirmed loss of function of EPHB4. The clinical features included multifocal CMs, telangiectasias, and AVMs. Conclusions - We found EPHB4 mutations in patients with multifocal CMs associated with AVMs. The phenotype, CM-AVM2, mimics RASA1-related CM-AVM1 and also HHT. RASA1 encoded p120RASGAP is a direct effector of EPHB4. Our data highlights the pathogenetic importance of this interaction and indicts EPHB4-RAS-ERK signaling pathway as a major cause for arterio-venous malformations.

Brambila-Tapia, A. J. L., et al. (2017). "GATA2 null mutation associated with incomplete penetrance in a family with Emberger syndrome." Hematology 22(8):467-471.

INTRODUCTION: GATA2 mutations are associated with several conditions, including Emberger syndrome which is the association of primary lymphedema with hematological anomalies and an increased risk for myelodysplasia and leukemia. OBJECTIVE: To describe a family with Emberger syndrome with incomplete penetrance. METHODS: A DNA sequencing of GATA2 gene was performed in the parents and offspring (five individuals in total). RESULTS: The family consisted of 5 individuals with a GATA2 null mutation (c.130G>T, p.Glu44*); three of them were affected (two of which were deceased) while two remained unaffected at the age of 40 and 13 years old. The three affected siblings (two boys and one girl) presented with lymphedema of the lower limbs, recurrent warts, epistaxis and recurrent infections. Two died due to hematological abnormalities (AML and pancytopenia). In contrast, the two other family members who carry the same mutation (the mother and one brother) have not presented any symptoms and their blood tests remain normal. DISCUSSION: Incomplete penetrance may indicate that GATA2 haploinsufficiency is not enough to produce the phenotype of Emberger syndrome. It could be useful to perform whole exome or genome sequencing, in cases where incomplete penetrance or high variable expressivity is described, in order to probably identify specific gene interactions that drastically modify the phenotype. In addition, skewed gene expression by an epigenetic mechanism of gene regulation should also be considered.

Cavalli, G. (2017). "SMAD4 gene mutation and risk of aortic dilation: Lessons from hereditary hemorrhagic telangiectasia." Int J Cardiol 245:145-146.

Couto JA, Huang AY, Konczyk DJ, Goss JA, Fishman SJ, Mulliken JB, Warman ML, Greene AK. Somatic MAP2K1 Mutations Are Associated with Extracranial Arteriovenous Malformation. Am J Hum Genet. 2017 Mar 2;100(3):546-554

Synopsis of article and methods: Arteriovenous malformation (AVM) is a fast-flow, congenital vascular anomaly that may arise anywhere in the body. AVMs typically progress, causing destruction of surrounding tissue and, sometimes, cardiac overload. AVMs are difficult to control; they often re-expand after embolization or resection, and pharmacologic therapy is unavailable.
Whole-exome sequencing (WES) and whole-genome sequencing (WGS) was performed on extracranial AVM tissue. Endothelial cells were separated from non-endothelial cells by immune-affinity purification. Droplet digital PCR (ddPCR) was used to confirm mutations found by WES and WGS, to determine whether mutant alleles were enriched in endothelial or non-endothelial cells, and to screen additional AVM specimens.

What this study adds: Somatic mutations in MAP2K1 are a common cause of extracranial AVM, leading to

endothelial cell dysfunction due to increased MEK1 activity. MEK1 inhibitors are potential therapeutic agents for individuals with extracranial AVM.
Maria Gnarra/Francine Blei

Cunha, S. I., et al. (2017). "Deregulated TGF-beta/BMP Signaling in Vascular Malformations." Circ Res 121(8):981-999.

Correct organization of the vascular tree requires the balanced activities of several signaling pathways that regulate tubulogenesis and vascular branching, elongation, and pruning. When this balance is lost, the vessels can be malformed and fragile, and they can lose arteriovenous differentiation. In this review, we concentrate on the transforming growth factor (TGF)-beta/bone morphogenetic protein (BMP) pathway, which is one of the most important and complex signaling systems in vascular development. Inactivation of these pathways can lead to altered vascular organization in the embryo. In addition, many vascular malformations are related to deregulation of TGF-beta/BMP signaling. Here, we focus on two of the most studied vascular malformations that are induced by deregulation of TGF-beta/BMP signaling: hereditary hemorrhagic telangiectasia (HHT) and cerebral cavernous malformation (CCM). The first of these is related to loss-of-function mutation of the TGF-beta/BMP receptor complex and the second to increased signaling sensitivity to TGF-beta/BMP. In this review, we discuss the potential therapeutic targets against these vascular malformations identified so far, as well as their basis in general mechanisms of vascular development and stability.

Guo, X., et al. (2017). "PLGA nanoparticles with CD133 aptamers for targeted delivery and sustained release of propranolol to hemangioma." Nanomedicine (Lond) 12(21): 2611-2624.

AIM: To develop propranolol-loaded poly (lactic-co-glycolic acid) nanoparticle with CD133 aptamers (PPN-CD133) to treat infantile hemangioma. MATERIALS & METHODS: The antihemangioma activity and mechanism of PPN-CD133 were evaluated. RESULTS & CONCLUSION: PPN-CD133 are of desired size (143.7 nm), drug encapsulation efficiency (51.8%) and sustained drug release for 8 days. PPN-CD133 could effectively bind to CD133+ hemangioma stem cells, resulting in enhanced cytotoxic effect and reduced expression of angiogenesis factors in hemangioma stem cells. The therapeutic effect of PPN-CD133 in hemangioma was superior to that of untargeted PPN and propranolol in vivo, as reflected by reduced hemangioma volume, weight and microvessel density. PPN-CD133 represents a very promising approach to locally and efficiently deliver propranolol leading to significant inhibition of infantile hemangioma.

Authors: Hägerling R, Drees D, Scherzinger A, Dierkes C, Martin-Almedina S, Butz S, Gordon K, Schäfers M, Hinrichs K, Ostergaard P, Vestweber D, Goerge T, Mansour S, Jiang X, Mortimer PS, Kiefer F.
Title: VIPAR, a quantitative approach to 3D histopathology applied to lymphatic malformations.
JCI Insight. 2017 Aug 17;2(16).

Synopsis of article and methods:
BACKGROUND:
Lack of investigatory and diagnostic tools has been a major contributing factor to the failure to mechanistically understand lymphedema and other lymphatic disorders in order to develop effective drug and surgical therapies. One difficulty has been understanding the true changes in lymph vessel pathology from standard 2D tissue sections. VIPAR (volume information-based histopathological analysis by 3D reconstruction and data extraction), a light-sheet microscopy based approach for the analysis of tissue biopsies, is based on digital

reconstruction and visualization of microscopic image stacks. VIPAR allows semi-automated segmentation of the vasculature and subsequent nonbiased extraction of characteristic vessel shape and connectivity parameters. VIPAR was applied to analyze biopsies from healthy lymphedematous and lymphangiomatous skin.

What this study adds: Lymphangiomatous skin and hyperplasia show greatly disrupted lymphatic vessels, with significant reduction of lymphatic segment length and for lymphedematous and lymphangiomatous skin, respectively. Blood vessel length was significantly increased in the lymphangiomatous sample. VIPAR can be applied to successfully distinguish healthy from lymphedematous and lymphangiomatous skin.
Submitted by: Maria Gnarra, MD, PhD; Francine Blei (Mentor), MD, MBA

Huang, J., et al. (2017). "MicroRNA-137 and microRNA-195* inhibit vasculogenesis in brain arteriovenous malformations." Ann Neurol 82(3): 371-384.

OBJECTIVE: Brain arteriovenous malformations (AVMs) are the most common cause of nontraumatic intracerebral hemorrhage in young adults. The genesis of brain AVM remains enigmatic. We investigated microRNA (miRNA) expression and its contribution to the pathogenesis of brain AVMs. METHODS: We used a large-scale miRNA analysis of 16 samples including AVMs, hemangioblastoma, and controls to identify a distinct AVM miRNA signature. AVM smooth muscle cells (AVMSMCs) were isolated and identified by flow cytometry and immunohistochemistry, and candidate miRNAs were then tested in these cells. Migration, tube formation, and CCK-8-induced proliferation assays were used to test the effect of the miRNAs on phenotypic properties of AVMSMCs. A quantitative proteomics approach was used to identify protein expression changes in AVMSMCs treated with miRNA mimics. RESULTS: A distinct AVM miRNA signature comprising a large portion of lowly expressed miRNAs was identified. Among these miRNAs, miR-137 and miR-195* levels were significantly decreased in AVMs and constituent AVMSMCs. Experimentally elevating the level of these microRNAs inhibited AVMSMC migration, tube formation, and survival in vitro and the formation of vascular rings in vivo. Proteomics showed the protein expression signature of AVMSMCs and identified downstream proteins regulated by miR-137 and miR-195* that were key signaling proteins involved in vessel development. INTERPRETATION: Our results indicate that miR-137 and miR-195* act as vasculogenic suppressors in AVMs by altering phenotypic properties of AVMSMCs, and that the absence of miR-137 and miR-195* expression leads to abnormal vasculogenesis.

Jh, M. D., et al. (2017). "Hypoglycaemia Represents a Clinically Significant Manifestation of PIK3CA- and CCND2-Associated Segmental Overgrowth." Clin Genet.

The PI3K-AKT signaling cascade has a highly conserved role in a variety of processes including cell growth and glucose homoeostasis. Variants affecting this pathway can lead to one of several segmental overgrowth disorders. These conditions are genetically heterogeneous and require tailored, multidisciplinary involvement throughout life. Hypoglycaemia is common in other overgrowth syndromes but has been described only sporadically in association with PIK3CA and CCND2 variants. We report a cohort of 6 children with megalencephaly-capillary malformation syndrome (MCAP) and megalencephaly-polydactyly-polymicrogyria-hydrocephalus syndrome (MPPH) who developed clinically significant hypoglycaemia. Based on our findings, we suggest that segmental overgrowth patients should be screened for low blood glucose levels during childhood and there should be early specialist endocrine review in any children who develop hypoglycaemia.

Molecular diagnosis of *PIK3CA*-related overgrowth spectrum (PROS) in 162 patients and recommendations for genetic testing

Paul Kuentz, Judith St-Onge, Yannis Duffourd, Jean-Benoît Courcet, Virginie Carmignac, Thibaud Jouan, Arthur Sorlin, Claire Abasq-Thomas, Juliette Albuisson, Jeanne Amiel, Daniel Amram, Stéphanie Arpin, Tania Attie-Bitach, Nadia Bahi-Buisson, Sébastien Barbarot, Geneviève Baujat, Didier Bessis, Olivia Boccara, Maryse Bonnière, Odile Boute, Anne-Claire Bursztejn, Christine Chiaverini, Valérie Cormier-Daire, Christine Coubes, Bruno Delobel, Patrick Edery, Salima El Chehadeh, Christine Francannet, David Geneviève, Alice Goldenberg, Damien Haye, Bertrand Isidor, Marie-Line Jacquemont, Philippe Khau Van Kien, Didier Lacombe, Ludovic Martin, Jelena Martinovic, Annabel Maruani, Michèle Mathieu-Dramard, Juliette Mazereeuw-Hautier, Caroline Michot, Cyril Mignot, Juliette Miquel, Fanny Morice-Picard, Florence Petit, Alice Phan, Massimiliano Rossi, Renaud Touraine, Alain Verloes, Marie Vincent, Catherine Vincent-Delorme, Sandra Whalen, Marjolaine Willems, Nathalie Marle, Daphné Lehalle, Julien Thevenon, Christel Thauvin-Robinet, Smaïl Hadj-Rabia, Laurence Faivre, Pierre Vabres and Jean-Baptiste Rivière

Genet Med 2017;19(9):989-997.

Lapinski, P. E., et al. (2017). "Somatic second hit mutation of RASA1 in vascular endothelial cells in capillary malformation-arteriovenous malformation." Eur J Med Genet.

Capillary malformation-arteriovenous malformation (CM-AVM) is an autosomal dominant vascular disorder that is associated with inherited inactivating mutations of the RASA1 gene in the majority of cases. Characteristically, patients exhibit one or more focal cutaneous CM that may occur alone or together with AVM, arteriovenous fistulas or lymphatic vessel abnormalities. The focal nature and varying presentation of lesions has led to the hypothesis that somatic "second hit" inactivating mutations of RASA1 are necessary for disease development. In this study, we examined CM from four different CM-AVM patients for the presence of somatically acquired RASA1 mutations. All four patients were shown to possess inactivating heterozygous germline RASA1 mutations. In one of the patients, a somatic inactivating RASA1 mutation (c.1534C > T, p.Arg512*) was additionally identified in CM lesion tissue. The somatic RASA1 mutation was detected within endothelial cells specifically and was in trans with the germline RASA1 mutation. Together with the germline RASA1 mutation (c.2125C > T, p.Arg709*) in the same patient, the endothelial cell somatic RASA1 mutation likely contributed to lesion development. These studies provide the first clear evidence of the second hit model of CM-AVM pathogenesis.

Authors: Lapinski PE, Lubeck BA, Chen D, Doosti A, Zawieja SD, Davis MJ, King PD.
Title: RASA1 regulates the function of lymphatic vessel valves in mice.
J Clin Invest. 2017 Jun 30;127(7):2569-2585.

Synopsis of article and methods: Capillary malformation-arteriovenous malformation (CM-AVM) is a blood and lymphatic vessel (LV) disorder caused by inherited inactivating mutations of the RASA1 gene, which encodes p120 RasGAP (RASA1), a negative regulator of the Ras small GTP-binding protein. How RASA1 mutations lead to the LV leakage defects that occur in CM-AVM is not understood.

What this study adds: The disruption of the Rasa1 gene in adult mice resulted in loss of LV endothelial cells (LECs) specifically from the leaflets of intraluminal valves in collecting LVs. As a result, valves were unable to prevent fluid backflow and the vessels were ineffective pumps. Furthermore, disruption of Rasa1 in mid-

gestation resulted in LEC apoptosis in developing LV valves and consequently failed LV valvulogenesis. Similar phenotypes were observed in induced RASA1-deficient adult mice and embryos expressing a catalytically inactive RASA1R780Q mutation. Thus, RASA1catalytic activity is essential for the function and development of LV valves. These data provide a partial explanation for LV leakage defects and potentially other LV abnormalities observed in CM-AVM.
Maria Gnarra/Francine Blei

Nathan, N. R., et al. (2017). "Pathogenetic insights from quantification of the cerebriform connective tissue nevus in Proteus syndrome." J Am Acad Dermatol.

BACKGROUND: The plantar cerebriform connective tissue nevus (CCTN) is the most common and problematic cutaneous manifestation of Proteus syndrome. OBJECTIVE: To gain insights into CCTN pathogenesis and natural history. METHODS: The size and location of plantar CCTN was measured on 152 images from 22 individuals with Proteus syndrome by two independent, blinded reviewers. Average measures of plantar CCTN were transformed into a linear mixed model to estimate proportionate change in size with age. RESULTS: Median patient age was 6.9 years at study onset. The intraclass correlation coefficient between two blinded reviewers was 0.946 for CCTN single measures. The CCTN relative area increased with age in children (n=18, p<.0001) by 5.6% per year. Confluent papules and nodules extending beyond the boundaries of CCTNs were gradually replaced by typical CCTN over time. The location of CCTN in different individuals overlapped near the ball of the foot. A positive relationship between CCTN growth rate and AKT1 mutant allele frequency was observed (.62, p=0.10, n=8). LIMITATIONS: This was a retrospective review using photographs. CONCLUSION: CCTN growth is affected by age, and extent of the CCTN precursor lesion. Monitoring of CCTN size may prove useful for evaluating drug response in the treatment of Proteus syndrome.

Nguyen, H. L., et al. (2017). "Vascular Anomalies Caused by Abnormal Signaling within Endothelial Cells: Targets for Novel Therapies." Semin Intervent Radiol 34(3): 233-238.

Vascular anomalies arise as a consequence of improper development and maintenance of the vasculature. Our knowledge on the pathophysiological bases of vascular anomalies has skyrocketed during the past 5 years. It is becoming clear that common intracellular signaling pathways are often activated by mutations, causing endothelial cell dysfunction. These mutations cause hyperactivation of two major intracellular signaling pathways that may be controlled by inhibitors developed for cancer treatment. Although we do not know yet all the downstream effects, it has become evident that normalization of the abnormal signaling is an interesting target for therapy. This is a major paradigm change, as developmental malformations were considered to be inert to any molecular treatment.

Ruiz-Llorente, L., et al. (2017). "Endoglin and alk1 as therapeutic targets for hereditary hemorrhagic telangiectasia." Expert Opin Ther Targets 21(10): 933-947.

INTRODUCTION: Hereditary Haemorrhagic Telangiectasia (HHT) is as an autosomal dominant trait characterized by frequent nose bleeds, mucocutaneous telangiectases, arteriovenous malformations (AVMs) of the lung, liver and brain, and gastrointestinal bleedings due to telangiectases. HHT is originated by mutations in genes whose encoded proteins are involved in the transforming growth factor beta (TGF-beta) family signaling of vascular endothelial cells. In spite of the great advances in the diagnosis as well as in the molecular, cellular and animal models of HHT, the current treatments remain just at the palliative level. Areas covered: Pathogenic mutations in genes coding for the TGF-beta receptors endoglin (ENG) (HHT1) or the

activin receptor-like kinase-1 (ACVRL1 or ALK1) (HHT2), are responsible for more than 80% of patients with HHT. Therefore, ENG and ALK1 are the main potential therapeutic targets for HHT and the focus of this review. The current status of the preclinical and clinical studies, including the anti-angiogenic strategy, have been addressed. Expert opinion: Endoglin and ALK1 are attractive therapeutic targets in HHT. Because haploinsufficiency is the pathogenic mechanism in HHT, several therapeutic approaches able to enhance protein expression and/or function of endoglin and ALK1 are keys to find novel and efficient treatments for the disease.

Tang AT, Choi JP, Kotzin JJ, Yang Y, Hong CC, Hobson N, Girard R, Zeineddine HA, Lightle R, Moore T, Cao Y, Shenkar R, Chen M, Mericko P, Yang J, Li L, Tanes C, Kobuley D, Võsa U, Whitehead KJ, Li DY, Franke L, Hart B, Schwaninger M, Henao-Mejia J, Morrison L, Kim H, Awad IA, Zheng X, Kahn ML. Endothelial TLR4 and the microbiome drive cerebral cavernous malformations. Nature. 2017 May 18;545(7654):305-310.

Synopsis of article and methods: Cerebral cavernous malformations (CCMs) are a cause of stroke and seizure for which no effective medical therapies yet exist. CCMs arise from the loss of an adaptor complex that negatively regulates MEKK3-KLF2/4 signaling in brain endothelial cells, but upstream activators of this disease pathway have yet to be identified.

What this study adds: This study identifies endothelial Toll-like receptor 4 (TLR4) and the gut microbiome as critical stimulants of CCM formation. Activation of TLR4 by Gram-negative bacteria or lipopolysaccharide accelerates CCM formation, and genetic or pharmacologic blockade of TLR4 signaling prevents CCM formation in mice. Polymorphisms that increase expression of the TLR4 gene or the gene encoding its co-receptor CD14 are associated with higher CCM lesion burden in humans. Germ-free mice are protected from CCM formation, and a single course of antibiotics permanently alters CCM susceptibility in mice. These studies identify unexpected roles for the microbiome and innate immune signaling in the pathogenesis of a cerebrovascular disease, as well as strategies for its treatment.
Submitted by: Maria Gnarra, MD, PhD; Francine Blei (Mentor), MD, MBA

Vorselaars, V. M. M., et al. (2017). "SMAD4 gene mutation increases the risk of aortic dilation in patients with hereditary haemorrhagic telangiectasia." Int J Cardiol 245: 114-118.

BACKGROUND: Mutations in the genes ENG, ACVRL1 and SMAD4 that are part of the transforming growth factor-beta signaling pathway cause hereditary haemorrhagic telangiectasia (HHT). Mutations in non-HHT genes within this same pathway have been found to associate with aortic dilation. Therefore, we investigated the presence of aortic dilation in a large cohort of HHT patients as compared to non-HHT controls. METHODS: Chest computed tomography of consecutive HHT patients (ENG, ACVRL1 and SMAD4 mutation carriers) and non-HHT controls were reviewed. Aortic root dilation was defined as a z-score>1.96. Ascending and descending aorta dimensions were corrected for age, gender and body surface area. RESULTS: In total 178 subjects (57.3% female, mean age 43.9+/-14.9years) were included (32 SMAD4, 47 ENG, 50 ACVRL1 mutation carriers and 49 non-HHT controls). Aortopathy was present in a total of 42 subjects (24% of total). Aortic root dilatation was found in 31% of SMAD4, 2% of ENG, 6% of ACVRL1 mutation carriers, and 4% in non-HHT controls ($p<0.001$). The aortic root diameter was 36.3+/-5.2mm in SMAD4 versus 32.7+/-3.9mm in the non-SMAD4 group ($p=0.001$). SMAD4 was an independent predictor for increased aortic root (beta-coefficient 3.5, $p<0.001$) and ascending aorta diameter (beta-coefficient 1.6, $p=0.04$). CONCLUSIONS: SMAD4 gene mutation in HHT patients is independently associated with a higher risk of aortic root and ascending aortic dilation as

compared to other HHT patients and non-HHT controls.

Wu, K. Q., et al. (2017). "M1 Macrophage-Induced Endothelial-to-Mesenchymal Transition Promotes Infantile Hemangioma Regression." Am J Pathol 187(9): 2102-2111.

Infantile hemangiomas are benign tumors of vascular endothelial cells (ECs), characterized by three distinct stages: proliferating phase, involuting phase, and involuted phase. The mechanisms that trigger involution of hemangioma into fibro-fatty tissue remain unknown. We report a novel mechanism by which M1-polarized macrophages induce endothelial-to-mesenchymal transition (EndMT) and promote hemangioma regression. M1- but not M2-polarized macrophages induced EndMT in ECs. Tumor necrosis factor-alpha and, to a lesser extent, IL-1beta and interferon-gamma were the most potent cytokines produced by the M1 macrophages that induce in vitro EndMT. Western blot analysis and gene expression profiling showed that ECs treated with M1 macrophages, tumor necrosis factor-alpha, or IL-1beta decreased the expression of endothelial markers, whereas mesenchymal markers increased concomitantly. Immunohistochemical staining of patient samples revealed that a significant perivascular infiltration of M1, but not M2, macrophages coincides with endothelial expression of the critical EndMT transcription factors Snail/Slug in involuting hemangiomas. Most strikingly, M1 macrophage-treated ECs isolated from patient hemangiomas (HemECs) but not untreated HemECs readily differentiated into adipocytes on adipogenic induction. Thus, in vitro EndMT and adipogenesis of HemECs have, in part, recapitulated the natural history of hemangioma regression. In conclusion, our findings indicate that EndMT induced by M1 macrophages promotes infantile hemangioma regression and may lead to novel therapeutic treatments for this vascular tumor.

Yang, C., et al. (2017). "A Novel CCM1/KRIT1 Heterozygous Nonsense Mutation (c.1864C>T) Associated with Familial Cerebral Cavernous Malformation: a Genetic Insight from an 8-Year Continuous Observational Study." J Mol Neurosci 61(4): 511-523.

Cerebral cavernous malformation (CCM) is a congenital vascular abnormality that predominantly affects the central nervous system, but that sometimes encroaches other vital tissues, including the retina, skin, and even liver. The familial form of CCM (FCCM) is considered to be an autosomal dominant disease with incomplete penetrance and variable expression, which is often attributed to mutations in three genes: CCM1, CCM2, and CCM3. We screened a Chinese family diagnosed with FCCM by using Sanger sequencing. A 29-year-old male proband with cutaneous angiomas was pathologically diagnosed but presented with an atypical form of CCM as revealed by magnetic resonance imaging (MRI) findings, prompting further clinical evaluation and genetic analyses of him and his immediate family. We performed continuous observation over an 8-year period using MRI gradient echo imaging and susceptibility-weighted imaging of these individuals. Sanger sequencing of the CCM1, CCM2, and CCM3 genes identified a novel heterozygous nonsense nucleotide transition (c.1864C>T; p.Gln622X) in exon 17 of the CCM1/KRIT1 gene; this mutation was predicted to cause a premature stop codon (TAG) at nucleotides 1864 to 1866 to generate a truncated Krev interaction trapped 1 (Krit1) protein of 621 amino acids. During this long-term observational study, one of the enrolled family members with neurological deficits progressed to a stage indicative of brain surgery. This study provides a new CCM gene mutation profile, which highlights the significance of genetic counseling for individuals suspected of having this condition.

Return to Scientific Article Reviews

LYMPHATIC DISORDERS

Return to Scientific Article Reviews

Baluk, P., et al. (2017). "Rapamycin reversal of VEGF-C-driven lymphatic anomalies in the respiratory tract." JCI Insight 2(16).

Lymphatic malformations are serious but poorly understood conditions that present therapeutic challenges. The goal of this study was to compare strategies for inducing regression of abnormal lymphatics and explore underlying mechanisms. CCSP-rtTA/tetO-VEGF-C mice, in which doxycycline regulates VEGF-C expression in the airway epithelium, were used as a model of pulmonary lymphangiectasia. After doxycycline was stopped, VEGF-C expression returned to normal, but lymphangiectasia persisted for at least 9 months. Inhibition of VEGFR-2/VEGFR-3 signaling, Notch, beta-adrenergic receptors, or autophagy and anti-inflammatory steroids had no noticeable effect on the amount or severity of lymphangiectasia. However, rapamycin inhibition of mTOR reduced lymphangiectasia by 76% within 7 days without affecting normal lymphatics. Efficacy of rapamycin was not increased by co-administration with the other agents. In prevention trials, rapamycin suppressed VEGF-C-driven mTOR phosphorylation and lymphatic endothelial cell sprouting and proliferation. However, in reversal trials, no lymphatic endothelial cell proliferation was present to block in established lymphangiectasia, and rapamycin did not increase caspase-dependent apoptosis. However, rapamycin potently suppressed Prox1 and VEGFR-3. These experiments revealed that lymphangiectasia is remarkably resistant to regression but is responsive to rapamycin, which rapidly reduces and normalizes the abnormal lymphatics without affecting normal lymphatics.

Bansal, N., et al. (2017). "Cardiac Lymphangioma Encasing Right Coronary Artery in an Infant." Ann Thorac Surg 104(3): e279-e281.

Cardiac lymphangioma is a rare primary benign tumor of the heart. We report a 3-year-old with cystic lymphangioma encasing the right coronary artery. Cardiac magnetic resonance imaging confirmed an intra-pericardial heterogeneous mass measuring 2.6 x 2.4 x 3.9 cm and situated right anterolateral to the ascending aorta and extending into the right atrioventricular groove. Furthermore, the right coronary artery traversed through the center of the mass. Surgical resection, on cardiopulmonary bypass, consisted of excision by skeletonizing the right coronary artery along the length of the mass. The pathology report was consistent with a lymphatic malformation. The postoperative course was uneventful without recurrence at follow-up.

Brouillard, P., et al. (2017). "Loss of ADAMTS3 activity causes Hennekam lymphangiectasia-lymphedema syndrome 3." Hum Mol Genet.

Primary lymphedema is due to developmental and/or functional defects in the lymphatic system. It may affect any part of the body, with predominance for the lower extremities. Twenty-seven genes have already been linked to primary lymphedema, either isolated, or as part of a syndrome. The proteins that they encode are involved in VEGFR3 receptor signaling. They account for about one third of all primary lymphedema cases, underscoring the existence of additional genetic factors. We used whole-exome sequencing to investigate the underlying cause in a non-consanguineous family with two children affected by lymphedema, lymphangiectasia and distinct facial features. We discovered bi-allelic missense mutations in ADAMTS3. Both were predicted to be highly damaging. These amino acid substitutions affect well-conserved

residues in the prodomain and in the peptidase domain of ADAMTS3. In vitro, the mutant proteins were abnormally processed and sequestered within cells, which abolished proteolytic activation of pro-VEGFC. VEGFC processing is also affected by CCBE1 mutations that cause the Hennekam lymphangiectasia-lymphedema syndrome syndrome type1. Our data identifies ADAMTS3 as a novel gene that can be mutated in individuals affected by the Hennekam syndrome. These patients have distinctive facial features similar to those with mutations in CCBE1. Our results corroborate the recent in vitro and murine data that suggest a close functional interaction between ADAMTS3 and CCBE1 in triggering VEGFR3 signaling, a cornerstone for the differentiation and function of lymphatic endothelial cells.

Itkin M. Magnetic Resonance Lymphangiography and Lymphatic Embolization in the Treatment of Pulmonary Complication of Lymphatic Malformation. Semin Intervent Radiol. 2017;34(3):294-300. Epub 2017/09/29.

Itkin and colleagues discuss lymphatic anomalies involving the chest and the morbidity and mortality they cause. They describe in detail their technique for performing dynamic contrast-enhanced magnetic resonance lymphangiography (DCMRL) for imaging the lymphatic system. The authors champion this technique for its ability not only to evaluate the typical lymphatic pathways, but also to demonstrate lymphatic involvement in bones, liver, spleen, intestine, and other locations. In particular, they detail the usefulness of this modality to identify pathological lymphatic flow towards the pulmonary parenchyma, which they label pulmonary lymphatic perfusion syndrome (PLPS). This abnormal lymphatic flow can lead to pulmonary lymphedema, plastic bronchitis, chylothorax, or chylopericardium. The authors also describe their technique in performing percutaneous thoracic duct embolization (TDE) or lymphatic interstitial embolization (LIE) of lymphatic masses to treat the challenging entity of PLPS.
Rush Chewning/Gulraiz Chaudry

Kato, H., et al. (2017). "MR imaging findings of vertebral involvement in Gorham-Stout disease, generalized lymphatic anomaly, and kaposiform lymphangiomatosis." Jpn J Radiol.

PURPOSE: To assess the MR imaging findings of vertebral involvement in Gorham-Stout disease (GSD), generalized lymphatic anomaly (GLA), and kaposiform lymphangiomatosis (KLA). METHODS: Nine patients (three patients with GSD, three with GLA, and three with KLA) who underwent whole-spine MR examinations were included. MR findings of fatty marrow replacement and prolonged T1 and T2 lesions of the vertebrae were retrospectively assessed. Prolonged T1 and T2 lesions were defined as well-defined and round-, oval-, or geographic-shaped areas. RESULTS: Six patients [one (33%) patient with GSD, two (67%) with GLA, and three (100%) with KLA] showed both fatty marrow replacement and prolonged T1 and T2 lesions. Fatty marrow replacement was seen in the cervical spine of two (33%) patients, thoracic spine of six (100%), lumbar spine of six (100%), and sacral spine of two (33%). Prolonged T1 and T2 lesions were seen in the cervical spine of three (50%) patients, thoracic spine of three (50%), lumbar spine of six (100%), and sacral spine of three (50%). CONCLUSION: Both fatty marrow replacement and prolonged T1 and T2 lesions of the vertebrae could be observed in GSD, GLA, and KLA. The most commonly affected site was the lumbar spine, followed by the thoracic spine.

Kato, M., et al. (2017). "Spontaneous Regression of Lymphangiomas in a Single Center Over 34 Years." Plast Reconstr Surg Glob Open 5(9): e1501.

BACKGROUND: A lymphangioma, also called a lymphatic malformation, is a congenital condition that

frequently occurs in young children. It is classified into 3 groups depending on the size of the cysts (macrocystic, microcystic, and mixed). Spontaneous regression occurs in some cases; however, the characteristics of patients who show regression have not been studied previously. Furthermore, the types and the timing of the initial treatment are still controversial. Therefore, we statistically analyzed the occurrence of short-term spontaneous regression, patient age at original occurrence, cyst types, cyst sizes, and cyst locations in patients diagnosed with peripheral localized lymphangiomas in a single children center over 34 years. METHODS: We retrospectively collected the data of 153 patients and reviewed the medical charts. RESULTS: Spontaneous regression occurred only in macrocystic or mixed type; regression was most frequent in patients who, at the time of onset, were more than 2 years old. CONCLUSIONS: We concluded that elderly patients with macrocystic or mixed type lymphangioma may have to wait for treatment for over 3 months from the initial onset. Conversely, microcystic type could not be expected to show regression in a short period, and prompt initiation of the treatments may be required. The difference of the regression or not may depend on the characteristics of the lymph flow.

Kim, S. H., et al. (2017). "Percutaneous Drainage and Povidone-Iodine Sclerotherapy of Cervical Lymphatic Malformation." Yonsei Med J 58(6): 1249-1251.

Lymphatic malformations in cases with macrocystic lesions can be treated with surgical excision or sclerotherapy using alcohol, bleomycin, doxycycline, or OK-432. We report a case of a 24-year-old woman who underwent percutaneous drainage and povidone-iodine sclerotherapy as primary treatment for cervical lymphatic malformation. The patient underwent povidone-iodine sclerotherapy for 3 consecutive days. After 8 months, ultrasonography of the lesion in the neck revealed complete resolution of the cervical lymphatic malformation without any complication. Povidone-iodine sclerotherapy can be a safe and cost-effective treatment option for cervical lymphatic malformation.

Liu, M., et al. (2017). "Mandibular Gorham-Stout disease: A case report and literature review." Medicine (Baltimore) 96(42): e8184.

RATIONALE: Gorham-Stout disease (GSD) is characterized by aggressive bone resorption, proliferation of vascular or lymphatic vessels, and soft-tissue swelling. Bones that initially appear normal start to resorb, partially or completely. However, the etiology of GSD is unknown. PATIENT CONCERNS: A 29-year-old man with a chief complaint of toothache and mobility in the lower right mandible for the previous 1 year. DIAGNOSES: Gorham-Stout disease (GSD). INTERVENTIONS: The RANK-ligand inhibitor denosumab was suggested to use to inhibit the development of osteoclasts and slow mandibular resorption. In addition, we proposed resection of the remaining mandible and reconstruction via vascularized bone graft, after resorption of the mandible had become stationary. OUTCOMES: Regular follow-ups were advised to this patient to monitor the stability of bone resorption prior to any surgical intervention. LESSONS: We strongly recommend that every attempt should be made for early diagnosis and prompt effective medical and surgical management. The failure to do so results in further complications and poor prognosis.

Ma, J., et al. (2017). "Diagnosis and surgical treatment of cervical macrocystic lymphatic malformations in infants." Exp Ther Med 14(2): 1293-1298.

The treatment of lymphatic malformations (LMs) represents a great clinical challenge. The present study reported on the treatment of 68 infants with cervical macrocystic LMs using surgical resection. The cases were retrospectively analyzed. All patients underwent pre-operative ultrasonography, computed tomography

(CT), and magnetic resonance imaging (MRI) examinations. The surgery was performed under general anesthesia with endotracheal intubation. Ultrasonograms showed that 24 cases were monolocular, 44 were multilocular, 16 had no echo, 20 had a uniform low-level echo and 32 had a non-uniform low-level echo. CT showed non-enhancing low-attenuating cystic lesions and attenuation values of 10-45 HU. The magnetic resonance images of the LMs showed a low signal intensity on T1-weighted imaging (WI) and a high signal intensity on T2-WI. Complete resection was achieved in 56 patients, subtotal resection in eight and partial resection in four. Two complications were noted, including reversible paresis of the marginal mandibular branch of the facial nerve and a surgical-site infection. One patient in whom partial resection was achieved had recurrence at ~2 months after the surgery. Ultrasonography, CT and MRI clearly demonstrated the size, shape, extent and adjacent structures of LMs, which aided in surgical planning and assessment of potential risks. Surgical excision increased the chances of cure and was relatively safe for infants aged <1 year. Location and extent, rather than age, were determined to be the most important factors for successful surgical treatment.

Malic, C. C., et al. (2017). "Lymphatic Malformation Architecture: Implications for Treatment With OK-432." J Craniofac Surg 28(7): 1721-1724.

PURPOSE: Herein, the authors aim to describe their findings of novel architectural types of lymphatic malformations (LM) and explain the relationship between these architectures and OK-432 treatment outcomes. METHODS: A retrospective review was conducted of all patients diagnosed with a LM treated with OK-432 at the Vascular Anomalies Clinic at BC Children's Hospital from December 2002 to January 2012. RESULTS: Twenty-seven patients were included in the study. Sixty percent of lesions were present by 2 years of age with the majority located in the head and neck (59%). The average number of sclerotherapy procedures was 1.4 per patient. Treatment under fluoroscopic guidance revealed 3 new LM architectures: open-cell microcystic, closed-cell microcystic, and lymphatic channel. Response to treatment was complete or good for 14/19 macrocystic and for 1/2 mixed lesions. Open-cell microcystic LMs gave a complete or good response for 3/3, which was attributed to OK-432 freely communicating between cysts. Closed-cell microcystic LM had localized cysts that did not allow OK-432 to freely communicate and were associated with partial responses, 2/2. The lymphatic channel had a partial response. There were 2 minor complications and 1 instance of recurrence. CONCLUSIONS: The identification of 3 new LM architectures expands the current accepted classification to include: open-cell microcystic, closed-cell microcystic, and lymphatic channels. The majority of complete responses to OK-432 were found with macrocystic lesions. Open-cell microcystic lesions respond better to OK-432 than closed-cell microcystic lesions, and lymphatic channels may respond to OK-432. These key architecture-response relationships have direct clinical implications for treatment with OK-432 sclerotherapy.

Menendez-Castro, C., et al. (2017). "Microbubbles in macrocysts - Contrast-enhanced ultrasound assisted sclerosant therapy of a congenital macrocystic lymphangioma: a case report." BMC Med Imaging 17(1): 39.

BACKGROUND: Congenital cystic lymphangiomas are benign malformations due to a developmental disorder of lymphatic vessels. Besides surgical excision, sclerosant therapy of these lesions by intracavitary injection of OK-432 (Picibanil(R)), a lyophilized mixture of group A Streptococcus pyogenes, is a common therapeutical option. For an appropriate application of OK-432, a detailed knowledge about the structure and composition of the congenital cystic lymphangioma is essential. SonoVue(R) is a commercially available contrast agent commonly used in sonography by intravenous and intracavitary application. CASE PRESENTATION: Here we report the case of 2 month old male patient with a large thoracic congenital cystic

lymphangioma. Preinterventional imaging of the malformation was performed by contrast-enhanced ultrasound after intracavitary application of SonoVue(R) immediately followed by a successful sclerotherapy with OK-432. CONCLUSIONS: Contrast agent-enhanced ultrasound imaging offers a valuable option to preinterventionally clarify the anatomic specifications of a congenital cystic lymphangioma in more detail than by single conventional sonography. By the exact knowledge about the composition and especially about the intercystic communications of the lymphangioma sclerosant therapy becomes safer and more efficient.

Sarah Mertlitz, Yu Shi, Martina Kalupa, Carsten Grötzinger, Jörg Mengwasser, Katarina Riesner, Steffen Cordes, Sefer Elezkurtaj and Olaf Penack. Lymphangiogenesis is a feature of acute GVHD, and VEGFR-3 inhibition protects against experimental GVHD. Blood 2017 129:1865-1875;

Although this article focuses on the role lymphangiogenesis plays in tumor metastasis and graft versus host disease (GVHD), it uniquely demonstrates how lymphatic vessels react in states of health, inflammation and disease. Using animal and human models, the authors showed that acute GVHD is associated with lymphangiogenesis and lymph vessels are increased in intestinal lesions during GVHD. They then studied anti-vascular endothelial growth factor receptor-3 (VEGFR-3) as a way to reduce the function and regulation of lymphangiogenesis and, ideally, decrease GVHD in allo-HSCT recipients. They demonstrated that anti-VEGFR-3 treatment could inhibit GVHD-associated lymphangiogenesis without reducing the efficacy and outcome of the allo-HSCT. It's theoretically possible that the link between various inflammatory triggers, upregulated lymphangiogenesis, and manipulation of the VEGFR-3 pathway could play a role in the development and propagation of lymphatic disorders.
Taizo Nakano/Denise Adams

Nitschke, M., et al. (2017). "Retrograde Lymph Flow Leads to Chylothorax in Transgenic Mice with Lymphatic Malformations." Am J Pathol 187(9): 1984-1997.

Chylous pleural effusion (chylothorax) frequently accompanies lymphatic vessel malformations and other conditions with lymphatic defects. Although retrograde flow of chyle from the thoracic duct is considered a potential mechanism underlying chylothorax in patients and mouse models, the path chyle takes to reach the thoracic cavity is unclear. Herein, we use a novel transgenic mouse model, where doxycycline-induced overexpression of vascular endothelial growth factor (VEGF)-C was driven by the adipocyte-specific promoter adiponectin (ADN), to determine how chylothorax forms. Surprisingly, 100% of adult ADN-VEGF-C mice developed chylothorax within 7 days. Rapid, consistent appearance of chylothorax enabled us to examine the step-by-step development in otherwise normal adult mice. Dynamic imaging with a fluorescent tracer revealed that lymph in the thoracic duct of these mice could enter the thoracic cavity by retrograde flow into enlarged paravertebral lymphatics and subpleural lymphatic plexuses that had incompetent lymphatic valves. Pleural mesothelium overlying the lymphatic plexuses underwent exfoliation that increased during doxycycline exposure. Together, the findings indicate that chylothorax in ADN-VEGF-C mice results from retrograde flow of chyle from the thoracic duct into lymphatic tributaries with defective valves. Chyle extravasates from these plexuses and enters the thoracic cavity through exfoliated regions of the pleural mesothelium.

Prenatal growth characteristics of lymphatic malformations. Peranteau WH, Iyoob SD, Boelig MM, Khalek N, Moldenhauer JS, Johnson MP, Hedrick HL, Flake AW, Coleman BG, Adzick NS. J Pediatr Surg. 2017 Jan;52(1):65-68

This article reviews a single center institution experience in the management of 30 fetuses between 19 and 39 weeks gestation with lymphatic malformations (LM). This study was performed at Children's Hospital of Philadelphia (CHOP), which is one of the pioneer institutions in fetal medicine. Prenatal growth patterns of LMs as they relate to gestational age, anatomical location, and postnatal management are described in a retrospective manner. Fetal pictures of LMs and comprehensive tables are included in the article.

In this study, none of the LMs spontaneously resolved. LMs located in the abdomen, mediastinum, and head and neck demonstrated both positive and negative growth profiles while those located in the axilla had only positive growth patterns. Subcutaneous lesions including cervicofacial and axillary LMs were associated with normal tissue distortion and an increased risk of aerodigestive tract obstruction and dystocia respectively. In contrast, growth of intracavitary lesions (i.e. intraabdominal) were associated with decreased perinatal consequences. Postnatally, 14 patients were managed with surgery alone, 8 were managed with intralesional sclerotherapy alone and 2 patients were managed with a combination of surgery and sclerotherapy.
Israel Fernández Pineda/Juan Carlos Lopez Gutierrez

Rasmussen, J. C., et al. (2017). "Near-infrared fluorescence lymphatic imaging of Klippel-Trenaunay syndrome." J Vasc Surg Venous Lymphat Disord 5(4): 533-537.

The relationship between lymphatic and venous malformations in Klippel-Trenaunay syndrome is difficult to assess. Herein the authors describe near-infrared fluorescence lymphatic imaging to assess the lymphatics of a subject with a large port-wine stain and right leg edema. Although lymphatic vessels in the medial, affected knee appeared dilated and perhaps tortuous, no definitive abnormal lymphatic pooling or propulsion was observed. The lymphatics in the affected limb were well defined but less numerous than in the contralateral limb, and active, contractile function was observed in all vessels. As demonstrated, near-infrared fluorescence lymphatic imaging enables the clinical assessment of lymphatics in lymphovenous malformations.

Shinkai T et al. (2017). "A large retroperitoneal lymphatic malformation successfully treated with traditional Japanese Kampo medicine in combination with surgery." Surg Case Rep 3(1): 80.

BACKGROUND: Current treatment options for lymphatic malformations (LMs) are multimodal. Recently, the effectiveness of treating LMs with Eppikajyutsuto (TJ-28) has been reported. TJ-28 is a kind of oral herbal medicine classified as the traditional Japanese Kampo medicine. CASE PRESENTATION: A 12-year-old girl was admitted to our hospital for intermittent upper abdominal pain. Radiological examinations revealed a large (9.5 x 5.8 x 10.0 cm) retroperitoneal LM, which was suspected to adhering and stretching both pancreas head and duodenum. The large retroperitoneal tumor resection might induce involving complications because of the size and the location. Therefore, we used TJ-28 in order to diminish the tumor size before surgery. The patient received oral doses of 7.5 g/day (2.5 g x 3 times/day) of TJ-28. Six months after the medication, the tumor decreased markedly to 3.5 x 1.5 x 1.2 cm in size. Thereafter, the mass was sub-totally resected (95%) via a 3 cm trans-umbilical incision without any surgical complications. CONCLUSIONS: We reported a case of successfully treated retroperitoneal LM with the combination treatment of TJ-28 and surgery. Based on our experience, this TJ-28 treatment option may be very useful in treating

cases of LMs having surgical difficulties because of size and/or location.

Sun, R. W., et al. (2017). "Current Status, Pitfalls and Future Directions in the Diagnosis and Therapy of Lymphatic Malformation." J Biophotonics.

Lymphatic malformations (LM) are complex congenital vascular lesions composed of dilated, abnormal lymphatic channels of varying size that can result in significant aesthetic and physical impairment due to relentless growth. LMs, comprised of micro-lymphatic channels (microcystic), integrate and infiltrate normal soft tissue, leading to a locally invasive mass. Ultrasonography (US) and magnetic resonance imaging (MRI) assist in the diagnosis but are unable to detect microvasculature present in microcystic LM. In this review, we examine existing tools and elaborate on alternative diagnostic methods in assessing LM. In particular, photoacoustics (PA), low-toxicity nanoparticles and optical clearing can overcome existing challenges in the examination of lymphatic channels in vivo. In combination with photothermal (PT) cytometry/flow cytometry (FC), PA may provide a versatile tool for lymphatic-related clinical applications, potentially leading to a single diagnostic and therapeutic platform to overcome limitations in current imaging techniques and permit targeted theranostics of microcystic LM.

Tu JH, Do HM, Patel V, Yeom KW, Teng JMC. Sclerotherapy for lymphatic malformations of the head and neck in the pediatric population. J Neurointerv Surg. 2017;9(10):1023-6. Epub 2016/11/01.

Tu and colleagues present a retrospective review of 41 pediatric patients with head and neck lymphatic malformations treated with sclerotherapy over a 15 year period. Their stated goal is to comparatively evaluate the safety and efficacy of different sclerosing agents in the pediatric population. Therapy was performed with doxycycline, ethanolamine, or OK-432 by physicians from neuro-interventional radiology, pediatric surgery, plastic surgery, or interventional radiology. The authors report that there was no significant difference in efficacy or complication rate between the three agents. Results of the study were comparable to those performed with these and other agents in the adult population. The authors conclude that these three agents are safe and effective for use in sclerotherapy of macrocystic and mixed head and neck lymphatic malformations in the pediatric population.
Rush Chewning/Gulraiz Chaudry

Yang, J. G., et al. (2017). "Lymphotoxins Promote the Progression of Human Lymphatic Malformation by Enhancing Lymphatic Endothelial Cell Proliferation." Am J Pathol 187(11): 2602-2615.

Formation of inflammation-related tertiary lymphoid organs promotes human lymphatic malformation (LM) development. However, the role of lymphotoxins (LTs) and LT-related inducible ligand, the crucial mediators for tertiary lymphoid organ formation, is undetermined in LMs. Herein, we show that LTs and LT-related inducible ligand promote LM development by enhancing lymphatic endothelial cell (LEC) proliferation via activating NF-kappaB pathways. The expression of LTs and their receptors was increased in LMs, especially the infected ones, when compared with normal skins. Nuclear translocation of p65, p52, and RelB in the LECs of LMs indicated the activation of classic and alternative NF-kappaB pathways. Pearson's correlation and cluster analysis suggested the close relationship between LEC proliferation and NF-kappaB activation. Moreover, in vitro data demonstrated LTs accelerated the proliferation of human dermal LECs (HdLECs) through activation of NF-kappaB. In addition, lipopolysaccharide (LPS) up-regulated LT receptor expression in HdLECs, leading to increased sensitivity to LTs. Suppression of LT receptors hampered LPS-enhanced HdLEC proliferation, indicating the crucial role of LT pathways in inflammatory lymphangiogenesis. Besides, evidence

from the LM rat models demonstrated LTalpha and LPS enhanced LEC proliferation, therefore promoting LM development. Blocking LT pathways by neutralizing antibodies against LTalpha and lymphotoxin beta receptor may decelerate the growth of the disease. In summary, our present study demonstrated activation of LT signaling pathways in LECs contributed to the progression of LMs.

Return to Scientific Article Reviews

VASCULAR MALFORMATIONS

Return to Scientific Article Reviews

Arbiser, J. L. and L. C. Gilbert (2017). "Double Jeopardy: The Rubber Ball Bounces Twice." J Invest Dermatol 2017 Jan;137(1): 15-17.

Soblet et al. describe cis mutations in TEK/Tie-2 in blue rubber bleb nevus and sporadic vascular malformations. This suggests that the remaining normal allele is required for the phenotype. Second, it suggests therapeutic approaches to treatment signal transduction inhibition.

Balzani, A., et al. (2017). "Efficacy of a Novel Optimized Pulsed Light Source (MaxG) for the Treatment of Facial Vascular Lesions." Photomed Laser Surg 35(1): 12-17.

BACKGROUND AND OBJECTIVE: Facial vascular malformations can cause a number of functional problems, including difficulties in breathing, eating, speech, and mobility. Psychological problems can also arise due to the possible unpleasant appearance of such lesions. Further, these lesions can lead to a number of complications, including pain, ulceration, infection, and significant bleeding. Many treatments have been proposed in the literature. Laser therapy (and its related treatments by non-coherent light sources) is now considered the gold standard in the treatment of the majority of vascular lesions. METHODS: Here, we present our experience with a novel optimized pulsed light source for the treatment of vascular anomalies. In this prospective study, we evaluate the clinical outcomes of 30 patients treated with this method. RESULTS: Our results confirm the efficacy and safety of this treatment for facial vascular lesions. CONCLUSIONS: Based on our experience and results, we believe this device could be considered as both an alternative monotherapy and a useful adjunctive to the already existing laser instruments.

Brinjikji, W., et al. (2017). "Pulmonary Arteriovenous Malformations Are Associated with Silent Brain Infarcts in Hereditary Hemorrhagic Telangiectasia Patients." Cerebrovasc Dis 44(3-4): 179-185.

BACKGROUND AND PURPOSE: There is a high prevalence of right-to-left shunting pulmonary arteriovenous malformations (PAVMs), which are stroke risk factors, in hereditary hemorrhagic telangiectasia (HHT) patients. While the prevalence of ischemic complications in HHT patients is known, the prevalence of silent brain infarcts (SBI) remains unknown. The purpose of this study was to determine the prevalence and risk factors for SBI in HHT patients. MATERIALS AND METHODS: Our institutional HHT database was queried to identify HHT patients who received a baseline screening brain MRI from January 2000 to February 2017. This study group was further refined by excluding patients who had a history of clinical ischemic disease as defined by having a stroke or transient ischemic attack (TIA). Brain MRIs were reviewed for SBI. Baseline data on demographics, Curacao criteria, presence of PAVMs, and cardiovascular risk factors were collected. The primary outcome was SBI prevalence. We also examined which baseline patient characteristics were associated with SBI through univariate chi-square and Student t tests and multivariate logistic regression analyses. RESULTS: Three hundred fifty three consecutive HHT patients from January 2000 to February 2017 with a screening brain MRI and no prior history of stroke/TIA were included. SBI prevalence was 9.9% (35/353). SBI patients were more likely to have PAVMs than non-SBI patients (80.6 vs. 53.1%, $p = 0.005$). The median age was 66 in the SBI group and 52 in the non-SBI group ($p = 0.006$). SBI patients had higher prevalence of hyperlipidemia (34.3 vs. 9.8%, $p < 0.0001$), hypertension (48.6 vs. 22.0%, $p = 0.005$), and tobacco use (25.7 vs. 9.8%, $p = 0.005$). No patients under 30 had SBI. In the 60-69 age group, the prevalence of SBI was

18.8% with rates of 28.6% in the PAVM group and 10.5% in the non-PAVM group. For patients >/=70 years old, the prevalence of SBI was 21.4% overall and 27.6% in the PAVM group and 10.5% in the non-PAVM group. On multivariate analysis, PAVMs (OR 3.62, 95% CI 1.46-10.40) and increasing age (OR 1.04, 95% CI 1.01-1.07) were independently associated with SBI. CONCLUSIONS: Overall, a similar 10% SBI prevalence in the HHT cohort was noted as compared to the general population. However, the prevalence of SBI was higher in HHT patients with PAVMs when compared to that of the general population, particularly among patients than 60 years old. These findings highlight the need to accurately identify, and when appropriate, treat PAVMs in the HHT population especially given the multiple significant, clinical consequences of SBI.

Burrows, P. E. (2017). "Angioarchitecture of Hereditary Arteriovenous Malformations." Semin Intervent Radiol 34(3):250-257.

This article describes three hereditary conditions known to be associated with arteriovenous malformation (AVM), along with their clinical and imaging features and angiographic angio-architecture. Hereditary hemorrhagic telangiectasia, capillary malformation-AVM (CM-AVM), and PTEN tumor hamartoma syndrome are conditions with autosomal dominant inheritance, caused by mutations in different molecular pathways, which frequently present with symptomatic AVMs. Imaging biomarkers, including sites of predilection, angio-architecture, and tissue overgrowth patterns, are helpful in identifying these patients and selecting appropriate treatment.

Chaturvedi S, Clancy M, Schaefer N, Oluwole O, McCrae KR. Depression and post-traumatic stress disorder in individuals with hereditary hemorrhagic telangiectasia: A cross-sectional survey. Thromb Res. 2017 May;153:14-18. Epub 2017 Mar 9.

Approximately 50% of patients with Hereditary Hemorrhagic Telangiectasia (HHT) experience complications of disease that negatively impact their health-related quality of life. Although several studies have called attention to those specific complications, few have addressed the psychological impact of HHT, particularly the presence of depression and post-traumatic stress disorder (PTSD). The authors recruited individuals greater than 18 years of age with HHT through the email list of Cure HHT. 185 individuals completed surveys that included 1) baseline participant characteristics, 2) PTSD checklist for Diagnostic and Statistical Manual of Mental Disorders (PCL-5), 3) Beck Depression Inventory II (BDI-II). 87.6% of patients identified a significant stressor or traumatic event related to HHT. 88.7% of individuals who completed the BDI-II had at least mild depressive symptoms (BDI-II > 13). 28.1% of individuals who completed the PCL-5 had a positive screen for PTSD (PCL-5 score > 38). This large cross-sectional survey identified a high prevalence of depressive symptoms in HHT patients, many of which were previously undiagnosed. It is the first study to report a prevalence of PTSD associated with HHT. The authors advocate for mental health screening in the HHT population and suggest referral to mental health providers for appropriate therapy.
Taizo Nakano/Denise Adams

Chen W et al. (2017). "Blue rubber bleb nevus syndrome: our experience and new endoscopic management." Medicine (Baltimore) 96(33): e7792.

The aim of our study is to enhance the awareness of blue rubber bleb nevus syndrome (BRBNS) through the patients in our hospital and introduced a new measure of endoscopic intervention. A retrospective review of 5 patients, who were diagnosed as BRBNS in our hospital from January 2013 to January 2017, was conducted. Data were collected with regard to demographics, clinical presentation,

endoscopic and imaging findings, management, and follow-up data. In total of 5 patients, the mean age was 28.8 years, range 16 to 44 years (male/female, 1/4) with the average initial age of onset 15.4 years. No family history was identified in our group. Physical examination showed multiple cutaneous lesions in 2 patients (40%, 2/5). All the 5 patients had gastrointestinal tract vascular malformations; stomach involved in 2 cases, large intestine in 2 cases, and small intestine involved in 3 cases. Lesions in the visceral organs and tissue were found in 1 patient. Gastrointestinal bleeding was its main symptom (3/5, 60%). Laboratory investigations revealed anemia in 4 patients and abnormality of coagulopathy in 2 patients with severe anemia. Conservative approach was recommended in 3 cases that included iron supplementation, drug hemostasis, and/or blood transfusion. An innovatively therapeutic approach with endoscopic submucosal dissection (ESD) procedure was used successfully in 1 patient with 2 polypoid BRBNS lesions in rectum. BRBNS is a very rare vascular malformation syndrome with unclear etiopathogenesis and noncurative treatments. ESD procedure was a feasible approach to remove the partial gastrointestinal lesions.

Dupuis-Girod, S., et al. (2017). "The Lung in Hereditary Hemorrhagic Telangiectasia." Respiration 94(4): 315-330.

Hereditary hemorrhagic telangiectasia (HHT) is a dominantly inherited genetic vascular disorder with an estimated prevalence of 1 in 6,000, characterized by recurrent epistaxis, cutaneous telangiectasia, and arteriovenous malformations (AVMs) that affect many organs including the lungs, gastrointestinal tract, liver, and brain. Its diagnosis is based on the Curacao criteria, and is considered definite if at least 3 of the 4 following criteria are fulfilled: (1) spontaneous and recurrent epistaxis, (2) telangiectasia, (3) a family history, and (4) pulmonary, liver, cerebral, spinal, or gastrointestinal AVMs. The focus of this review is on delineating how HHT affects the lung.

Dymerska, M., et al. (2017). "Size of Facial Port-Wine Birthmark May Predict Neurologic Outcome in Sturge-Weber Syndrome." J Pediatr 188: 205-209 e201.

OBJECTIVE: To determine whether the size of the birthmark in patients with Sturge-Weber syndrome (SWS) who have brain involvement can help predict neurologic disability. STUDY DESIGN: Fifty-one patients with SWS with facial birthmarks and brain involvement documented on magnetic resonance imaging were included in this retrospective chart review. A neuroradiologist, blinded to all clinical information, assigned a previously validated SWS neuroimaging score. A pediatric neurologist prospectively assigned previously validated neurologic severity scores, based on seizures, hemiparesis, visual field cut, and cognitive impairments. Three raters, blinded to clinical scores, independently graded the size of facial birthmark in each patient based on photographs. Their scores were averaged. Birthmark scores were compared with the imaging and neurologic severity results using nonparametric correlation analysis. RESULTS: Size of facial port-wine birthmark correlates with magnetic resonance imaging scores on the left and right sides (rho = 0.57 and 0.66 [$P < .001$], respectively). Size is also positively associated with the neurologic severity rating for patients age 6 years and above (1-sided Fisher exact, $P = .032$). CONCLUSIONS: The size of facial port-wine birthmark in SWS brain involvement can be developed as a tool to predict neurologic severity of the disease.

Etievant, J., et al. (2017). "Pulmonary arteriovenous malformations in hereditary haemorrhagic telangiectasia: Correlations between computed tomography findings and cerebral complications." Eur Radiol.

OBJECTIVES: Computed tomography (CT) is the modality of choice to characterise pulmonary

arteriovenous malformations (PAVMs) in patients with hereditary haemorrhagic telangiectasia (HHT). Our objective was to determine if CT findings were associated with frequency of brain abscess and ischaemic stroke. METHODS: This retrospective study included patients with HHT-related PAVMs. CT results, i.e. PAVM presentation (unique, multiple, disseminated or diffuse), the number of PAVMs and the largest feeding artery size, were correlated to prevalence of ischaemic stroke and brain abscess. All CTs were reviewed in consensus by two radiologists. RESULTS: Of 170 patients, 73 patients had unique (42.9 %), 49 multiple (28.8 %), 36 disseminated (21.2 %) and 12 diffuse (7.1 %) PAVMs. Fifteen patients presented with brain abscess; 26 patients presented with ischaemic stroke. The number of PAVMs was significantly correlated with brain abscess (11.5 vs. 6.2, respectively; p=0.025). The mean diameter of the largest feeding artery was significantly correlated with ischaemic stroke frequency (4.9 vs. 3.2 mm, respectively; p=0.0098). CONCLUSIONS: The number of PAVMs correlated significantly with risk of brain abscess, and a larger feeding artery significantly with more ischaemic strokes. These findings can lead to a better recognition and management of the PAVMs at risk of cerebral complications. KEY POINTS: * Chest CT helps clinicians to facilitate appropriate PAVM management strategies. * Pulmonary arteriovenous malformation CT findings are correlated with risk of cerebral complications. * Risk of brain abscess is significantly correlated with number of PAVMs. * Risk of ischaemic stroke is significantly correlated with large feeding artery PAVMs. * Prevalence of observed of brain abscess and ischaemic stroke is 26 %.

Gurien LA, Jackson RJ, Kiser MM, Richter GT. Nd:YAG laser therapy for rectal and vaginal venous malformations. Pediatr Surg Int. 2017 Aug;33(8):887-891

BACKGROUND: Limited therapeutic options exist for rectal and vaginal venous malformations (VM). We describe our center's experience using Nd:YAG laser for targeted ablation of abnormal veins to treat mucosally involved pelvic VM. METHODS: Records of patients undergoing non-contact Nd:YAG laser therapy of pelvic VM at a tertiary children's hospital were reviewed. Symptoms, operative findings and details, complications, and outcomes were evaluated. RESULTS: Nine patients (age 0-24) underwent Nd:YAG laser therapy of rectal and/or vaginal VM. Rectal bleeding was present in all patients and vaginal bleeding in all females (n = 5). 5/7 patients had extensive pelvic involvement on MRI. Typical settings were 30 (rectum) and 20-25 W (vagina), with 0.5-1.0 s pulse duration. Patients underwent the same-day discharge. Treatment intervals ranged from 14 to 180 (average = 56) weeks, with 6.1-year mean follow-up. Five patients experienced symptom relief with a single treatment. Serial treatments managed recurrent bleeding successfully in all patients, with complete resolution of vaginal lesions in 40% of cases. No complications occurred. CONCLUSIONS: Nd:YAG laser treatment of rectal and vaginal VM results in substantial improvement and symptom control, with low complication risk. Given the high morbidity of surgical resection, Nd:YAG laser treatment of pelvic VM should be considered as first line therapy.

In this report, 9 patients undergoing Nd:YAG laser therapy for pelvic venous malformations were reviewed. Rectal bleeding was seen in all patients and vaginal bleeding was documented in the 5 female patients. Nd:YAG laser therapy was helpful to temporize the on-going bleeding and to allow for symptom-free periods. No major complications were recorded and all patients were discharged home the day of the procedure. Treatment intervals ranged from 14 to 180 (average = 56) weeks, with 6.1-year mean follow-up. Five patients experienced symptom relief with a single treatment. Serial treatments managed recurrent bleeding successfully in all patients, with complete resolution of vaginal lesions in 40% of cases.

This study is the first to report a series of patients with pelvic venous malformations effectively palliated using Nd:YAG laser therapy without surgery. This therapeutical modality has shown effectivity in different mucosal

vascular anomalies (intraoral, glans...) and therefore its successful application in the rectum and vagina would be expected. Recent management of venous malformations in this location has shifted towards endorectal pull-through procedures, which it is a curative procedure with a higher complication rate.
Israel Fernández Pineda/Juan Carlos Lopez Gutierrez

Horbach, S. E. R., et al. (2017). "Development of an international core outcome set for peripheral vascular malformations (OVAMA project)." Br J Dermatol.

BACKGROUND: An important limitation in vascular malformation research is the heterogeneity in outcome measures used for the evaluation of treatment outcome. OBJECTIVE: The Outcome measures for VAscular MAlformations (OVAMA) project aimed to reach international consensus on a core outcome set (COS) for clinical research on peripheral vascular malformations: lymphatic (LM), venous (VM) and arteriovenous malformations (AVM). In this consensus study, we determined what domains should constitute the COS. METHODS: Thirty-six possibly relevant outcome domains were proposed to an international group of physicians, patients and the parents of patients. In a 3-round e-Delphi process using online surveys, participants repeatedly rated the importance of these domains on a 5-point Likert scale. Participants could also propose other relevant domains. This process was performed for LM, VM and AVM separately. Consensus was pre-defined as 80% agreement on the importance of a domain amongst both the physician group and the patient/parent group. Outcomes were then reevaluated in an online consensus meeting. RESULTS: 167 physicians and 134 patients and parents of patients with LM (n=50), VM (n=71) and AVM (n=29) participated in the study. After three rounds and a consensus meeting, consensus was reached for all three types of vascular malformations on the core domains of radiological assessment, physician-reported location-specific signs, patient-reported severity of symptoms, pain, quality of life, satisfaction and adverse events. Vascular malformation type-specific signs and symptoms were included for LM, VM and AVM, separately. CONCLUSION: It is recommended to measure at least these core outcome domains in therapeutic-efficacy studies on peripheral vascular malformations. This article is protected by copyright. All rights reserved.

Jackson, S. B., et al. (2017). "Gastrointestinal Manifestations of Hereditary Hemorrhagic Telangiectasia (HHT): A Systematic Review of the Literature." Dig Dis Sci 62(10): 2623-2630.

Hereditary hemorrhagic telangiectasia (HHT), also called Osler-Weber-Rendu syndrome, is an autosomal dominant genetic disease that affects the vasculature of numerous organs. The prevalence of HHT is estimated to be between 1.5 and 2 persons per 10,000. While there is still much to learn about this condition, there is an increasing understanding its underlying pathophysiology, genetic basis, presentations, and management. Recognizing that the clinical manifestations of HHT can involve a number of organ systems will provide clinicians with a higher index of suspicion for the disease. This early diagnosis and genotyping can greatly reduce mortality for a patient with HHT through appropriate screening for complications. This review will focus on the gastrointestinal manifestations of HHT and how these can dictate treatment and prognosis.

Johnson CM, Navarro OM (2017) “Clinical and sonographic features of pediatric soft-tissue vascular anomalies part 2: vascular malformations”. Pediatr Radiol. 47(9):1196-1208.

Vascular malformations are a heterogeneous group of entities, many of which present in the pediatric age group. Sonography plays a major role in the management of children with these vascular anomalies by providing information that helps in diagnosing them, in assessing lesion extent and complications, and in monitoring response to therapy. The interpretation of sonographic findings requires correlation with clinical

findings, some of which can be easily obtained at the time of scanning. This has to be combined with the use of appropriate nomenclature and the most updated classification in order to categorize these patients into the appropriate management pathway. Some vascular malformations are part of combined vascular anomalies or are associated with syndromes that include other disorders, frequently limb overgrowth, and these are now being reclassified based on their underlying genetic mutation. Sonography has limitations in the evaluation of some vascular malformations and in these cases MR imaging might be considered the imaging modality of choice, particularly for lesions that are large, that involve multiple compartments or are associated with other soft-tissue and bone abnormalities. In this article, which is part 2 of a two-part series, the authors review the most relevant clinical and sonographic features of arteriovenous, capillary, venous and lymphatic malformations as well as vascular malformations that are part of more complex conditions or associated with syndromes, including Parkes-Weber syndrome, phosphatase and tensin homologue (PTEN) hamartoma tumor syndromes, Klippel-Trénaunay syndrome, CLOVES (congenital lipomatous overgrowth, vascular malformations, epidermal nevi and skeletal anomalies) syndrome, fibro-adipose vascular anomaly and Proteus syndrome.

Kasthuri RS, Montifar M, Nelson J, Kim H, Lawton MT, Faughnan ME, Brain Vascular Malformation Consortium HHT Investigator Group. Prevalence and predictors of anemia in hereditary hemorrhagic telangiectasia. Am J Hematol. 2017 Jun 22. [Epub ahead of print]

The clinical impact of iron deficiency anemia in patients with Hereditary Hemorrhagic Telangiectasia (HHT) has not been well defined. The authors of this study set out to extrapolate the prevalence and risk factors for anemia in HHT using data previously collected in “the HHT project” carried out by the Brain Vascular Malformation Consortium. Of the 763 HHT patients recruited into the HHT project, 680 patients had self-reported variables related to anemia available for analysis. Roughly 50% (339/680) demonstrated anemia and risk factors included epistaxis and GI bleeding. The ACVRL-1 mutation was an independent predictor of bleeding. Young and middle-aged females with HHT were more likely to be anemic. The study highlights an impressive prevalence of anemia that translates to a clinical burden with potential impact on disease related morbidity, productivity, and health related quality of life.
Taizo Nakano/Denise Adams

Keppler-Noreuil, K. M., et al. (2017). "Characterization of thrombosis in patients with Proteus syndrome." Am J Med Genet A. [EPub June 19, 2017]

Patients with overgrowth and complex vascular malformation syndromes, including Proteus syndrome, have an increased risk of thromboembolism. Proteus syndrome is a mosaic, progressive overgrowth disorder involving vasculature, skin, and skeleton, and caused by a somatic activating mutation in AKT1. We conducted a comprehensive review of the medical histories and hematologic evaluations of 57 patients with Proteus syndrome to identify potential risk factors for thrombosis. We found that six of ten patients, who were deceased, died secondary to deep venous thrombosis and/or pulmonary embolism. Of the remaining 47 living patients, six had thromboembolic events that all occurred postoperatively and in an affected limb. Eleven of 21 patients had an abnormal hypercoagulable panel including Factor V Leiden heterozygotes, antithrombin III deficiency, positive lupus anticoagulant, or Protein C or S deficiencies. We observed that eight of 17 patients had an abnormal D-dimer level >0.5 mcg/dl, but deep venous thromboses occurred in only four of those with D-dimer >1.0 mcg/dl. We conclude that the predisposition to thrombosis is likely to be multifaceted with risk factors including vascular malformations, immobility, surgery, additional prothrombotic factors, and possible pathophysiologic effects of the somatic AKT1 mutation on platelet function or the vascular endothelium. The

D-dimer test is useful as a screen for thromboembolism, although the screening threshold may need to be adjusted for patients with this disorder. We propose developing a registry to collect D-dimer and outcome data to facilitate adjustment of the D-dimer threshold for Proteus syndrome and related disorders, including PIK3CA-Related Overgrowth Spectrum.

Kim, S. W. and H. Song (2017). "Multimodal Imaging in Klippel-Trenaunay-Weber Syndrome: Clinical Photography, Computed Tomoangiography, Infrared Thermography, and 99mTc-Phytate Lymphoscintigraphy." Clin Nucl Med.

We report the case of a 19-year-old man who presented with a 12-year history of progressive fatigue, feeling hot, excessive sweating, and numbness in the left arm. He had undergone multimodal imaging and was diagnosed as having Klippel-Trenaunay-Weber syndrome (KTWS). This is a rare congenital disease, defined by combinations of nevus flammeus, venous and lymphatic malformation, and hypertrophy of the affected limbs. Lower extremities are affected mostly. Conventional modalities for evaluating KTWS are ultrasonography, CT, MRI, lymphoscintigraphy, and angiography. There are few reports on multimodal imaging of upper extremities of KTWS patients, and this is the first report of an infrared thermography in KTWS.

Li, J., et al. (2017). "Pingyangmycin Pretreatment Influences the Biological Behavior of Ocular Venous Malformation and Relates with Galectin-3 Expression." Chin Med J (Engl) 130(15): 1804-1809.

BACKGROUND: Galectin-3 (Gal-3) plays a role in the mechanisms underlying ocular venous malformation. We conducted this study to investigate the effect of pingyangmycin pretreatment on the Gal-3 expressions and biological behavior of ocular venous malformation. METHODS: Tissue samples were collected from 136 patients with ocular venous malformation. Patients were randomly divided into pingyangmycin (n = 69) and nonpingyangmycin group (n = 67). Patients in the pingyangmycin group received a local injection of 0.02% pingyangmycin once every 2 days for 2 weeks (7 doses) before removal surgery, whereas patients in the nonpingyangmycin group underwent removal surgery without local injection. The protein and messenger RNA (mRNA) expression of Gal-3 were detected by using immunohistochemistry and in situ hybridization. RESULTS: Gal-3 protein was expressed in 35 (52%) of 67 samples in the nonpingyangmycin group and in 19 (28%) of 69 samples in the pingyangmycin group ($P < 0.05$). Gal-3 mRNA expression was detected in 39 (58%) of 67 samples in the nonpingyangmycin group and 22 (32%) of 69 samples in the pingyangmycin group ($P < 0.05$). The higher Gal-3 expressions were detected in samples with deeper invasiveness than those with superficial invasiveness before ($chi2 = 12.720$ and 13.369, respectively, both $P < 0.05$) and after pingyangmycin treatment ($chi2 = 8.429$ and 4.590, respectively, both $P < 0.05$). It was more frequently detected in mesh-like lesions with unclear boundary than round lesions with clear boundary before ($chi2 = 30.291$ and 41.466, respectively, both $P < 0.05$) and after pingyangmycin treatment ($chi2 = 14.619$ and 15.130, respectively, both $P < 0.05$). Pingyangmycin treatment led to a significant difference in Gal-3 expressions at both protein and mRNA levels ($chi2 = 8.664$ and 9.524, respectively, both $P < 0.05$). CONCLUSIONS: Gal-3 expression may be involved in the development and invasiveness of ocular venous malformation, and pingyangmycin can inhibit Gal-3 expression, indicating a role of pingyangmycin treatment before the removal of ocular venous malformation.

Martin, J. L., et al. (2017). "Antithrombotic Use Predicts Recanalization of Embolized Pulmonary Arteriovenous Malformations in Hereditary Hemorrhagic Telangiectasia." Can Assoc Radiol J 68(4): 463-467.

Martins L, Giovani PA, Rebouças PD, Brasil DM, Haiter Neto F, Coletta RD, Machado RA, Puppin-Rontani RM, Nociti FH Jr, Kantovitz KR. "Computational analysis for GNAQ mutations: New insights on the molecular

etiology of Sturge-Weber syndrome." J Mol Graph Model 2017;76:429-440.

Somatic activating mutations in the GNAQ have been recently associated with several congenital genetic disorders and tumors; however, the molecular mechanism/etiology that leads to GNAQ somatic mosaic mutation are unknown. Here, we reported a case of Sturge-Weber Syndrome (SWS) manifesting cutaneous vascular malformations (hemifacial Port-wine stain), cerebral and ocular vascular abnormalities (including epilepsy and glaucoma) and harboring a c.548G>A (p.R183Q) somatic mosaic mutation in GNAQ. Computational modeling studies were performed to assistant with the comprehension of the functional impact of p.R183Q and p.Q209L mutations in GNAQ, which encodes a G protein subunit alpha q (Gαq). The p.R183Q mutation was predicted to abolish hydrogen bonds between R183 residue and GDP molecule, destabilizing the inactive GDP-bound conformation of the Gαq mutants. Furthermore, replacement of R183 by Q183 residue was predicted to promote conformation changes in protein surface features affecting the switch I region, a key region that undergoes conformational changes triggered by receptor binding during signal transduction. In addition, replacement of Q209 by L209 residue was predicted to affect the molecular interaction between Gαq and Gβ subunit, impairing formation of the inactive heterotrimeric complex. These findings, in association with PPI network analysis, indicate that p.R183Q and p.Q209L mutations result in the over-activation of different downstream effectors, which in turn will determine the distinct cell responses and phenotype. These findings bring new insights on molecular etiology of vascular malformations associated to SWS and on different mechanisms underlying hyperactivation of downstream pathways to Gαq.

Mei-Zahav, M., et al. (2017). "Topical propranolol improves epistaxis in patients with hereditary hemorrhagic telangiectasia - a preliminary report." J Otolaryngol Head Neck Surg 46(1):58.

BACKGROUND: Severe epistaxis is often difficult to control in patients with hereditary hemorrhagic telangiectasia (HHT). Propranolol has been shown to have antiangiogenic properties in vitro and in vivo and is commonly used to treat hemangiomas. We present our experience with topical nasal propranolol for the treatment of moderate to severe epistaxis in patients with HHT. METHODS: Retrospective case series. Six patients with HHT were treated with 0.5 cm3 of 1.5% propranolol gel, applied to each nostril twice daily for at least 12 weeks. Outcome measures were epistaxis severity score (ESS), hemoglobin level, and number of blood transfusions prior to and while on treatment. Local and systemic side effects were recorded. RESULTS: The mean duration of treatment was 30 +/- 5.6 weeks. A significant improvement in the ESS was found in all patients, with a mean decrease from 6.4 +/- 2.1 at treatment onset to 3.5 +/- 1.7 at 12 weeks (p = 0.028). Hemoglobin level increased significantly from 8.4 +/- 3.1 to 11.0 +/- 1.8 g/dL at 12 weeks (p = 0.043). The mean number of blood transfusions decreased from 4.5 +/- 4.9 before treatment to 2.5 +/- 2.9 at 12 weeks and 0.3 +/- 0.8 at 24 weeks, but the difference did not reach statistical significance (p = 0.109 for both). No significant side effects of treatment were recorded. CONCLUSIONS: These preliminary results suggest that topical propranolol may be effective for the treatment of epistaxis in patients with HHT. A prospective controlled trial is required to confirm our findings.

Menegozzo, C. A. M., et al. (2017). "Postoperative disseminated intravascular coagulation in a pregnant patient with Blue Rubber Bleb Nevus Syndrome presenting with acute intestinal obstruction: Case report and literature review." Int J Surg Case Rep 39: 235-238.

BACKGROUND: Blue Rubber Bleb Nevus Syndrome (BRBNS) is a rare condition which usually manifests as multiple hemangioma-like skin and gastrointestinal lesions. The latter often present with chronic bleeding. There is no consensus regarding the optimal management of such patients. Although rare, complications such

as intestinal intussusception might occur, demanding surgical treatment. Postoperative complications such as coagulation disorders can increase morbidity and should be timely addressed. This is the first report of a life-threatening postoperative disseminated intravascular coagulation in such patients. The main objectives of this case report are to present diagnostic and treatment features of this condition and, more importantly, address the optimal management of postoperative disseminated intravascular coagulation. CASE PRESENTATION: Twenty-five year-old female pregnant patient presents to the emergency department with colicky pain and oligohydramnios. After C-section, persistent symptoms and further investigation led to the diagnosis of intestinal intussusception. After surgical management she showed clinical and laboratory signs of disseminated intravascular coagulation (DIVC), which was corrected with transfusional therapy and intraperitoneal clot evacuation. After optimal management, she was discharged home. Sirolimus was initiated further improving her condition. CONCLUSION: This rare presentation of acute intestinal intussusception in a patient with Blue Rubber Bleb Nevus Syndrome was further complicated with postoperative coagulation disorder. Prompt surgical evaluation is essential especially when complications are suspected. Operative treatment might be necessary in the emergent setting. Close monitoring of infectious and coagulation parameters is essential in the postoperative period, and aggressive treatment should be timely initiated when disseminated intravascular coagulation is suspected.

Mu, W., et al. (2017). "Characterization of pulmonary arteriovenous malformations in ACVRL1 versus ENG mutation carriers in hereditary hemorrhagic telangiectasia." Genet Med. online publication, 19 October 2017.

Purpose - Pulmonary arteriovenous malformations (pAVMs) are major contributors to morbidity and mortality in hereditary hemorrhagic telangiectasia (HHT). Mutations in ENG and ACVRL1 underlie the vast majority of clinically diagnosed cases. The aims of this study were to characterize and compare the clinical and morphologic features of pAVMs between these two genotype groups. Methods - Sixty-six patients with HHT and affected family members were included. Genotype, phenotypic data, and imaging were obtained from medical records. Morphologic features of pAVMs were analyzed using computed tomography angiography. HHT symptoms, pAVM imaging characteristics, frequency of procedural intervention, and HHT severity scores were compared between ENG and ACVRL1 genotype groups. Results - ENG mutation carriers were more likely than ACVRL1 mutation carriers to have pAVMs ($P < 0.001$) or multiple lesions ($P = 0.03$), and to undergo procedural intervention ($P = 0.02$). Additionally, pAVMs in ENG carriers were more likely to exhibit bilateral lung involvement and growth over time, although this did not reach statistical significance. The HHT severity score was significantly higher in ENG than in ACVRL1 ($P = 0.02$). Conclusion - The propensity and multiplicity of ENG-associated pAVMs may contribute to the higher disease severity in this genotype, as reflected by the HHT severity score and the frequency of interventional procedures.

Nagano M, Ichinose J, Sasabuchi Y, Nakajima J, Yasunaga H. Surgery versus percutaneous transcatheter embolization for pulmonary arteriovenous malformation: Analysis of a national inpatient database in Japan. J Thorac Cardiovasc Surg. 2017 Sep;154(3):1137-1143

This extensive review on nearly 1,000 patients provides not only accurate information regarding the role of video assisted thoracoscopy surgery and embolization in the management of pulmonary arteriovenous malformations but precious epidemiological data.

Interestingly, mean age of needed treatment of pulmonary AVM´s has been progressively increasing which is a sign of significant improvement in the medical management of this entity.
Surgery had a high certainty of eliminating the fistula on the first treatment compared with embolization but it was superior to surgery in terms of complications and postoperative length of stay.

Despite important study limitations as the lack of accurate information about fistulas size, number and location, or post-procedural lung function, this large group analysis give us again the positive feeling of effective multidisciplinary protocols in the management of this uncommon disorder
Israel Fernández Pineda/Juan Carlos Lopez Gutierrez

Nassiri N, Crystal D, Huntress LA, Murphy S. "Transcatheter embolization of persistent embryonic veins in venous malformation syndromes." J Vasc Surg Venous Lymphat Disord 2017;5(5):749-755.

Persistent embryonic veins represent a major source of venous hypertension and morbidity in venous malformation syndromes, such as Klippel-Trenaunay syndrome and congenital lipomatous overgrowth, vascular malformations, epidermal nevus, and skeletal deformities syndrome. Surgical stripping and phlebectomy are the most commonly reported alternatives to compression therapy for refractory cases. These techniques, although effective in those patients who meet the necessary anatomic criteria, can be associated with bleeding, wound-related complications, and recurrence. Herein, we present a less invasive endovascular technique for elimination of these incompetent persistent embryonic veins. This technique has fewer anatomic restrictions and can be a suitable first-line option for management of refractory venous insufficiency in this particular population of patients.

Nassiri and colleagues present 3 case examples of their technique of endovascular closure of persistent embryonic veins (PEV) in patients with KTS or CLOVES as a less invasive alternative to surgical stripping or phlebectomy. They suggest that these veins, given their subdermal location and lack of fascial encasement, are not amenable to ablation by RFA or endovenous laser therapy. The authors postulate that these veins are largely – if not solely – responsible for morbid venous hypertension in this patient population, and suggest embolization of these veins prior treating other venous or lymphatic anomalies. They first evaluate for the presence and patency of the deep venous system with either venous duplex ultrasound or ascending venography. They access the distal most aspect of the PEV and perform ascending venography. This is followed by coil embolization of the venous outflow and perforating branches of the PEV. Finally, they describe deposition of sodium tetradecyl sulfate (STS) foam throughout the remaining length of the PEV. Case descriptions include 2 cases of lateral marginal vein of the lower extremity in KTS and 1 case of truncal marginal vein in CLOVES. This paper provides numerous images from each of the cases highlighting the patient's venous anomalies and the authors' treatment technique.
Rush Chewning/Gulraiz Chaudry

Nassiri N, Cirillo-Penn NC, Crystal DT. Direct stick embolization of extremity arteriovenous malformations with ethylene vinyl alcohol copolymer. Journal of Vascular Surgery 2017 Apr;65(4):1223-1228.

Nassiri and colleagues present three cases in which they use ethylene vinyl alcohol copolymer (Onyx) via direct stick embolization to treat arteriovenous malformations in the extremities. They acknowledge that many physicians have avoided use of this agent in the periphery due to concerns about technique for safe delivery, skin discoloration, or ulceration. Despite these concerns, they report relief of symptoms without recurrence or complications in these three patients, whom they followed for six months after the procedures. The authors

use this approach in conjunction with more traditional transarterial or transvenous embolization when these other approaches do not allow for penetration of the embolic into the nidus of the AVM. The article also provides a helpful review of the Yakes classification for AVM.
Rush Chewning/Gulraiz Chaudry

Offermann EA, Sreenivasan A, DeJong MR, Lin DDM, McCulloch CE, Chung MG, Comi AM; National Institute of Health Sponsor; Rare Disease Clinical Research Consortium (RDCRN); Brain and Vascular Malformation Consortium (BVMC); National Sturge-Weber Syndrome Workgroup. Collaborators: Ball KL, Fisher BJ, Hammill A, Juhász C, Koenig J, Lawton M, Lo W, Marchuk D, Miles D, Moses M, Wilfong A. "Reliability and Clinical Correlation of Transcranial Doppler Ultrasound in Sturge-Weber Syndrome." Pediatr Neurol 2017;74: 15-23 e15.

BACKGROUND: The reproducibility of transcranial Doppler (TCD) ultrasound measurements in Sturge-Weber syndrome (SWS) and TCD's ability to predict neurological progression is unknown. METHODS: In 14 individuals with SWS, TCD measured mean flow velocity, pulsatility index, peak systolic velocity, and end-diastolic velocity in the middle, posterior, and anterior cerebral arteries of the affected and unaffected hemisphere. TCD was performed either once (n = 5) or twice in one day (n = 9). We assessed the reproducibility of the measurements performed twice on the same day on subjects and compared the TCD measurements to previously published age-matched controls. Clinically obtained neuroimaging was scored for extent and severity of SWS brain involvement. Patients were prospectively assigned SWS neuroscores. RESULTS: Middle cerebral artery velocity (r = 0.79, P = 0.04, n = 7), posterior cerebral artery velocity (r = 0.90, P = 0.04, n = 5), and anterior cerebral artery pulsatility index (r = 0.82, P = 0.02, n = 7) were reproducible TCD measurements comparing same-day percent side-to-side differences. In subjects with SWS, affected and unaffected mean peak systolic velocity and end-diastolic velocity in the middle, posterior, and anterior cerebral arteries were globally lower compared with age-matched control subjects. Subjects with the lowest affected middle cerebral artery velocity had the greatest worsening in the total neurological score between time 1 and 2 (r = -0.73, P = 0.04, n = 8) and the most severe magnetic resonance imaging involvement of the affected frontal lobe (r = -0.82, P = 0.007, n = 9). CONCLUSIONS: TCD may be a reliable measure with potential clinical value, indicating that blood flow may be globally decreased in SWS patients with unilateral brain involvement.

Peterman CM, Fevurly RD, Alomari AI, Trenor CC 3rd, Adams DM, Vadeboncoeur S, Liang MG, Greene AK, Mulliken JB, Fishman SJ. "Sonographic screening for Wilms tumor in children with CLOVES syndrome." Pediatr Blood Cancer 2017 64(12).

BACKGROUND: CLOVES syndrome is associated with somatic mosaic PIK3CA mutations and characterized by congenital lipomatous overgrowth, vascular malformations, epidermal nevi, and skeletal anomalies. Wilms tumor (WT) is a malignant embryonal renal neoplasm associated with hemihypertrophy and certain overgrowth disorders. After identifying WT in a child with CLOVES, we questioned whether ultrasonographic screening was necessary in these patients. METHODS: We retrospectively reviewed patients with CLOVES syndrome in our Vascular Anomalies Center at Boston Children's Hospital between 1998 and 2016 to identify those who developed WT. A PubMed literature search was also conducted to find other patients with both conditions. RESULTS: A total of 122 patients with CLOVES syndrome were found in our database (mean age 7.7 years, range 0-53 years). Four patients developed WT; all were diagnosed by 2 years of age. The incidence of WT in our CLOVES patient population (3.3%) was significantly greater than the incidence of WT in the general population (1/10,000) (P < 0.001). Four additional patients with WT and

CLOVES syndrome were identified in our literature review. CONCLUSION: Patients with CLOVES syndrome have an increased risk of WT. Given the benefits of early detection and treatment, children with CLOVES syndrome should be considered for quarterly abdominal ultrasonography until age 7 years. Screening may be most beneficial for patients under 3 years of age.

Wilms tumor (WT) is a renal neoplasm known to occur in some overgrowth disorders including hemihypertrophy and Beckwith-Wiedemann syndrome. Patients with CLOVES syndrome (congenital lipomatous overgrowth, vascular malformations, epidermal nevi, and scoliosis/skeletal anomalies) demonstrate similar patterns of overgrowth were to be at increased risk for WT. The authors reviewed an institutional database to identify four institutional cases of WT in CLOVES patients (3.3%). They additionally performed a comprehensive literature review to identify an additional four cases previously reported. They conclude that children with CLOVES syndrome have an increased risk of WT, perhaps related to somatic PIK3CA mutations. Given the impact of early detection and treatment, the authors recommend abdominal ultrasonography every 3 months until 7 years of age in this patient population.

Peterman C M et al. (2017). "Wilms tumor screening in diffuse capillary malformation with overgrowth and macrocephaly-capillary malformation: A retrospective study." J Am Acad Dermatol 77(5): 874-878.

BACKGROUND: CLOVES (congenital lipomatous overgrowth, vascular malformations, epidermal nevi, and skeletal anomalies) syndrome is associated with regional bony and/or soft tissue overgrowth, capillary malformation, and an increased risk for Wilms tumor. OBJECTIVE: To evaluate the frequency of Wilms tumor in patients with 2 similar conditions: diffuse capillary malformation with overgrowth (DCMO) and macrocephaly-capillary malformation (M-CM). METHODS: Culling our Vascular Anomalies Center database, we retrospectively reviewed patients in whom DCMO and M-CM had been diagnosed and who were evaluated between 1998 and 2016 for possible development of Wilms tumor. Patients younger than 8 years of age at their last visit and not seen in more than 2 years were contacted for follow-up. RESULTS: The study comprised 89 patients: 67 with DCMO, 17 with M-CM, and 5 with an indeterminate diagnosis. No case of Wilms tumor was found in these groups. LIMITATIONS: Some patients were younger than 8 years of age at last follow-up visit and the sample size was small. CONCLUSION: Patients with DCMO do not appear to be at increased risk for Wilms tumor. Screening is probably unnecessary in DCMO unless there is associated hemihypertrophy. Although there were no cases in our cohort, there are 2 reports of M-CM associated with Wilms tumor in the literature.

Poje, G. and M. M. Kavanagh (2017). "Hereditary hemorrhagic telangiectasia-laser treatment of epistaxis." Ear Nose Throat J 96(9):E10-E14.

Hereditary hemorrhagic telangiectasia (HHT) is a rare, autosomal dominant disorder characterized by recurrent epistaxis, telangiectasias, and multiorgan vascular dysplasia. Various modalities exist for the treatment of HHT-related chronic epistaxis, although no method is preferred over another. The aim of this study was to review the effectiveness of diode laser photocoagulation in the treatment of epistaxis in patients with HHT. The study included 17 patients (7 men, 10 women) treated with diode laser photocoagulation from year 2008 to 2012. All patients met the Curacao criteria for a diagnosis of HHT. Patients were followed for 1 year. Treatment success was assessed using a custom questionnaire and total blood counts. After laser photocoagulation, the frequency and intensity of bleeds were reduced significantly and average hemoglobin concentrations improved at the 4-month assessment. After laser treatment, no patient required septodermoplasty; therefore, we suggest that every patient with HHT should be treated with laser

photocoagulation. Diode laser treatment is a simple and effective procedure that should be considered when treating HHT.

Samimi, M., et al. (2017). "Clinical and hemodynamic risk factors associated with discrepancies in lower limb length with capillary malformations - data from the national paediatric French cohort CONAPE." Br J Dermatol.

BACKGROUND: Genetics discoveries have allowed for better understanding capillary malformations (CMs) with overgrowth syndrome. However, molecular analyses are still not easy to perform or interpret. Other analytical methods are needed. OBJECTIVE: We aimed to identify clinical and hemodynamic factors associated with leg length discrepancy (LLD) in children with CM of lower limbs. METHODS: Data were obtained from the multicentre French national cohort CONAPE (COhorte Nationale d'enfants atteints d'Angiome Plan de membrE inferieur), including children from 2 to 12 years old with CM of lower limbs. Clinical characteristics were prospectively collected. Hemodynamic factors were measured by an echographer who calculated the arterial blood flow (ABF) in both lower limbs. An ABF difference >/=50% between the two lower limbs was considered relevant. LLD >/= 2% was determined by the same radiologist on centralized radiographs. RESULTS: We analyzed data at baseline for 96 children. The mean (SD) age was 5.6 (3.1) years; 49 (51%) were male; and 14 (15%) showed LLD. Thirty-two patients (33%) had venous anomalies, 13 (14%) lymphatic anomalies, and in 1 child, diagnosis of Parkes Weber syndrome was made. Only increased circumference above the knee was more frequent with than without LLD (50% vs 13%, p=0.02). In all, 10/79 patients (13%) showed a difference in ABF >/=50%: 4 had LLD. The frequency of differences in ABF >/=50% was greater with than without LLD [33.3% (n=4/12) vs 9.0% (n=6/67), p=0.04]. CONCLUSIONS: ABF measured by Duplex ultrasonography is a simple, low-cost and non-invasive complementary examination for help in detecting LLD, with a difference >/= 50% possibly associated. This article is protected by copyright. All rights reserved.

Sapp, J. C., et al. (2017). "Quantifying survival in patients with Proteus syndrome." Genet Med. [EPub June 29, 2017]

Purpose - Proteus syndrome is a rare mosaic overgrowth disorder that is associated with severe complications. While anecdotal data have suggested that the life span of affected patients is reduced, this has not been measured. Mortality data on rare diseases is critical for assessing treatments and other interventions. Methods - To address this we used the clinical research records of 64 patients in a longitudinal natural history cohort at the National Institutes of Health to ascertain the data in an organized manner and estimate survival using a Kaplan-Meier approach. Results - The median age of diagnosis was 19 months. Based on this analysis, there was 25% probability of death by 22 years of age. Ten of the 11 patients who died were younger than 22 years of age, and there was only a single death after this age. Conclusion - These data quantify the risk of premature death in Proteus syndrome, which can be used to support interventions and trials. Although the risk of death is substantial, the fact that only one patient died after 22 years of age supports anecdotal evidence that the disease process moderates after the end of adolescence. Interventions to reduce mortality should be targeted to the pediatric age range.

Schreiber, A., et al. (2017). "A case of congenital lipomatous overgrowth, vascular malformations, epidermal nevi, spinal/skeletal anomalies and/or scoliosis syndrome with lipoatrophy as an important clinical manifestation." Pediatr Dermatol.

Congenital lipomatous overgrowth, vascular malformations, epidermal nevi, spinal/skeletal anomalies and/or scoliosis syndrome is a PIK3CA-related overgrowth spectrum presenting with congenital, asymmetric, disproportionate overgrowth associated with dysregulated adipose tissue, enlarged bony structures, and mixed primarily truncal vascular malformations. We present this case to raise awareness that very thin body habitus (lipoatrophy) contrasting with areas of overgrowth can be an important clinical feature of this syndrome and, if not recognized, can lead to unnecessary investigations.

Sharma, P., et al. (2017). "A case of pulmonary arteriovenous malformation: role of interventional radiology in diagnosis and treatment." Ann Transl Med 5(17): 345.

Pulmonary arteriovenous malformations (PAVMs) are abnormal pulmonary arteries and pulmonary veins communicating directly without interposition of a capillary bed and about 80-90% of patients with PAVMs eventually may present with hereditary hemorrhagic telangiectasia (HHT), remaining ones are sporadic cases. On the other hand, about 15-35% of HHT patients may present with PAVMs. The PAVMs have a tendency to grow and increase in size over time and various factors like puberty, pregnancy and pulmonary arterial hypertension (PAH) affect growth. This condition needs early diagnosis, aggressive management and vigilant follow up. Our article aims to review pulmonary AVMs as a rare cause of strokes in young patients. We will discuss the clinical presentation, diagnosis, complications, the therapeutic options and the follow up.

Strickland, C. D., et al. (2017). "Familial Cerebral Cavernous Malformations Are Associated with Adrenal Calcifications on CT Scans: An Imaging Biomarker for a Hereditary Cerebrovascular Condition." Radiology 284(2): 443-450.

Purpose - To determine if adrenal calcifications seen at computed tomography (CT) are associated with familial cerebral cavernous malformations (fCCMs) in carriers of the CCM1 Common Hispanic Mutation. Materials and Methods - This study was approved by the institutional review board. The authors retrospectively reviewed abdominal CT scans in 38 patients with fCCM, 38 unaffected age- and sex-matched control subjects, and 13 patients with sporadic, nonfamilial cerebral cavernous malformation (CCM). The size, number, and laterality of calcifications and the morphologic characteristics of the adrenal gland were recorded. Brain lesion count was recorded from brain magnetic resonance (MR) imaging in patients with fCCM. The prevalence of adrenal calcifications in patients with fCCM was compared with that in unaffected control subjects and those with sporadic CCM by using the Fisher exact test. Additional analyses were performed to determine whether age and brain lesion count were associated with adrenal findings in patients with fCCM. Results - Small focal calcifications (SFCs) (</=5 mm) were seen in one or both adrenal glands in 19 of the 38 patients with fCCM (50%), compared with 0 of the 38 unaffected control subjects ($P < .001$) and 0 of the 13 subjects with sporadic CCM ($P = .001$). Adrenal calcifications in patients with fCCM were more frequently left sided, with 17 of 19 patients having more SFCs in the left adrenal gland than the right adrenal gland and 50 of the 61 observed SFCs (82%) found in the left adrenal gland. No subjects had SFCs on the right side only. In patients with fCCM, the presence of SFCs showed a positive correlation with age ($P < .001$) and number of brain lesions ($P < .001$). Conclusion - Adrenal calcifications identified on CT scans are common in patients with fCCM and may be a clinically silent manifestation of disease. (c) RSNA, 2017.

Tan, E. M. S., et al. (2017). "Embryonic Stem Cell-Like Subpopulations in Venous Malformation." Front Med (Lausanne) 4: 162.

BACKGROUND: Venous malformation (VM) consists of a network of ectatic anomalous thin-walled venous

channels. A role for an activating TIE2 mutation in the development of the dilated luminal vessels in VM, and its proposed involvement of embryonic stem cells (ESCs), led us to investigate the expression of ESC markers in subcutaneous VM (SCVM) and intramuscular VM (IMVM). METHODS: Formalin-fixed paraffin-embedded sections of SCVM from seven patients and IMVM samples from seven patients were analyzed for the expression of Nanog, pSTAT3, OCT4, SOX2, SALL4, and CD44, using 3,3'-diaminobenzidine (DAB) immunohistochemical (IHC) staining. All these samples did not express lymphatic marker D2-40. NanoString mRNA analysis and RT-PCR were performed on snap-frozen samples of SCVM (n = 3) and IMVM (n = 3) from the respective original cohorts of patients included in DAB IHC staining. To confirm co-expression of two proteins, immunofluorescent (IF) IHC staining on two representative samples of IMVM and SCVM samples from the original cohorts of patients included for DAB IHC staining was performed. RESULTS: DAB IHC staining demonstrated expression of all of the above ESC markers in both SCVM and IMVM samples. IF IHC staining showed that these markers were localized to the endothelium within these lesions and that Nanog, pSTAT3, SOX2, and CD44 were also expressed by cells outside of the endothelium. NanoString mRNA analysis confirmed transcription activation of pSTAT3, OCT4, and CD44. RT-qPCR confirmed transcription activation of Nanog, SOX2, and SALL4. CONCLUSION: Our findings support the presence of two ESC-like subpopulations, one within and one outside of the endothelium, of both SCVM and IMVM. Given that the endothelial ESC-like subpopulation expresses the more primitive marker, OCT4, it is exciting to speculate that they give rise to the non-endothelial subpopulation.

Teusch VI, Wohlgemuth WA, Hammer S, Piehler AP, Muller-Wille R, Goessmann H, Uller W. Ethanol-Gel Sclerotherapy of Venous Malformations: Effectiveness and Safety. AJR Am J Roentgenol. 2017:1-6.

Teusch and colleagues presented her experience in using a commercially available ethanol gel as a sclerosant for treatment of venous malformations. In this study, they evaluate the safety and efficacy of ethanol gel for treatment of 31 patients with venous malformations. The authors described their technique of ethanol gel sclerotherapy as well as their methodology in evaluating treatment response. There were no major complications, and minor complications included skin ulceration, necrosis, and blistering. They cited research indicating ethanol is the most effective agent for sclerotherapy in venous malformation, but that it has the highest rate of complications and side effects among sclerosants. They theorized that this gelified form of ethanol might increase local effects and reduce systemic effects as compared to traditional liquid ethanol. This well-designed study presents ethanol gel as a safe and effective option for use in sclerotherapy for VM.
Rush Chewning/Gulraiz Chaudry

Vorselaars, V., et al. (2017). "Pulmonary Hypertension in a Large Cohort with Hereditary Hemorrhagic Telangiectasia." Respiration. 94(3):242-250.

BACKGROUND: Hereditary hemorrhagic telangiectasia (HHT) is a vascular disorder characterized by arteriovenous malformations in the brain, liver, and lungs. Pulmonary hypertension (PH) is increasingly recognized as a severe complication of HHT. However, there are no studies describing the prevalence of PH in HHT compared to HHT-negative controls. OBJECTIVE: To assess the estimated prevalence of PH in patients with HHT compared to HHT-negative controls. METHODS: All consecutive subjects screened for HHT with available genetic testing and echocardiography-based peak tricuspid regurgitation velocity (TRV) measurement were included. Increased-probability PH was defined as a TRV >2.8 m/s. RESULTS: In 578 subjects, both echocardiography and genetic testing were available. A reliable TRV was measured in 383 (66.3%), of whom 127 had HHT type 1 (HHT1), 150 had HHT type 2 (HHT2), and 106 were HHT-negative controls, with a mean TRV of 2.3 +/- 0.4, 2.4 +/- 0.5, and 2.2 +/- 0.3 m/s, respectively ($p = 0.008$ and $p < 0.001$

vs. controls). Increased-probability PH was found in 42 subjects (8.7% in HHT1, 18.0% in HHT2, and 3.8% in HHT-negative controls). HHT2 and hepatic arteriovenous malformations (HAVMs) were the most important predictors for increased-probability PH (odds ratio 5.6, p = 0.002, and odds ratio 11.3, p < 0.001, respectively). Heritable pulmonary arterial hypertension (HPAH) was diagnosed in 2 patients (0.7%) and only found in HHT2 (1.3%). CONCLUSION: The estimated prevalence of PH is higher in HHT patients compared to HHT-negative controls. This increase is especially present in HHT2 and mainly associated with the presence of HAVMs. HPAH appears to be rare in HHT patients and was only diagnosed in HHT2.

Yu, J., et al. (2017). "EPHB4 Mutation Implicated in Capillary Malformation-Arteriovenous Malformation Syndrome: A Case Report." Pediatr Dermatol. [EPub July 21, 2017]

Capillary malformation-arteriovenous malformation (CM-AVM) syndrome, due to inactivating mutations in RASA1 in 68% of cases, is characterized by the development of cutaneous capillary malformations and arteriovenous malformations or fistulas; no known genetic etiology has been identified in patients with CM-AVM syndrome without RASA1 mutations. We present the case of a child with RASA1-negative CM-AVM syndrome with a de novo missense mutation in EPHB4, a transmembrane tyrosine kinase receptor essential for vasculogenesis. Inactivating the mutation in EPHB4 has been shown to upregulate the mitogen-activated protein kinase pathway and the mammalian target of rapamycin complex 1, possibly contributing to the development of vascular malformations.

Zallmann, M., et al. (2017). "Screening for Sturge-Weber syndrome: A state-of-the-art review." Pediatr Dermatol.

Infants with a high-risk distribution of port-wine stains are commonly screened for Sturge-Weber syndrome using brain magnetic resonance imaging. There is no consensus about which port-wine stain phenotypes to screen, optimal timing, screening sensitivity, or whether presymptomatic diagnosis improves neurodevelopmental outcomes. This state-of-the-art review examines the evidence in favor of screening for Sturge-Weber syndrome, based on its effect on neurodevelopmental outcomes, against the risks and limitations of screening magnetic resonance imaging and electroencephalography. A literature search of PubMed/MEDLINE was conducted between January 2005 and May 2017 using key search terms. Relevant articles published in English were reviewed; 34 articles meeting the search criteria were analyzed according to the following outcome measures: neurodevelopmental outcome benefit of screening, diagnostic yield, financial costs, procedural risks, and limitations of screening magnetic resonance imaging and electroencephalography. There is no evidence that a presymptomatic Sturge-Weber syndrome diagnosis with magnetic resonance imaging results in better neurodevelopmental outcomes. The utility of electroencephalographic screening is also unestablished. In Sturge-Weber syndrome, neurodevelopmental outcomes depend on prompt recognition of neurologic red flags and early seizure control. Small numbers and a lack of prospective randomized controlled trials limit these findings. For infants with port-wine stain involving skin derived from the frontonasal placode (forehead and hemifacial phenotypes), we recommend early referral to a pediatric neurologist for parental education, counselling, and monitoring for neurologic red flags and seizures and consideration of electroencephalography regardless of whether magnetic resonance imaging is performed or its findings.

Return to Scientific Article Reviews

HEMANGIOMAS – PATHOGENESIS AND TREATMENT

Return to Scientific Article Reviews

Alexopoulos A et al. (2017). "Atenolol treatment for severe Infantile Hemangiomas: a single-centre prospective study." J Eur Acad Dermatol Venereol.

Infantile hemangiomas (IHs) are common benign vascular tumors of infancy with an incidence of 4-5%. The majority of IHs are self-limited, though in approximately 10% of patients, when their lesions compromise vital and sensory functions or cause disfigurement, medical treatment is warranted. The most exciting development in the treatment for IHs over the last decade has been the discovery of propranolol's effects during the proliferative phase of the hemangioma cycle. This article is protected by copyright. All rights reserved.

Borok J et al. (2017). "Safety and efficacy of topical timolol treatment of infantile haemangioma: A prospective trial." Br J Dermatol.

Topical timolol therapy is considered a relatively "safer" alternative for the treatment of infantile haemangiomas (IH); however, sufficient supportive pharmacokinetic data does not exist. Most efficacy studies have not evaluated systemic absorption. To our knowledge, this is the first prospective trial to assess the clinical response of proliferating IH to topical timolol maleate 0.5% gel-forming solution and to determine if systemic absorption occurred. Twenty-six subjects enrolled in this trial approved by the UCSD IRB. This article is protected by copyright. All rights reserved.

Brennan T E et al. (2017). "The Tissue Expander Effect in Early Surgical Management of Select Focal Infantile Hemangiomas." JAMA Facial Plast Surg 19(4):282-286.

Importance: The current standard of treatment for infantile hemangiomas (IHs) involves initial observation for regression throughout infancy and childhood, with or without medical management with beta-blocker medications. Approximately 50% of the lesions respond almost completely to this regimen. However, the remaining 50% of the lesions, especially established focal IHs of the lip, nose, eyelids, forehead, cheek, and scalp, do not regress completely with this regimen or do so leaving a deformity; among these lesions, early surgical management may result in a superior aesthetic and functional outcome. Objective: To identify select focal head and neck lesions of IH that will likely not completely involute with medical management and that are ideal for a 1-stage surgical excision. Design, Setting, and Participants: In this case series, records of infants and children presenting to a tertiary care vascular anomalies center for management of IHs by the senior author were reviewed. Representative examples of focal IHs of the lips, nose, eyelids, cheek, and glabella demonstrating the tissue expansion effect were selected for presentation. Expert opinion based on more than 20 years of experience of the senior surgeon treating more than 2000 patients with focal IH and long-term clinical follow-up is also provided. Main Outcomes and Measures: Eradication of the IH while restoring aesthetic form and function to the face. Results: Five examples of patients with focal IHs of the lip, nose, eyelid, cheek, and glabella demonstrating the tissue expander effect who were successfully treated with surgery are presented. The 5 patients with these lesions ranged in age from 3 months to 5 years old, and all of them were female. One of these patients was treated with beta-blockers, and another with steroids, with

incomplete response to treatment prior to undergoing surgery. The tissue expander effect of a focal IH on adjacent, unaffected tissue facilitated excision of the lesion and primary closure without distortion of anatomical subunits in all 5 of these cases. Improved cosmesis with either improved or unaffected function was demonstrated. Conclusions and Relevance: Clinicians should consider early surgical intervention in infants with select focal infantile hemangiomas in lieu of prolonged observation or medical management. The psychological benefit of early removal of these disfiguring lesions has not been quantified, but is subjectively apparent to clinicians and the families of patients. Furthermore, the costs and unknown long-term sequelae of beta-blocker medication, which is the current standard of treatment for IHs along with observation for regression, have not yet been quantified but will gain increasing salience in the current medical climate. Level of Evidence: 5.

Chakraborty PP et al. (2017). "Consumptive hypothyroidism in solitary cutaneous haemangioma." BMJ Case Rep Jul 19;2017.

Chang L et al. (2017). "Infantile hemangioma: factors causing recurrence after propranolol treatment." Pediatr Res.

Background - Propranolol is the first-choice treatment for severe infantile hemangioma (IH). However, 10- 30% of lesions relapse after propranolol treatment. The mechanisms underlying IH recurrence after propranolol treatment have not been completely elucidated. Methods - This study combined an examination of hemodynamic changes with research regarding hemangioma stem cells (hscs) with differentially expressed microRNAs (miRNAs) to identify the factors affecting IH recurrence after propranolol treatment. Hemodynamic changes were monitored in 21 recurrent cases using high-frequency color Doppler ultrasound, and hscs were treated with different concentrations of propranolol. The levels of differentially expressed miRNAs and the activity of related pathways were then compared between 18 recurrent and 20 non-recurrent IH cases. Results - During treatment, lesion depth and vessel density decreased, and the lesion resistance index increased. Obvious lesions and vessel signals were observed in recurrent cases compared with non-recurrent cases. Propranolol effectively inhibited hscs proliferation. Twenty-two differentially expressed miRNAs were found in the recurrent group compared with the non-recurrent group. Conclusion - Recurrence may be attributed to a combination of events. Serum biomarkers and drug treatments for IH recurrence must be studied further.Pediatric Research advance online publication, 11 October 2017.

Chen J et al. (2017). "Mechanisms of Action of MicroRNAs in Infantile Hemangioma Tissue and Vascular Endothelial Cells in Different Periods." Med Sci Monit 23:4214-4224.

Chen Y Z et al. (2017). "Propranolol inhibits the proliferation, migration and tube formation of hemangioma cells through HIF-1alpha dependent mechanisms." Braz J Med Biol Res 50(12): e6138.

The aim of this study was to investigate the mechanism of propranolol on the regression of hemangiomas. Propranolol-treated hemangioma tissues were collected and the expression of hypoxia inducible factor-1alpha (HIF-1alpha) was examined. We also established HIF-1alpha overexpression and

knockdown hemangioma cells, and determined the effects of HIF-1alpha on the hemangioma cells proliferation, apoptosis, migration and tube formation. Significantly increased HIF-1alpha level was found in the hemangioma tissues compared to that in normal vascular tissues, whereas propranolol treatment decreased the HIF-1alpha level in hemangioma tissues in a time- and dose-dependent manner. Moreover, propranolol treatment significantly decreased cell proliferation, migration and tube formation as well as promoted cell apoptosis in HIF-1alpha overexpression and knockdown hemangioma cells. Propranolol suppressed the cells proliferation, migration and tube formation of hemangioma cells through HIF-1alpha dependent mechanisms. HIF-1alpha could serve as a novel target in the treatment of hemangiomas.

Dornhoffer J R et al. (2017). "The expression of renin-angiotensin-aldosterone axis components in infantile hemangioma tissue and the impact of propranolol treatment." Pediatr Res 82(1):155-163.

Background. Propranolol's mechanism of action for controlling infantile hemangioma (IH) remains unclear. We hypothesize that this nonselective beta antagonist downregulates renin-angiotensin-aldosterone (RAA) axis components, preventing angiogenic substrate induction of IH. Methods. IH tissue and serum were collected from children with propranolol-treated or -untreated IH during surgery. Normal skin and serum from demographically matched children were used as controls. Real-time PCR and western blot quantified RAA components in proliferative (n=10), involuting (n=10), propranolol-treated (n=12) IH, and normal specimens (n=11). Serum was analyzed by enzyme-linked immunosorbent assay (ELISA). Results. There were significantly greater messenger RNA (mRNA) levels of angiotensinogen (AGT) in proliferating IH, but not in involuting or treated IH, when compared with controls ($P<0.05$). Angiotensin-converting enzyme (ACE) and angiotensin II receptor 1 (AGTR1) mRNA expression was higher in all IH specimens when compared with controls ($P<0.05$). ACE and AGTR1 protein expression was greater in proliferating IH tissue compared with that in controls and in involuting and treated IH tissue ($P<0.05$). ELISA showed no significant difference in ACE serum levels but did show a significant reduction in renin in involuting compared with proliferating IH ($P<0.05$). Conclusions. The protein and mRNA expression of several RAA pathway constituents is elevated in IH tissue when compared with that in normal tissue. The action of propranolol on IH may be the result of reductions in ACE and AGTR1.

Gonzalez-Llorente N et al. (2017). "Study of Cognitive Function in Children Treated with Propranolol for Infantile Hemangioma." Pediatr Dermatol 34(5):554-558.

BACKGROUND: Oral propranolol is considered the first choice for the treatment of infantile hemangiomas (IHs). There is a concern that administering propranolol in newborns and infants could induce adverse effects in learning and memory processes in the long term. The purpose of this study was to assess cognitive and memory functions in children who had been treated with propranolol for IH during their infancy. METHODS: A total of 23 children between 5 and 7.5 years of age who had been treated with oral propranolol for IH during infancy were tested for cognitive functions with the Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition (WPPSI-IV) test and for memory functions with the Test of Memory and Learning (TOMAL). RESULTS: Comparison of our sample with a normal distribution by a Shapiro-Wilk W test showed no significant difference for any of the composite scores in the WPPSI-IV and TOMAL tests except for positive asymmetry and concentration of scores around average ($p = 0.01$) in the WPPSI-IV composite score (mean intelligence), due to one atypically high score. CONCLUSIONS: The distribution of scores for intelligence and

memory scales in our study population was similar to that in the reference general population. These results fail to support any significant disturbance in intelligence and memory development in children treated during infancy with propranolol for IH.

Goss J A et al. (2017). "Propranolol Treatment of Vascular Anomalies Other Than Infantile Hemangioma." J Craniofac Surg.

BACKGROUND: Oral propranolol has become first-line intervention for problematic infantile hemangioma (IH) that is not amenable to topical or intralesional therapies. Consensus data supporting its efficacy for other vascular anomalies does not exist. The purpose of this study was to determine the frequency and causes of propranolol use for vascular lesions other than IH. METHODS: Referrals to our Vascular Anomalies Center between 2008 and 2017 were reviewed for patients treated with propranolol at an outside institution. Patient history, photographs, imaging studies, and/or histopathology were evaluated by an interdisciplinary team to diagnose the vascular anomaly. Our center's diagnosis was compared to the referral diagnosis to categorize patients into 3 groups: Group 1 (patients were appropriately labeled with an IH); Group 2 (individuals were erroneously diagnosed with IH); and Group 3 (subjects were diagnosed with a vascular anomaly other than IH). RESULTS: Two hundred thirty-six patients met inclusion criteria. Group 1 (39%; n = 91) had an IH and were treated appropriately. Group 2 (20%; n = 49) was misdiagnosed with IH and incorrectly received propranolol. Group 3 (41%; n = 96) was given propranolol to treat another vascular anomaly. Propranolol did not have efficacy for vascular anomalies other than IH. CONCLUSIONS: Propranolol commonly is used to treat lesions other than IH; misdiagnosis of a lesion as IH is a common cause. Propranolol should be used with caution to treat other types of vascular anomalies because patients are subjected to the risks of the drug without data supporting its efficacy.

He X, Liu Y, Li K, Yang A, Wang R, Liu S. Sildenafil suppresses the proliferation and enhances the apoptosis of hemangioma endothelial cells. Exp Ther Med. 2017 Jun;13(6):2645-2650.

Abstract

Treatment of infantile hemangiomas (IH) with propranolol was first reported in 2008. Regressions of lymphatic malformations combined with pulmonary hypertension was first reported in 2012 after three children received treatment with oral sildenafil, which serves as an antagonist of phosphodiesterase isoform-5 (PDE-5). A marked expression of endothelial cells in the cytoplasm of IH tissues was obtained in our previous study. Therefore, the present study hypothesized that the antagonist of PDE-5, sildenafil, may lead to the regression of hemangiomas. To assess this hypothesis, the proliferation and apoptosis of specimen-derived hemangioma endothelial cells (HemECs) was determined *in vitro* by an MTT assay and flow cytometry, respectively, following treatment with sildenafil. The potential mechanisms underlying the mRNA and protein expression levels of inhibitor of differentiation 1 (Id-1) were determined by reverse transcription-quantitative polymerase chain reaction and western blotting. The results demonstrated that 5 µM sildenafil suppressed the proliferation of HemECs and significantly enhanced the rate of apoptosis after 24 h. Additionally, the mRNA and protein expression levels of Id-1 were downregulated following treatment with sildenafil. Therefore, the present study concluded that PDE-5 may be a potential therapeutic target for hemangiomas and Id-1 may serve a vital role in the associated signaling transduction pathways.

KEYWORDS:

apoptosis; hemangioma endothelial cells; inhibitor of differentiation 1; proliferation; sildenafil

Hutchins K K et al. (2017). "Treatment of Refractory Infantile Hemangiomas and Pulmonary Hypertension With Sirolimus in a Pediatric Patient." J Pediatr Hematol Oncol 39(7):e391-e393.

Infantile hemangioma is a benign vascular neoplasm that spontaneously involutes over time. Management, when needed, consists of medications, laser treatment and surgical excision. We describe a 3-year-old girl who presented shortly after birth with diffuse cutaneous hemangiomas, hepatosplenomegaly with liver lesions, anemia, and acute heart failure. She was diagnosed with hepatic and cutaneous infantile hemangioma based on skin biopsy. She developed progressive pulmonary hypertension with numerous pulmonary nodules suspicious for pulmonary arteriovenous malformations. She was started on sirolimus and had significant improvement in her pulmonary hypertension and liver lesions. This report supports prior studies that sirolimus is effective for vascular anomalies including IH refractory to conventional therapy.

Lewis J et al. (2017). "The impact of facial abnormalities and their spatial position on perception of cuteness and attractiveness of infant faces." PLoS One 12(7):e0180499.

Research has demonstrated that how "cute" an infant is perceived to be has consequences for caregiving. Infants with facial abnormalities receive lower ratings of cuteness, but relatively little is known about how different abnormalities and their location affect these aesthetic judgements. The objective of the current study was to compare the impact of different abnormalities on the perception of infant faces, while controlling for infant identity. In two experiments, adult participants gave ratings of cuteness and attractiveness in response to face images that had been edited to introduce common facial abnormalities. Stimulus faces displayed either a haemangioma (a small, benign birth mark), strabismus (an abnormal alignment of the eyes) or a cleft lip (an abnormal opening in the upper lip). In Experiment 1, haemangioma had less of a detrimental effect on ratings than the more severe abnormalities. In Experiment 2, we manipulated the position of a haemangioma on the face. We found small but robust effects of this position, with abnormalities in the top and on the left of the face receiving lower cuteness ratings. This is consistent with previous research showing that people attend more to the top of the face (particularly the eyes) and to the left hemifield.

Li H et al. (2017). "Inhibition of hemangioma growth using polymer-lipid hybrid nanoparticles for delivery of rapamycin." Biomed Pharmacother 95:875-884.

Although infantile hemangioma is benign, its rapid growth may induce serious complications. However, only one drug Hemangeol has been approved by US Food and Drug Administration (FDA) to treat infantile hemangiomas. Thus it is necessary to develop novel alternative drugs to treat infantile hemangiomas. Rapamycin is a well-known potent antiangiogenic agent, whereas the daily oral administration of rapamycin exerts undesired metabolic effects due to its inhibition of mechanistic target of rapamycin (mTOR) which is critical in cell metabolism. We hereby developed rapamycin-loaded polymer-lipid hybrid nanoparticles (Rapamycin-PLNPs) as a local controlled release system to realize local and sustained release of rapamycin,

aiming to reduce the side effects and frequency of administration of rapamycin. Rapamycin-PLNPs are of a small size (129.1nm), desired drug encapsulation efficiency (63.7%), and sustained drug release for 5 days. Rapamycin-PLNPs were shown to be able to effectively bind to hemangioma endothelia cells (HemECs), induce significant proliferation inhibition and reduce expression of angiogenesis factors in HemECs. The therapeutic effect of Rapamycin-PLNPs against infantile hemangioma in vivo was superior to rapamycin, as reflected by reduced hemangioma volume, weight and microvessel density. Taken together, Rapamycin-PLNPs represent a very promising local approach in the treatment of infantile hemangiomas.

Li M et al. (2017). "Clinical Evaluation of Color Doppler Ultrasound in Selecting the Optimal Treatment Modality for Infantile Hemangioma." Chin Med Sci J 32(2):100-106.

Objective - We investigated the efficacy and safety of 1064 nm Nd: YAG laser, intense pulsed light (IPL), and lauromacrogol injection in the treatment of hemangioma, in order to evaluate the value of color Doppler ultrasound guidance in choosing the optimal treatment modality. Methods - Infantile patients who were clinical diagnosed as hemangiomas were randomly divided into group A, who had color Doppler ultrasound examinations before the treatment, and group B who had the treatment without ultrasound evaluation. Patients in the group A were assigned into subgroups according to the depth of lesion by sonography: group A-1 for those who had a lesion depth <1.2 mm, and took intense pulsed light therapy; group A-2 for those who had a lesion depth >/=1.2mm and < 3 mm, and took long pulse 1064 nm Nd:YAG laser therapy; group A-3 for those who had a lesion depth >/=3mm and <5 mm, and were treated by IPL combined with long pulse 1064 nm Nd:YAG laser treatment; Group A-4 for those who had a lesion depth >/=5 mm, and took lauromacrogol injection therapy. Patients in the group B took long pulse 1064 nm Nd:YAG laser treatment without preoperative ultrasound evaluation. The efficacy and adverse reactions of the treatments between the groups were evaluated and compared statistically. Results - Totally 113 patients with 128 skin lesions were enrolled in this study, 85 in the group A (mean age 6.8+/-7.9 months) and 28 in the group B (mean age 6.9+/-9.9 months). The mean depth of hemangioma was 3.3+/-1.1 mm in the group A, ranging from 0.5-7.8 mm, with 0.8+/-0.4 mm, 2.2+/-0.4 mm, 4.2+/-0.6 mm and 6.2+/-0.7 mm in group A1, A2, A3 and A4, respectively. The cure rates and effective rates in the group A were significantly higher than those in the group B (cure rates: 64.5% vs 56.3%, U=3.378, P=0.045; effective rates: 89.5% vs 78.1%, U=4.163, P=0.041). The adverse effect rates of the group A (vesicle 20.0%, pigmentation 46.9%, scarring 17.7%) were lower than those of the group B (vesicle 21.9%, pigmentation 60.4%, scarring 25.0%). Incidences of pigmentation and scarring were statistically significantly different (U=3.884, P=0.034, and U=4.016, P=0.032 respectively) between the two groups. Conclusion - With the guidance of color Doppler ultrasound, the efficacy and safety of long pulse 1064 nmNd: YAG laser, intense pulsed light, and lauromacrogol injection in the treatment of infantile hemangioma have better outcomes compared to laser treatment alone without preoperative ultrasound examination.

Lie E, Puttgen KB (2017). "Corticosteroids as an adjunct to propranolol for infantile haemangiomas complicated by recalcitrant ulceration." Br J Dermatol 176(4):1064-1067.

A small subset of patients with infantile haemangiomas (IHs) can present with serious complications, the most common of which is ulceration. Ulcerated IHs can be extremely painful and always result in scarring. Numerous studies support the efficacy and reduced side-effects of propranolol relative to systemic

corticosteroids, which led to the adoption of propranolol as the mainstay of IH treatment. However, in certain cases of IH with complex ulceration, propranolol monotherapy may not be sufficient. In this case report, we present two cases that illustrate the effectiveness of the adjunctive use of oral corticosteroids for the treatment of select IHs with recalcitrant painful ulceration, which were refractory to conservative wound care, laser therapy and oral propranolol. We suggest a continuing niche role for the brief use of corticosteroids as an effective adjunct to oral propranolol in managing a subset of complex IHs complicated by intractable ulceration.

Marey H M et al. "Combined Oral and Topical Beta Blockers for the Treatment of Early Proliferative Superficial Periocular Infantile Capillary Hemangioma." J Pediatr Ophthalmol Strabismus. 2017 Oct 9:1-6.

PURPOSE: To evaluate the safety and efficacy of combined oral and topical beta blockers for the treatment of superficial periocular infantile hemangioma at the early proliferative stage. METHODS: This was a randomized, controlled comparison trial involving 25 patients. Patients were randomly enrolled into two groups: the topical and systemic treatment and systemic treatment only groups. The topical and systemic treatment group was treated with oral propranolol (1 mg/kg per day initially, increased to 2 mg/kg per day gradually in 2 weeks) and timolol maleate 0.5% gel. The systemic treatment only group received oral propranolol (1 mg/kg per day initially, increased to 2 mg/kg per day gradually in 2 weeks) and simple eye ointment to be applied to the lesion. The Hemangioma Activity Score was used to record the proliferative activity of the hemangioma. The main outcomes of the study were the change in the hemangioma size, the proliferative activity, and the treatment side effects. RESULTS: At the end of the treatment period, the Hemangioma Activity Score was significantly improved in both groups from their values before treatment. However, the score obtained after treatment was significantly better in the topical and systemic treatment group ($P < .05$). Regarding the response to treatment, 10 and 3 cases in the topical and systemic treatment and systemic treatment only groups, respectively, showed a good response, with a significant difference between the two groups ($P < .50$). There were no recorded serious local or systemic complications during treatment in either group. CONCLUSIONS: The results from combining topical with oral beta blockers showed that topical beta blockers are of additive value in treating superficial periocular infantile hemangioma in the early proliferative stage.

Mashiah J et al. (2017). "Assessment of the effectiveness of topical propranolol 4% gel for infantile hemangiomas." Int J Dermatol 56(2):148-153.

BACKGROUND: Infantile hemangiomas (IHs) are the most common vascular tumors in children. Because of their benign character and natural involution, the vast majority of IHs do not require any treatment. In the past few years, topical beta blockers have been reported to be an effective treatment of superficial IHs. OBJECTIVE: We sought to evaluate the clinical effectiveness and safety profile of topical propranolol 4% gel for the treatment of IHs. METHODS: A retrospective study of all cases of IHs treated with topical propranolol 4% gel between 2013 and 2015 was performed. All patients were evaluated in a pediatric dermatology unit of a tertiary medical center. Epidemiologic, clinical, and treatment data, including effectiveness score and safety, were reviewed. RESULTS: The study included 63 patients with a total of 75 IHs. Of the total number of IHs, 43 (57.3%) showed a good response to treatment, 19 (25.3%) a partial response,

and 13 (17.33%) poor or no response, thus 62 (82.6%) had good or partial response to treatment. Age at treatment initiation, treatment time, thickness of the superficial component, and size of the lesions were shown to predict response to therapy. Out of the entire examined group, only two patients reported minor local side effects manifested by irritation, redness, and scaling of the treated area. No systemic adverse effects were reported. LIMITATIONS: This is an uncontrolled retrospective study. CONCLUSION: Propranolol 4% gel is a safe and efficient topical therapy for IH.

Moyakine AV, Herwegen B, van der Vleuten CJM. "Use of the Hemangioma Severity Scale to facilitate treatment decisions for infantile hemangiomas." J Am Acad Dermatol 2017;77(5):868-873.

BACKGROUND: The Hemangioma Severity Scale (HSS) assesses the severity of an infantile hemangioma (IH). OBJECTIVE: First, to compare HSS scores between patients with IH for whom propranolol treatment was indicated at their first visit and those who were not treated. Second, to assess suitable cutoff values for the need for propranolol treatment. METHOD: All patients with IH who attended our tertiary referral center since 2008 and were 0 to 6 months of age at their first visit were included. They were divided into propranolol and no-propranolol groups on the basis of choice of treatment at their first visit. HSS scores were assessed, and median scores were compared. RESULTS: A total of 657 children (342 in the propranolol group) were included. The median HSS score (25th-75th percentile) in the propranolol group was 10 (range, 8-14) compared with 7 (range, 4-9) in the no-propranolol group ($P < .001$). Cutoff values of 6 or lower (no indication for treatment) and 11 or higher (indication for treatment) resulted in 94% sensitivity and 89% specificity, respectively. LIMITATIONS: HSS scoring was not completely blinded. CONCLUSION: The HSS with cutoff values of 6 or lower and 11 or higher could be used as a triage tool for propranolol treatment. Patient age, IH type, and parental preference may also contribute to treatment decisions.

Interesting study which analyses infantile hemangioma (IH) Severity Scale (HSS) in large group of 657 children between 0-6 months referring in a tertiary referral center. Patients were divided into 2 groups (propranolol and no-propranolol) depending on the course of the treatment by the attending physician at the first visit. The results were significantly different in the 2 groups: cuttoff values of 11 for propranolol group and 6 for the no-propranolol group resulting in a specificity of 89% (HSS≥11) and sensitivity of 94% (HSS≤6). HSS score may be a triage tool to help less experienced physicians to decide whether a child with IH should be referred for propranolol treatment: ≥11 treatment, ≤6 no indication for treatment 6<HSS score>11 factors such as age of the child at first consultation, IH type and parental preference may help in guiding treatment decision.

Morgane Barreau /Anne Dompmartin

Moyakine AV, Spillekom-van Koulil S, van der Vleuten CJM. Propranolol treatment for infantile hemangiomas is not associated with psychological problems at 7 years of age. J Am Acad Dermatol. 2017 Jul;77(1):105-108.

This is a new reassuring study on psychological (social, emotional, behavioral or executive) state of the children treated with propranolol for an infantile hemangioma.

In their prospective study, the authors included 81 patients who had been treated for more (or equal) than 6 months and aged 6 and older at the time of assessment. The exclusion criteria were treatment period lower

than 6 months, gestational age lower than 36 weeks, relevant comorbidity and use of relevant co-medication. To assess psychologic functioning, parents completed 4 questionnaires (Child Behavior Checklist (CBCL), Strengths and Difficulties Questionnaire (SDQ), Social Emotional Questionnaire (SEQ) and Behavior Rating Inventory of Executive Function (BRIEF)). And these results have been correlated with hemangioma severity, socioeconomic status, age at the start of propranolol treatment and treatment duration.

Regarding the 27 eligible patients, no evidence of psychologic problems was found. Only 1 had an abnormal score (BRIEF, CBCL, SDQ, and SEQ), but this might be better explained by a positive family history for autistic spectrum disorders. Furthermore, longer treatment duration was correlated with better executive function and fewer attention-deficit hyperactivity disorder.

This study strengthens the results of two other studies (by the same authors), by considering this time older children and specific aspects of psychologic functioning. No evidence is produced for potential impacts on central nervous system function. But, the sample size is small and children born preterm were excluded. Other studies are required using neuropsychologic examination at a later age.

Morgane Barreau /Anne Dompmartin

HSS tool Haggstrom AN, Beaumont JL, Lai JS, et al. Measuring the severity of infantile hemangiomas: instrument development and reliability. Arch Dermatol. 2012;148:197-202.

Morgane Barreau /Anne Dompmartin

Park JU et al. (2017). "Statistical Analysis of Influences on the Psychosocial Status of Children With Hemangiomas and Their Families." J Craniofac Surg.

The psychologic stress on the child and family, which arise from hemangiomas, the most common neoplasm of childhood, cannot be overestimated. This study determined the preoperative and postoperative psychosocial status and variation among Oriental children with hemangiomas and their families by questionnaire. Thirty patients who underwent surgery for hemangiomas were assessed for preoperative and postoperative psychosocial status by questionnaire. The distribution of the total mean score and variation between the preoperative and postoperative status was estimated. Based on these results, the significance was statistically analyzed according to variable determinants. This study showed that hemangiomas have harmful effects on psychosocial status of patients and families. After corrective surgery, an improvement in psychosocial status was noted with respect to the self-esteem category or categories related to social activity, and in the following variables, women, face, and dissatisfaction with appearance. When the authors care for patients with hemangiomas and their families, the psychosocial health must be presumed to be at particular risk. Earlier surgical interventions with esthetic concerns have permitted the patient and family the opportunity to reduce the psychologic impact that the hemangioma may otherwise have.

Planas-Ciudad S et al. (2017). "Infantile hemangiomas with minimal or arrested growth associated with soft tissue hypertrophy: a case series of 10 patients." J Eur Acad Dermatol Venereol.

BACKGROUND: Infantile hemangiomas with minimal or arrested growth (IH-MAGs) are characterized by a proliferative component of <25% of its surface area. The co-occurrence of IH-MAGs and soft tissue anomalies is rare, and case series of this association are lacking. OBJECTIVE: We present 10 cases of IH-MAGs associated with soft tissue hypertrophy and describe their clinical features. METHODS: We reviewed all infantile hemangiomas with minimal or arrested growth seen between 2009 and 2016 in the dermatology clinic department at Hospital Santa Creu i Sant Pau, Barcelona. To collect more patients, we also requested cases from the Hemangioma Investigator Group and members of the Spanish Society of Vascular Anomalies. RESULTS: Ten patients had IH-MAGs associated with soft tissue hypertrophy; seven involving the arm and three involving the leg. All displayed a segmental pattern, a doughy and puffy texture and prominent surface veins. No significant asymmetries in limbs and no other visceral anomalies were observed at follow-up (range 15 months to 7 years). One patient reported coldness in the limb with infantile hemangioma, but RMI-angiography did not disclose a vascular malformation underneath the lesion. Ulceration was observed in three patients. The proliferative component in all IH-MAGs had faded at 1-year follow-up, while soft tissue hypertrophy and prominent vessels remained unchanged. CONCLUSIONS: In this first case series of IH-MAGS associated with soft tissue hypertrophy, soft tissue hypertrophy was not progressive and remained unchanged over time, unlike the proliferative component of classic infantile hemangioma. The origin of the prominent vessels and the higher ulceration risk are unknown; however, these findings are probably related to a minor disruption of local vessels not detected in imaging tests.

Pourazizi M et al. (2017). "Intralesional Bevacizumab (Avastin(R)) as a Novel Addition to Infantile Hemangioma Management: A Medical Hypothesis." J Res Pharm Pract 6(3):190-191.

Schilter K F et al. (2017). "RNF213 variants in a child with PHACE syndrome and moyamoya vasculopathy." Am J Med Genet A 173(9):2557-2561.

Segmental infantile hemangiomas (IH) can be associated with congenital anomalies in a regional distribution. PHACE refers to large cervicofacial segmental IH in association with congenital anomalies of the aortic arch and medium-sized arteries of the head and neck, as well as structural anomalies of the posterior fossa and eye. A subset of PHACE patients have arterial anomalies that progress to moyamoya vasculopathy (MMV). MMV is defined as stenosis of the supraclinoid segment of the internal carotid arteries and/or their major branches, with subsequent development of a compensatory collateral vessel network. We describe a patient with MMV and segmental IH on the back and lower body who meets diagnostic criteria for PHACE based on a posterior segment eye anomaly and cerebral arterial anomalies. Whole exome sequencing demonstrated two inherited heterozygous variants in RNF213. Variants in RNF213 are associated with increased susceptibility to MMV. Our findings suggest that RNF213 variants may play a role in the development of MMV in patients with hemangioma syndromes associated with congenital cerebral arterial anomalies.

Schwartz T et al. (2017). "Efficacy and rebound rates in propranolol-treated subglottic hemangioma: A literature review." Laryngoscope 127(11):2665-2672.

OBJECTIVE: Propranolol has recently become the treatment of choice for management of subglottic and airway hemangiomas. This literature review aimed to determine the success rate of propranolol for managing these lesions as well as the rate of rebound growth following propranolol treatment cessation. STUDY DESIGN: Literature search involving MEDLINE and Scopus to identify English-language articles. METHODS: Studies were identified using hemangioma, subglottic or airway, and propranolol for search terms. Studies were eligible for inclusion if they reported the treatment used, individual deidentified patient data, and contained patients without medical or surgical treatment prior to propranolol therapy RESULTS: Initial review included 107 abstracts. Twenty-four articles including case reports and case series met inclusion criteria and were included in the qualitative analysis. Forty-nine patients were included. Twenty-eight (57%) were treated with propranolol alone, and 20 (41%) were treated with a combination of propranolol and a corticosteroid. Thirty-seven (76%) of patients were treated with a dose of 2 mg/kg/d of propranolol. The initial treatment was successful in 43 (88%) of patients. Rebound growth occurred in four (9%) patients. Overall, six (12%) patients underwent surgical resection. CONCLUSIONS: Propranolol is efficacious for treating subglottic hemangiomas. Rebound growth does occur in a small subset of patients during the propranolol wean. Close observation for children during weaning of propranolol therapy for subglottic hemangioma is essential. Adjunctive management strategies need to be used in patients with rebound growth. Laryngoscope, 127:2665-2672, 2017.

Seiffert A et al. (2017). "Incidence, Treatment Patterns, and Health Care Costs of Infantile Hemangioma: Results of a Retrospective German Database Analysis." Pediatr Dermatol 34(4):450-457.

OBJECTIVES: To determine the incidence, effect (defined according to treatment rate), and health care costs of infantile hemangiomas (IHs) in Germany from 2007 to 2012 by analyzing patient data of German statutory health insurances. METHODS: A retrospective analysis using data from a database matched with the overall population covered by German statutory health insurance was performed. To describe the treatment rate and costs of IHs, a search algorithm was developed dividing the study population into three groups (patients with IHs, patients with IHs possibly requiring treatment, and patients with IHs receiving treatment). RESULTS: The incidence of IHs was 2.0% to 3.2%, with a slight increase during the later years of the study period and a female:male ratio of 1.4:1. IH incidence was lower and girls were less likely to present with IHs than in previous reports. The mean treatment rate of IHs was 11.3%. Mean health care costs during first year of life for infants diagnosed with IHs in 2012 were slightly lower (euro2,396) than for all infants (euro2,649), whereas costs for infants diagnosed and treated for IHs were considerably higher (euro10,550). The majority of these costs were due to hospitalization (euro8,658). CONCLUSION: This retrospective study is the first to analyze the incidence and sex ratio of IHs based on German claims data. The treatment rate of IHs was consistent with previous reports. The mean health care costs for treated patients with IHs were substantially higher than those for all newborns. Limitations of this study are coding bias, a limited sample size, and claims perspective (nonclinical approach).

Shilpakar R et al. (2017). "Unexpected Effect of Propranolol and Prednisolone on Infantile Facial Rhabdomyosarcoma." J Pediatr Hematol Oncol 39(8):e460-e462.

A 14-month-old Nepalese infant had developed a rapidly growing facial tumor originating from a dark spot on her upper eyelid. A cavernous hemangioma was suspected and treated with high doses of propranolol and prednisolone. Remission was dramatic. Histology confirmed alveolar rhabdomyosarcoma. Chemotherapy was planned but not carried out due to complicated logistics. The girl died at the age of 3. We present this case for discussion as to whether propranolol and prednisolone might be effective in rapidly growing rhabdomyosarcomas.

Wan J et al. (2017). "Prenatal Risk Factors for PHACE Syndrome: A Study Using the PHACE Syndrome International Clinical Registry and Genetic Repository." J Pediatr.

The cause of PHACE syndrome is unknown. In a study of 218 patients, we examined potential prenatal risk factors for PHACE syndrome. Rates of pre-eclampsia and placenta previa in affected individuals were significantly greater than in the general population. No significant risk factor differences were detected between male and female subjects.

Yang L et al. (2017). "The expression and function of miR-424 in infantile skin hemangioma and its mechanism." Sci Rep 7(1):11846.

Infantile hemangioma is the most common benign tumor in infants. Many studies have confirmed that basic fibroblast growth factor (bFGF) and its key receptor FGFR1 are highly expressed in hemangioma. Moreover, several miRNAs can regulate angiogenesis. In this regard, miR-424 often plays a role as tumor suppressor gene. This study was designed to investigate the mechanism of miR-424 in infantile skin hemangioma. Our results showed low expression of miR-424 in infantile skin hemangioma tissues, and that miR-424 overexpression downregulated FGFR1 expression in hemangioma-derived endothelial cells, while miR-424 inhibition upregulated FGFR1 expression. Luciferase reporter analysis confirmed that FGFR1 was a target gene of miR-424. CCK-8, flow cytometry, transwell migration and tube formation assays demonstrated that miR-424 overexpression inhibited cell proliferation, migration and tube formation, at least in part by blocking the bFGF/FGFR1 pathway. In contrast, miR-424 inhibition significantly enhanced these functions. Furthermore, miR-424 overexpression significantly inhibited ERK1/2 phosphorylation, whereas miR-424 inhibition enhanced ERK1/2 phosphorylation. In conclusion, miR-424 could suppress the bFGF/FGFR1 pathway, thereby inhibit ERK1/2 phosphorylation, and thus inhibit cell proliferation, migration and tube formation capabilities and the development of infantile skin hemangioma.

Zhang L et al. (2017). "Estrogen-mediated hemangioma-derived stem cells through estrogen receptor-alpha for infantile hemangioma." Cancer Manag Res 9:279-286.

BACKGROUND: Infantile hemangiomas (IHs) are the most common benign vascular tumor of infancy. They occur more frequently in female infants. The cause of hemangioma is currently unknown; however, current studies suggested the importance of estrogen (E2) signaling in hemangioma proliferation. METHODS: Hemangioma-derived stem cells (HemSCs) were cultured with estrogen for 48-72 h; the cell viability and

proliferation were evaluated with the messenger RNA (mRNA) and protein expression levels of fibroblast growth factor 2 (FGF2), vascular endothelial growth factor-A (VEGF-A) and estrogen receptor-alpha (ER-alpha), by application of several in vitro assays, such as methyl thiazolyl tetrazolium (MTT), reverse transcriptase-polymerase chain reaction (RT-PCR), real-time PCR, enzyme-linked immunosorbent assay (ELISA) and Western blotting. Also, the cell population's response to external estrogen was investigated by in vivo experiments. HemSCs and human umbilical vein endothelial cells (HUVECs) were mixed and injected subcutaneously into 20 flank of BALB/c-nu mice, which were randomly divided into 5 groups based on different E2 treatment doses (0, 0.01, 0.1 and 1 mg, respectively), 0.1 mg dimethyl sulfoxide (DMSO) as control. Each group of mice were treated intramuscularly every week, then 2 and 4 weeks later, the subcutaneous implants were harvested and evaluated the tumor tissues with microvessel density (MVD) assay and immunohistochemistry. RESULTS: The study demonstrated that application of E2 increased the expression of FGF2, VEGF-A, and ER-alpha in HemSCs with the optimal concentration from 10-9 to 10-5 M. Two-week treatment of E2 promoted expression of VEGF-A and FGF2 in HemSCs culture. Morphological, histological and immunohistological improvements were observed in vivo using murine IH model in which HemSCs and HUVECs were implanted into BALB/c-nu mice that were post-injected with E2. In the grafts, mean MVD was markedly increased. CONCLUSION: The results suggested that E2 promotes angiogenesis via combination with ER-alpha to up-regulate the expression of VEGF-A in HemSCs, promoting proliferation of IHs. These findings provide critical insight into the potential mechanisms of E2 action on IHs.

Return to Scientific Article Reviews

VASCULAR MALIGNANCIES

Return to Scientific Article Reviews

Adams DM, Brandao LR, Peterman CM, Gupta A, Patel M, Fishman S, Trenor CC. "Vascular anomaly cases for the pediatric hematologist oncologists-An interdisciplinary review." Pediatr Blood Cancer. 2017. Epub 2017/07/21.

Vascular anomalies (VAs) are classified as tumors or malformations depending on their clinical characteristics, pathological diagnosis, and genomic information. Diagnosis can be challenging because of the heterogeneity of clinical presentation; thus, the best diagnosis and care are provided by an interdisciplinary team of specialists. Over the past 10 years, an increasing number of pediatric hematologists/oncologists are caring for patients with VAs secondary to new medical therapy options and clinical trials. This paper focuses on complicated VA issues often seen by the pediatric hematologists/oncologists. The paper reviews clinical pearls on diagnosis, histology, radiology, and treatment options.

Taizo Nakano/Denise Adams

Boccara, O., et al. (2017). "Sirolimus effects on Kasabach-Merritt phenomenon coagulopathy." Br J Dermatol.

Kasabach-Merritt phenomenon (KMP) is a very rare life-threatening condition that combines a vascular tumor belonging to the kaposiform hemangioendothelioma (KHE) spectrum lesions, and thrombocytopenia. Thrombocytopenia results from platelet trapping within the tumor. Platelet activation leads to various degrees of decreased fibrinogen and elevated D-dimer levels. This coagulopathy is frequently protracted after thrombocytopenia resolution. Several treatments have been proposed with variable efficiency. This article is protected by copyright. All rights reserved.

Grassia KL, Peterman CM, Lacobas I, Margolin JF, Bien E, Padhye B, Meyers RL, Adams DM. Clinical case series of pediatric hepatic angiosarcoma.

Pediatric hepatic angiosarcoma is a rare, aggressive, malignant neoplasm with a poor prognosis. The authors report eight cases of pediatric hepatic angiosarcoma most of which were misdiagnosed as more benign vascular tumors. They conclude that providers should closely evaluate and monitor all infantile hepatic hemangioendotheliomas (IHHE) or hepatic hemangiomas for the potential misdiagnosis of an angiosarcoma.

Taizo Nakano/Denise Adams

Ji, Y., et al. (2017). "Sirolimus for the treatment of progressive kaposiform hemangioendothelioma: A multicenter retrospective study." Int J Cancer 141(4): 848-855.

Kaposiform hemangioendothelioma (KHE) is an aggressive disease with high morbidity and mortality. The aim of this study was to retrospectively evaluate the efficacy and safety of sirolimus for the treatment of progressive KHE. A multicenter, retrospective cohort study was conducted in patients with progressive KHE

treated with sirolimus. A total of 52 patients were analyzed. Thirty-seven (71%) patients exhibited Kasabach-Merritt phenomenon (KMP) and were significantly younger than the patients without KMP [95% confidence interval (CI), 14.39-41.61; $p < 0.001$]. Patients without KMP were all treated with sirolimus alone, whereas 21 KMP patients with severe symptoms received short-term combination therapy with prednisolone. Overall, 96% and 98% of patients showed improved relief of notable symptoms and/or improved complications at 6 and 12 months after treatment, respectively. After sirolimus treatment, significant decreases in mean severity scores occurred at 6 months (95% CI, 2.23-2.54, $p < 0.001$) and 12 months (95% CI, 1.53-1.90, $p < 0.001$). Compared to KMP patients, patients without KMP showed a response that was similar to but less pronounced during the 12 months of treatment (95% CI, 40.87-53.80; $p < 0.001$). For subgroup analysis of KMP patients, there were no significant differences in tumor shrinkage between those treated with combination therapy and those receiving sirolimus alone (95% CI, 18.11-25.02; $p > 0.05$). No patients permanently discontinued treatment due to toxicity-related events, and no drug-related deaths occurred. Sirolimus was effective and safe for the treatment of progressive KHE. Sirolimus may be considered as a first-line therapy or as part of a multidisciplinary approach for the treatment of KHE.

Johnson C M, Navarro OM (2017). "Clinical and sonographic features of pediatric soft-tissue vascular anomalies part 1: classification, sonographic approach and vascular tumors." Pediatr Radiol 47(9):1184-1195.

Sonography can be used in the management of pediatric soft-tissue vascular anomalies for diagnosing, for assessing lesion extent and for evaluating complications and response to therapy. The sonographic technique includes a combination of gray-scale imaging with color and spectral Doppler techniques. However the interpretation of the sonographic findings requires correlation with the clinical findings, some of which can be easily obtained at the time of scanning. This has to be combined with the use of appropriate nomenclature and the most updated classification in order to categorize these children into the appropriate management pathway. In this article, which is part 1 of a two-part series, the authors review the current classification of vascular anomalies, provide a clinical and a sonographic approach to these lesions, and review the most relevant clinical and sonographic features of vascular tumors including infantile and congenital hemangiomas, tufted angioma, kaposiform hemangioendothelioma, pyogenic granuloma, intramuscular capillary-type hemangioma and angiosarcoma.

Morbidity and healthcare costs of vascular anomalies: a national study.
Kim J, Sun Z, Leraas HJ, Nag UP, Benrashid E, Allori AC, Pabon-Ramos WM, Rice HE, Shortell CK, Tracy ET. Pediatr Surg Int. 2017 Feb;33(2):149-154.

This study aimed to define morbidities and costs related to medical care for families affected with children diagnosed with vascular anomalies. The Kids' Inpatient Database for pediatric patients (age/21 years) hospitalized with diagnosis of hemangioma, arteriovenous malformation or lymphatic malformation between 2003 and 2009 was reviewed. They compared patient characteristics, hospital complications and hospital charges by vascular anomaly type in a total of 7485 pediatric patients.

The most common inpatient recorded complications from children with vascular anomalies were related to blood loss or infection. Patients with arteriovenous malformations experienced higher hospital costs secondary to the complexity of their disease which requires a higher level of care.

Unfortunately, venous malformations were not included and relevant data regarding the cost of surgical or sclerosis management are lacking. As economical aspects of vascular anomalies are not frequently reviewed, studies from experienced vascular anomalies centers are welcome. Prospective analysis from international perspective should be promoted.

Israel Fernández Pineda/Juan Carlos Lopez Gutierrez

Mizuno T, Fukuda T, Emoto C, Mobberley-Schuman PS, Hammill AM, Adams DM, Vinks AA. Developmental pharmacokinetics of sirolimus: implications for precision dosing in neonates and infants with complicated vascular anomalies. Pediatr Blood Cancer. 2017 Aug;64(8). Epub 2017 Feb 16.

The indications for initiating sirolimus as a novel pharmacotherapy in complex vascular anomalies continues to grow. Although many of these lesions present in infancy, dosing information for neonates and infants is lacking. This study set out to identify age-appropriate sirolimus starting doses for infants based on the developmental changes in pharmacokinetics. The authors used clinical data from a previous Phase 2 study to extrapolate a mathematical equation that relating sirolimus clearance to patient age (sirolimus maturation model; Emoto et al. CPT Pharmacometrics Syst Pharmacol, 2016). With this tool, sirolimus concentrations at steady state were simulated in 8,000 virtual neonates and infants. They produced age-appropriate starting doses that represent a meaningful starting point for the optimal dosing in this unique patient population. A prospective evaluation is being planned.

Taizo Nakano/Denise Adams

Pahl, K. S., et al. (2017). "Inconsistency in classifying vascular anomalies: What's in a name?" Pediatr Blood Cancer. 2017 Oct 8. doi: 10.1002/pbc.26836. [Epub ahead of print]

BACKGROUND: Vascular anomalies are a heterogeneous group of disorders seen in children and adults. A standard nomenclature for classification has been offered by the International Society for the Study of Vascular Anomalies. Its application is important for communication among the multiple specialties involved in the care of patients and for planning treatment, as well as for research and billing. We hypothesized that terminology still is not uniformly applied, and that this could have an impact on treatment. METHODS: We retrospectively reviewed the medical records of patients with nonbrain lesions from our institutional vascular anomalies database seen during 2010-2016 for whom at least one clinic visit, radiologic imaging report, and pathology report were available to compare diagnoses among and within disciplines, and treatment recommendations. Diagnoses and referral patterns by community healthcare providers were also reviewed. RESULTS: Of 400 patients seen during the targeted time interval, 35 had clinical, imaging, and pathology reports. Agreement in terminology from initial clinic notes with imaging and pathology reports was noted in only three cases (9%). "Hemangioma" was often misused; "lymphangioma" and "cystic hygroma" persist as diagnostic labels. Community healthcare providers referred vascular malformations with a diagnosis of "mass" or "hemangioma" in 17 of 18 cases where that information was available. Incomplete or mislabeling of

vascular anomalies sometimes delayed referrals to appropriate clinics, though it did not have a major impact on treatment. CONCLUSIONS: An understanding of vascular anomalies as tumors or malformations is not uniform. Ongoing education will be needed to promote consensus terminology and facilitate referrals.

Schaefer BA, Wang D, Merrow AC, Dickie BH, Adams DM. Long-term outcome for kaposiform hemangioendothelioma: a report of two cases. Pediatr Blood Cancer. 2017 Feb;64(2):284-286. Epub 2016 Oct 4.

Great strides have been made to rapidly diagnose and treat the aggressive and infiltrative nature of Kaposiform hemangioendothelioma (KHE) with or without its associated life-threatening consumptive coagulopathy known as Kasabach-Merritt phenomenon (KMP). However, little is known about the long term natural history of KHE and we lack standardized surveillance strategies after a primary clinical remission is achieved. The authors present two cases of KHE that demonstrate long term comorbidities related to their KHE, both of which redeveloped symptoms with the onset of puberty. They highlight the ongoing struggle with pain, functional impairment and physical disfigurement that can greatly impact a child's quality of life. They recommend that children treated for a KHE receive indefinite long-term follow up by a physician experienced in vascular anomalies.

Taizo Nakano/Denise Adams

Zhang G, Gao Y, Liu X. Kaposiform haemangioendothelioma in a nine-year-old boy with Kasabach-Merritt phenomenon. Br J Haematol. 2017 Oct;179(1):9.

Although more commonly a vascular tumor of infancy, this care report describes the acute presentation of Kaposiform Hemangioendothelioma (KHE) with Kasabach-Merritt phenomenon (KM) in a 9 year old boy. The patient presented with a large, expanding, firm mass on his back that infiltrated into subcutaneous tissues. Labs demonstrated severe thrombocytopenia, elevated D-dimer, and a moderate coagulopathy. Tissue biopsy confirmed a CD34+, D2-40+ KHE and he was treated successfully with sirolimus and prednisone.

Taizo Nakano/Denise Adams

Return to Scientific Article Reviews

SURGERY

Return to Scientific Article Reviews

Hu D, Flick RP, Zaccariello MJ, Colligan RC, Katusic SK, Schroeder DR, Hanson AC, Buenvenida SL, Gleich SJ, Wilder RT, Sprung J, Warner DO. Association between Exposure of Young Children to Procedures Requiring General Anesthesia and Learning and Behavioral Outcomes in a Population-based Birth Cohort. Anesthesiology. 2017 Aug;127(2):227-240.

In this study 116 multiply exposed, 457 singly exposed, and 463 unexposed children were analyzed. Multiple, but not single, exposures were associated with an increased frequency of both learning disabilities and attention-deficit/hyperactivity disorder (hazard ratio for learning disabilities = 2.17 [95% CI, 1.32 to 3.59], unexposed as reference). Multiple exposures were associated with decreases in both cognitive ability and academic achievement. Single exposures were associated with modest decreases in reading and language achievement but not cognitive ability.

The U.S. Food and Drug Administration (FDA) has been investigating the potential adverse effects of general anesthetic and sedation drugs on children's brain development since the first animal study on this topic was published in 1999 and recently warning that repeated or lengthy (more than 3 hours) use of general anesthetic and sedation drugs during surgeries or procedures in children younger than 3 years or in pregnant women during their third trimester may affect the development of children's brains. Additionally the American Academy of Pediatrics, the American Surgical Pediatric Association, the American Society of Anesthesiologists, the International Anesthesia Research Society, the Society for Pediatric Anesthesia and the Society for Pediatric Pain Medicine, among others, have declared that this statement should never be the origin of delayed, or avoided necessary treatments in this group of patients.

Considering this statement and despite most procedures can be performed in a short periods of time, **vascular anomalies specialists** should consider discussing, in the context of a multidisciplinary team, the benefits and risks of repeated surgeries, embolization or laser treatments that require general anesthesia and the use of sedation drugs .

Israel Fernández Pineda/Juan Carlos Lopez Gutierrez

Beaulieu RJ, Lue J, Ehlert BA, Grimm JC, Hicks CW, Black JH 3rd. Surgical Management of Peripheral Vascular Manifestations of Loeys-Dietz Syndrome.
Ann Vasc Surg. 2017 Jan;38:10-16

This article reviews the single center institution experience in the management of 18 patients with Loeys-Dietz Syndrome and arterial aneurysms. It is the largest report of peripheral arterial repair to date. Averages of 4 interventions per patient were performed (open procedures in 76% of the cases and endovascular repair in 24%) with no perioperative mortality reported. In the absence of reliable predictors of peripheral vascular

involvement or known medical mechanisms to prevent expansion, the authors use close radiological monitorization with yearly echocardiogram and full body MRA´s.

This paper adds a better understanding of those rare diseases helping the surgeon in the decisions making process as management of arterial tortuosity disorders remains a surgical challenge. A significant number of patients develop arterial dilatation or stenosis in the context of Tuberous sclerosis, Loeys-Dietz, Ehler-Danlos and Marfan syndromes. Currently no protocols are available for their appropriate management and patients are treated in an individual basis, so reported information about improvements with the use of endovascular repair is extremely useful. Unfortunately, as the paper remarks, despite maximum medical management, nearly all patients with LDS will progress to require at least one cardiothoracic or vascular repair, and most of the population will require multiple operations. Long term mortality remains significantly high. In addition aneurysm repair in young children remain a technical problem as there is no adequate vascular graft material for vascular reconstruction in this group of patients. Use of prosthetic grafts, in children younger than 8 years of age, raises the potential risk of mismatching between the graft diameter that is fixed and native vessel diameter that is growing. Hopefully, progressive knowledge of molecular mechanisms involved in arterial elastogenesis will soon improve therapeutical outcomes in this group of patients.

Israel Fernández Pineda/Juan Carlos Lopez Gutierrez

Return to Scientific Article Reviews