hematology meeting reports

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8th International Hereditary Hemorrhagic Telangiectasia Scientific Conference

Santander, Spain, May 27-31, 2009

Guest editors
Roberto Zarrabeitia, Carmelo Bernabeu

on behalf of the International Committee
(Marianne Clancy, Marie E. Faughnan, Urban Geisthoff, Paul Oh, Carlo Sabba, James Gossage, Carmelo Bernabeu, Roberto Zarrabeitia)

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HEMATOLOGY MEETING REPORTS

INSTRUCTIONS TO AUTHORS

HEMATOLOGY MEETING REPORTS (HMR) (ISSN 1234-5678) publishes proceedings of congresses and meetings in all fields of clinical as well experimental hematology.
All papers will be subject to peer review before publication.

Preparation of the manuscript. Manuscripts must be written in English and should be prepared according to the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, N Engl J Med 1997; 336:309-15 (available from *http://www.icmje.org*). The first page of the manuscript must contain: (a) title, first and last name of the Authors; (b) name(s) of the institution(s) of each Author; (c) a running title of no more than 50 letters; (d) acknowledgments; (e) the name and full postal address of the Author to whom correspondence regarding the manuscript as well as requests for abstracts should be sent; (f) three to five key words. To accelerate communication, phone, fax number and e-mail address of the corresponding Author should also be included.
No particular format for the article is required, as Authors will be free of formatting their manuscript according to their judgement; nevertheless, an abstract of no more than 250 words should be always provided, summarizing the major findings as well as the open questions addressed in the review. References should be prepared strictly according to the Vancouver style (for details see: N Engl J Med 1997; 336:309-15, also available from URL: *http://www.icmje.org* - the Vancouver style is present in EndNote®). References must be numbered consecutively in the order in which they are first cited in the text, and they must be identified in the text by arabic numerals. Journal abbreviations are those of the List of the Journals Indexed, printed annually in the January issue of Index Medicus. List all authors when six or fewer; when seven or more, list only the first six and add *et al*. Figures and graphs must be provided either in *TIFF* or *JPG* format as separate files numbered accordingly to citations in the manuscript.
Examples of correct forms of references follow (please note that the last page must be indicated with the minimum number of digits):

Journals [standard journal article,[1,2] corporate author,[3] no author given,[4] journal supplement[5]]:

1. Zhang YA, Nemunaitis J, Samuel SK, Chen P, Shen Y, Tong AW. Antitumor activity of an oncolytic adenovirus-delivered oncogene small interfering RNA. Cancer Res 2006;66:9736-43.
2. Eliassen AH, Missmer SA, Tworoger SS, Spiegelman D, Barbieri RL, Dowsett M, et al. Endogenous steroid hormone concentrations and risk of breast cancer among premenopausal women. J Natl Cancer Inst 2006;98:1406-15.
3. Breast Cancer Association Consortium. Commonly studied single-nucleotide polymorphisms and breast cancer: results from the Breast Cancer Association Consortium. J Natl Cancer Inst 2006;98:1382-96.
4. Reed E. ERCC1 measurements in clinical oncology. N Engl J Med 2006; 355:1054-5.
5. Mouridsen H.T. Letrozole versus tamoxifen as first-line treatment for metastatic breast cancer: a survival analysis. Am J Cancer 2003; 2 supplement 1:7-11.

Books and other monographs [personal authors,[6,7] chapter in a book,[8] abstract book,[9]:

6. Abeloff MD, Armitage JO, Lichter AS, Niederhuber JE, eds. Clinical oncology. 2nd ed. Churchill Livingstone. 2000.
7. Pizzo PA, Poplack DG. Principles and Practice of Pediatric Oncology. 4th ed. Philadelphia, Lippincott Williams & Wilkins, 2001.
8. Coleman RE, Rubens RD. Bone metastases. In: Abeloff MD, Armitage JO, Lichter AS, Niederhuber JE, eds. Clinical Oncology. 2nd ed. Churchill Livingstone. 2000. pp 836-871.
9. Lung LKW, Hui AMY, Leung WK, Sung JY, Ng EKW. Gene expressions of human peritoneal mesothelial cells in gastric cancer. Proceedings of the 97th AACR Annual Meeting, April 1-5, 2006, Washington, DC, USA, Proc Amer Assoc Cancer Res 2006;47: [Abstract #122].

Forthcoming[13] or URL[14]:

13. Leshner AI. Molecular mechanisms of cocaine addiction. N Engl J Med In press 1996.
14. Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis [serial online] 1995 Jan-Mar [cited 1996 Jun 5];1(1):[24 screens]. Available from URL: http://www.cdc.gov/ncidod/EID/ eid.htm

References to personal communications and unpublished data should be incorporated in the text and not placed under the numbered References. Please type the references exactly as indicated above and avoid useless punctuation (e.g. periods after the initials of authors' names or journal abbreviations).

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8th International Hereditary Hemorrhagic Telangiectasia Scientific Conference

Health Counsellor of the Goverment of Cantabria

It is a pleasure for me to welcome you to the 8th Hereditary Hemorrhagic Telangiectasia International Scientific Meeting. As you well know, the Cantabrian Health Service has got a specific unit for diagnose and management of HHT located in Hospital Sierrallana, that step by step is consolidating this approach and receives patients not only from Spain but from other countries.
The quality certification of the unit considering the ISO 9001:2000 rule, supports the effort that the multidisciplinary team lead by Dr. Zarrabeitia is performing. The organization of this international meeting is an additional boost and also a challenge that I am sure will reach the end with great success.
My best regards,
Luis María Truan Silva
Health Counsellor

Tourism city councillor of the Townhall of Santander

Dear delegates, professionals and everyone interested on HHT, Santander, a city that shares great medical advances with remarkable touristic attractions, opens the doors of the Magdalena Palace and its premises to host such an important international congress as the 8th Rendu Osler Weber International Scientific meeting represents.
It is a great pleasure for me to welcome you to our city, I wish you have a pleasant meeting work sessions and you enjoy our modern, opened and cosmopolitan city. With the certainty of a successful result, I wish you the best time in Santander
Gema Igual Ortiz
Tourism and protocol Councilor of Santander Townhall.
President of the Santander Convention Bureau

President of the Spanish HHT Association

Dear friends and colleagues,
It is for me a pleasure to welcome all of you to our next HHT meeting in Santander, on behalf of our Spanish HHT patient 's association.
As involved in the organisation of the next HHT meeting in Santander, we feel highly motivated in preparing a very fruitful workshop, since it is for the health of our families that we are working.
We want to provide the best forum to exchange the latest developments in medicine, research and HHT social diffusion.
I hope this meeting will be also the occassion to enjoy the beautiful Santander landscape, to share our experiences and to learn the improvements in the knowledge and treatments of HHT.
Looking forward to meeting you soon in Santander,
Yours sincerely,
Santiago de la Riva Compadre
President of the Spanish HHT Association

Chair GRMAB

On behalf of the International organizing committee, I would like to welcome you to the 8th International Scientific Conference in Santander, May 27-31, 2009. Our goal is to provide a meeting point for clinicians and basic scientists where participants will have access to the most recent advances in clinical research, therapeutics, and basic research in the field of HHT. I believe that this Conference represents a great opportunity to strengthen the collaborations between clinicians and scientists with the aim of finding better treatments for HHT, and I encourage you to join this exciting event.
Carmelo Bernabeu
Chair Global Research and Medical Advisory Board (GRMAB)
HHT International Foundation Inc.
Centro de Investigaciones Biológicas (CSIC)
C/ Ramiro de Maeztu 9 - 28040 Madrid

Executive Director HHT Foundation International

Welcome from the HHT Foundation International.
It is a great pleasure to welcome all of you to the 8th International HHT Scientific Conference. The HHT Foundation International is grateful for your participation within the dedicated and internationally renowned HHT community. Your continued scholarship in scientific and clinical research is leading to breakthroughs that benefit over one million people worldwide affected with HHT. We are pleased to support this important conference and wish you a very successful meeting!
Sincerely yours,
Marianne S. Clancy
Executive Director
HHT Foundation International

Conference Host

The Spanish HHT community welcomes you to the 8th Internacional Scientific HHT Conference. It is at the same time a real honour and a great challenge to host this meeting next May 2009 in our city, Santander. Our clinical unit is a young one but we will try to do our best to provide you with a forum to share experiences and advances in clinical practice, basic research and patients´ associations working all together to achieve our common goal which is offering our patients the best attention. We encourage you to give us suggestions to design a complete program trying to fullfill everyone's expectatives. We sincerely hope you get a successfull experience and enjoy your stay.
Sincerely yours,
Roberto Zarrabeitia Puente
Coordinador Unidad HHT
Hospital Sierrallana (Servicio Cántabro de Salud)
Bº Ganzo s/n 39300 (Torrelavega-Cantabria) Spain.

Honorary Presidency

Their RRMM The King and the Queen of Spain
D. Juan Carlos and Dña. Sofía

Members

Spanish Minister of Science and Innovation
Mrs. Cristina Garmendia Mendizábal

Spanish Minister of Health and Consume
Dr. Bernat Soria Escoms

President of the Cantabrian Government
Mr. Miguel Angel Revilla Roiz

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Mr. Iñigo de la Serna Hernáiz

International Organizing Committee

Marianne Clancy
Executive Director HHT Foundation International, Monkton, MD, USA; *E-mail: mariannes.clancy@hht.org*

Marie E. Faughnan M.D. Msc
Pneumology, Toronto HHT Center Director, Canada; *E-mail: faughnanm@smh.toronto.on.ca*

Urban Geisthoff M.D.
ENT, Kliniken of the stadt Kolhn, Germany; *E-mail: geisthoffu@kliniken-koeln.de*

Paul Oh PH.D.
Dept. of Physiology and Functional Genomics, University of Florida, USA; *E-mail: ohp@phys.med.ufl.edu*

Carlo Sabbá M.D.
Internal Medicine, Bari HHT Center Director, Italy; E-mail: c.sabba@dimimp.uniba.it

James Gossage M.D.
Pneumology, Medical College of Georgia, Augusta, GA, USA; *E-mail: jgossage@mcg.edu*

Carmelo Bernabeu Ph.D. (Scientific Chair)
Chair GRMAB, Centro de Investigaciones Biologicas, CSIC, and Centro de Investigaciones Biomedicas en Red de Enfermedades Raras (CIBERER), Madrid, Spain; *Tel : 34-91-8373112 ext. 4246*
E-mail: bernabeu.c@cib.csic.es

Roberto Zarrabeitia (Conference Host)
Internal Medicine, Coordinator of Spanish HHT Unit, Hospital Sierrallana, Torrelavega, Cantabria, Spain;
Tel: 34-942-847400 ext. 8053, Fax: 34-942-847501, E-mail: rzarrabeitia@hsll.scsalud.es

Local Committee HHT Spain

Hospital Sierrallana & Hospital Universitario Marques de Valdecilla Team (Torrelavega/Santander)

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Instituto Valenciano de Infertilidad (Dra. Sandra González)
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Auxiliary team ward: Rebeca Calderón, Eugenia Martínez
Nursery team: Mar Rodríguez, Paz Baudín, Elena Ruiz, Elena Pérez, Mercedes Angulo
Secretaries: Concepción Ruiz, Ana Rosa Saiz

(All workers mainly in Sierrallana Hospital deal with HHT. As it is almost impossible make a complete directory we have just include chiefs of services and most related personnel)

Centro de Investigaciones Biologicas (CIB) (CSIC. Madrid)

Members

Carmelo Bernabeu (biochemist)
Luisa Mª Botella (geneticist)
Francisco J. Blanco (biochemist)

Fellows

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Roberto Zarrabeitia (clinical area)

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Antonio Cabezón (General practitioner)

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Members

Miguel Quintanilla (oncologist)

Fellow

Eduardo Pérez Gómez (cellular biologist)

We would like to thank all people dealing with HHT in our country. It is impossible to name everyone: clinicians, researchers, members of associations and mainly patients to whom to whom we devote our efforts.

EL JEFE DE LA CASA DE
S. M. EL REY

bo.
050/09

SS.MM. los Reyes, accediendo a la petición que tan amablemente Les ha sido formulada, han tenido a bien aceptar la

PRESIDENCIA DEL COMITÉ DE HONOR

de la **"8ª CONFERENCIA INTERNACIONAL DE LA ASOCIACIÓN ESPAÑOLA DE TELANGIECTASIA HEMORRÁGICA HEREDITARIA (HHT)"**, que se celebrará en Santander (Cantabria) del 27 al 31 de mayo próximo.

Lo que me complace participarle para su conocimiento y efectos.

PALACIO DE LA ZARZUELA, 23 de febrero de 2009

EL JEFE DE LA CASA DE S.M. EL REY

SEÑOR PRESIDENTE DEL COMITÉ ORGANIZADOR INTERNACIONAL DE LA CONFERENCIA.

SANTANDER (Cantabria)

8th International Hereditary Hemorrhagic Telangiectasia Scientific Conference

PROGRAM

Wednesday May 27th

17:00-20:00 Registration and welcome cocktail (La Magdalena Palace)

Thursday May 28th

7:30-8:00 Registration (Paraninfo gardens)

8:00-8:15 Welcome and opening remarks (Paraninfo Hall)
- Santiago de la Riva. *President of the Spanish HHT Association*
- Michael Nolan. *Member of the Board of Directors. HHT Foundation Int., USA*
- Carmelo Bernabéu. *Chair of the Global Research and Medical Advisory Board for HHT (GRMAB)*
- Roberto Zarrabeitia. *Coordinator of the HHT Unit (Hospital Sierrallana), Spain*

8:15-8:45 Official inauguration conference:
The European Network for Rare and Congenital Anemias (ENERCA)
Joan L. Vives Corrons
Director of ENERCA. Hospital Clinic, Barcelona, Spain.

8:45-10:45 **Session I: Arteriovenous malformations and animal models. Angiogenesis and vascular development** (Paraninfo Hall)
Chairs: Helen Arthur and Paul Oh

8:45-9:15 Lecture:
Notch signaling in vascular development
Thomas Gridley
The Jackson Laboratory, Bar Harbour, Maine, USA

9:15-10-45 Oral presentations:

(B11) Correlation of HHT type and characteristics of pulmonary AVMs by CT
J Carlisle, J Mc Donald, P Bayrak-Toydemir, K Whitehead
University of Utah, USA

(B14) Cellular changes during formation of arteriovenous malformations in a mouse model of HHT 1
M Mahmoud, K Allinson, ZH Zhai, R Oakenfull, M Fruttiger, HM Arthur
Institute of Human Genetics, Newcastle University, UK. Institute of Ophtalmology, University College London, UK

(B19) Repetitive mechanical stress on skin of HHT model mice induces tortuous blood vessels
Y Yonenaga, R Suzuki, F Lan, T Seki
Medical College of Georgia, USA

(B22) Angiogenic stimuli are required for development of the novo arteriovenous malformations in ALK-1 deficient adult mice
SO Park, M Wankhede, E Choi, YJ Lee, B Sorg, SP Oh
Department of Physiology and Functional Genomics, College of Medicine, University of Florida, Gainesville, FL 32610 Department of Biomedical Engineering, College of Engineering, University of Florida, Gainesville, FL, USA

(B27) ALK1 regulates blood vessel caliber in response to flow
PA Corti, SA Young, DW Laux, BL Roman
Department of Biological Sciences, University of Pittsburgh, USA

(B7) The antioxidant tempol prevents onset of pulmonary arterial hypertension in endoglin and ALK1 heterozygous mice
M Jerkic, MG Kabir, A Davis, J Leen, B McIntyre, N Husain, J Belik, M Husain, M Toporsian, M Letarte
Molecular structure and function Program, Hospital for Sick children, Toronto. Heart and Stroke Richard Lewar Center of Excellence, University of Toronto. Immunology Department, University of Toronto. Physiology and Experimental Medicine Program, Hospital for Sick Children, Toronto. Department of Pediatrics, University of Toronto, Toronto General Hospital Research Institute, Toronto. Beth Israel Deaconess Medical Center, Boston.

10:45-11:15 Coffee break and poster viewing (Paraninfo gardens)

11:15-13:15 **Session II: Genetics and Genotype/Phenotype in HHT** (Paraninfo Hall)
Chairs: Jamie McDonald and Sophie Dupuis-Girod

Oral presentations:

(C12) Influence of HHT status on radiological aspect of pulmonary arteriovenous malformations
MF Carette, F Coulet, A Lavolé, B Monod, J Cadranel, A Khalil
Departments of Interventional Radiology and Pneumology, Tenon; Hospital; Pierre and Marie Curie University, Molecular Genetic; Department-Pitié Salpêtriere Hospital; Competent Center for HHT en Ile de France, Paris, France

(C23) Prevalence of pulmonary right-to-left shunt in hereditary haemorrhagic telangiectasia: assessment of differences between HHT 1 and 2
MWF van Gent, MC Post, RJ Snijder, CJJ Westermann, HWM Plokker, JH Mager
Department of Cardiology and Pulmonology. St Antonius Hospital, Nieuwegein, The Netherlands

(B28) Beyond genotype-phenotype correlations in hereditary haemorrhagic telangiectasia
CL Shovlin, E Kulinskaya
NHLI Cardiovascular Sciences and Statistical Advisory Service, Imperial College London, UK

(B3) Family members of patients with hereditary hemorrhagic telangiectasia: HHT center Paris experience in 217 relatives from 80 families with genotyping
J Roume, F Coulet I Bourgault-Villada, JH Blondel, S Blivet, JP Pelage, A Ozanne, C Fagnou, G Lesur, P Lasjaunias, B Raffestin, T Chinet, F Soubrier, P Lacombe
HHT Center Paris AP-HP. CHV Ambroise Paré. CHV Kremlin Bicêtre. CHV Pitié Salpêtriere, Paris, France

(B37) Pulmonary arteriovenous shunting is more severe in HHT2
K Whitehead, J McDonald, J Carlisle
University of Utah HHT Center, USA

(B9) In silico evaluation of splice-site mutation of ENG and ACVRL1 genes
C Olivieri, L Boeri, A Colombo, E Matti, F Chu, M Perego, A Minelli, C Canzonieri, F Ornati and on behalf of the HHT-NET (C Danesino, E Buscarini, G Manfredi, P Gazzaniga, L Reduzzi, F Pagella, M Grosso, G Pongiglione, E Boccardi
Medical Genetics-University of Pavía, Pavía, Italy. ENT Unit-IRCCS Policlínico San Matteo, Pavía, Italy. GI Endoscopy Unit, IRCCS Policlínico San Matteo, Pavía, Italy

(B15) Role of noncoding region mutations of ACVRL1 and ENG in the pathogenesis of hereditary hemorrhagic telangiectasia
K Damjanovich, H Escobar, J McDonald, F Gedge, LS Chou, P Bayrak-Toydemir
ARUP Institute for Clinical and Experimental Pathology. DNA, Sequencing and Genomics Core Facility, University of Utah. Department of Radiology, University of Utah. Department of Pathology, University of Utah, USA

(B17) Missense and intronic variants in ENG and ALK1 genes: identification of pathogenic mutations may be difficult
S Giraud, S Dupuis-Girod, G Lesca, C Gressier, C Chretien, O Boute, P Kaminsky, B Leheup, H Plauchu, A Calender
Hospices Civils de Lyon, Hôpital E. Herriot, Service de Génétique moléculaire et clinique, Lyon. Hospices Civils de Lyon, Hôpital de l'Hotel Dieu, Service de Génétique et centre de référence pour la maladie de Rendu Olser, Lyon, France

13:15-14:30 Working lunch and poster viewing (Paraninfo gardens)

14:00-14:30 Evaluation of posters candidates for Best Junior Award (Committee)

14:30-16:30 **Session III (simultaneous): Cellular and molecular involvement in HHT and related pathologies** (Paraninfo Hall)
Chairs: Mirjana Jerkic and Marie-Jose Goumans

Oral presentations:

(B12) Impaired recruitment of HHT1 mononuclear cells to the ischemic heart is due to an altered CXCR4/CD26 balance
S Post, A Smits, A Vdn Broek, J Sluijter, I Hoefer, B Janssen, R Snijder, J Mager, G Pasterkamp, C Mummery, P Doevendans, MJ Goumans
Leiden University Medical Center, Leiden, The Netherlands

(B16) Age dependent changes in pulmonary vascular reactivity and superoxide production in endoglin and ALK1 heterozygous mice
M Jerkic, B McIntyre, J Pan, J Leen, D Li, M Toporsian, J Belik, M Letarte
Molecular structure and Function Program, Hospital for Sick Children, Toronto; Heart and Stroke Richard Leward Center of Excellence and Immunology Department, University of Toronto; Physiology and Experimental Medicine Program Hospital for Sick Children, Toronto; Beth Israel Deaconess Medical Center, Boston; Departments of Pediatrics, University of Toronto, Canada

(B23) Immunological profile in 42 patients with HHT: are they immunocompromised?
CH Malcus, S Dupuis-Girod, F Poitevin, S Giraud, H Plauchu, F Touraine-Moulin
Hospices Civils de Lyon, Hôpital E. Herrriot, Service d'Inmunologie et Laboratorie de Genetieuqe moleculaire, Lyon, F-69437 ; Hospices Civils de Lyon, Hôpital de l'Hotel Dieu, Service de Genétique et centre de reference pour la maladie de Rendu Osler, Lyon F-69288

(B24) A role for endoglin as a modulator of tumor progression
E Pérez-Gómez, G del Castillo, M Villa Morales, J Santos, J Fernández-Piqueras, C Gamallo, C Bernabéu, M Quintanilla
Instituto de Investigaciones Biomédicas Alberto Sols, Consejo Superior de Investigaciones Científicas (CSIC)-Universidad Autónoma de Madrid (UAM), Madrid (Spain); Laboratorio de Genética Molecular Humana, Departamento de Biología, UAM, Madrid, Spain; Departamento de Anatomía Patológica, Hospital Universitario de La Princesa, UAM, Madrid, Spain; Centro de Investigaciones Biológicas, CSIC, Madrid, Spain

(B25) S-endoglin upregulation as a senescence marker of endothelial cells and its role in vascular pathology
FJ Blanco, MT Grande, C Langa, B Oujo, S Velasco, A Rodriguez-Barbero, E Pérez-Gómez, M Quintanilla, JM López-Novoa, C Bernabéu
Centro de Investigaciones Biológicas (CSIC) and CIBER de Enfermedades Raras (ISCIII), Madrid, Spain; Instituto Reina Sofía de Investigación Nefrológica, Departamento de Fisiología y Farmacología, Universidad de Salamanca and Red de Investigación Renal, Salamanca, Spain; Instituto de Investigaciones Biomédicas Alberto Sols (CSIC-UAM), Madrid, Spain

(B31) Endoglin promotes endothelial tubule stability and survival
NY Lee, GC Blobe
Duke University, Durham, NC 27708, USA

(B1) Reduced plasma levels of ANG-2, s-ENG and sFlt1 as novel biomarkers in HHT
L Ojeda-Fernández, L Barrios, A Rodriguez Barbero, C Bernabéu, LM Botella
Centro de Investigaciones Biológicas (CSIC) and Centro de Investigaciones Biomédicas en Red de Enfermedades Raras (CIBERER), Madrid; Centro Técnico de Informática (CSIC), Madrid; Departamento de Fisiología y Farmacología, Universidad de Salamanca and Red de Investigación Renal, Salamanca, Spain

14:30-16:30 **Session IV (simultaneous): Clinical management and outcomes in HHT** (C2 Hall)
Chairs: Carlo Sabba and Peter Terry

Oral presentations:

(C53) Outcomes of pregnancy in hereditary hemorrhagic telangiectasia
E de Gussem, AY Lausman, AJ Beder, CP Edwards, JJ Mager, ME Faughnan
Department of Respirology, St Antonius Hospital, Netherlands; Department of Medicine and Li Ka Shing Knowledge Institute, St Michael's Hospital, University of Toronto, Canada; Department of Obstetrics & Gynaecology, St Michael's Hospital, University of Toronto, Canada

(C58) Estimates of maternal risks of pregnancy for women with hereditary hemorrhagic telangiectasia: suggested approach for obstetric services
C Shovlin, V Sodhi, A McCarthy, P Lasjaunias, JE Jackson, MN Sheppard
NHLI Cardiovascular Sciences, Imperial College London; Respiratory Medicine and Department of Imaging, Hammersmith Hospital; Anaesthetics and Obstetrics, Queen Charlotte's Hospital, London W12 ONN; Histopathology, Royal Brompton Hospital, London; Neuroradiologie, Bicêtre Hospital, Kremlin Bicetre, France

(C38) Management of venous thromboembolism in hereditary hemorrhagic telangiectasia
D Goodenberger, M Chakinala, D Picus
Washington University HHT Center, St Louis, Missouri, USA; Dallas Veterans Affairs Medical Center, Dallas, Texas, USA; University of Texas Southwestern Medical School, Dallas, Texas, USA

(C42) Life expectancy in patients with hereditary hemorrhagic telangiectasia
E de Gussem, CP Edwards, CJJ Westermann, ME Faughnan, JJ Mager
Department of Pulmonology, St Antonius Hospital, Nieuwegein, The Netherlands; Department of Medicine, Division of Respirology, St Michaels's Hospital, University of Toronto, Canada; Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, Canada

(C51) Survival in hereditary hemorrhagic telangiectasia
J Goodwin, R Nisenbaum, C Edwards, ME Faughnan
Department of Medicine and Li Ka Shing Knowledge Institute, St Michael's Hospital, University of Toronto, Canada; Centre for Research in Inner City Health and Applied Health Research Centre, The Keenan Research Centre, Li Ka Shing Knowledge Institute, St Michael's Hospital, Dalla Lana School of Public Health, University of Toronto, Canada

(C52) Pre-visit nursing assessment educates hereditary hemorrrhagic telangiectasia patients and prepares physician
R Pantalone, E Leek, S Gupta, ME Faughnan
Department of Medicine and Li Ka Shing Knowledege Institute, St Michael's Hospital, University of Toronto, Canada

(C2) Transilumination of the fingers for vascular anomalies
ER Mohler, Vijay Doriswamy, A Sibley, BA Bernhardt, R Pyeritz
University of Pennsylvania School of Medicine, PA, USA

(C25) Diagnostic Curaçao criteria for hereditary hemorrhagic telangiectasia: are they still valid?
M van Gent, MC Post, JJ Mager, HWM Plokker, TGW Letteboer, H Kelder, CJJ Westermann
Department of Cardiology, Pulmonology, St Antonius Hospital, Nieuwegein; Department of Medical Genetics, University Medical Center, Utrecht, The Netherlands

14:30-16:30 **Patients' Associations Committee Workshop (1st part)** (Magdalena Palace)
Chairs: Michael Nolan and Santiago de la Riva

16:30-17:00 Coffee break and poster viewing (Paraninfo gardens)

17:00-19:00 **Session V (simultaneous): Molecular diagnostics for HHT** (Paraninfo Hall)
Chairs: Luisa M. Botella and Cesare Danesino

Oral presentations:

(B36) Will genetic testing aid diagnosing relatives at risk? An exploratory study
B Bernhardt, C Zayac, S Keddem, R Pyeritz
HHT Center, Hospital at the University of Pennsylvania and Penn Center for the Integration of Genetic Healthcare Technologies (CIGHT), USA

(B8) Assessing the impact of molecular genetic testing for hereditary hemorrhagic telangiectasia
K Hart, L Ellington, A Brothman, P Bayrak-Toydemir, J McDonald
University of Utah, USA

(B10) ALK1 and ENG mutations in Norwegian patients with hereditary hemorrhagic telangiectasia: recurrent mutations and a probable founder effect
K Heimdal, S Al-Deen, G Bachmann-Harildstad, M Kronen, K Eidlid
Department of Medical Genetics and Department of ENT, Oslo University Hospital Rikshospitalet. Department of Medical Genetics, Oslo University Hospital Ullevål, Norway

(B32) Comparison between different mutation detection methods in HHT, and some new mutations
K Brusgaard, P Tørring, AD Kjeldsen
Department of Clinical Biochemistry and Molecular Genetics, Department of Otorhinolaryngology, Odense University Hospital, Denmark

(B33) Homozygosity for a novel mutation in ENG discovered in a patient with hereditary hemorrhagic telangiectasia (HHT)
P Tørring, AD Kjeldsen, K Brusgaard
Odense University Hospital, Department of Clinical Genetics and Department of Otorhinolaryngology, Denmark

17:00-19:00 **Session VI (simultaneous): Central Nervous System involvement and treatment in HHT** (C2 Hall)
Chairs: Karel ter Brugge and Augustin Ozanne

Oral presentations:

(C4) The spectrum of phenotypes in CAVMs; is there a difference between micro arteriovenous malformations (AVMs) and micro capillary vascular malformations (CAVMs)
K ter Brugge, T Krings, R Willinsky, R Agid
Toronto Western Hospital, University of Toronto, Canada

(C33) Brain and spinal arteriovenous shunts in hereditary hemorrhagic telangiectasia type 1 or 2: angiography and genetics results
A Ozanne, J Roume, F Coulet, I Bourgault-Villada, S Blivet, JP Pelage, C Fagnou, G Lesur, P Lasjaunias, F Toulgoat, G Saliou, D Ducreux, B Raffestin, T Chinet, F Soubrier, P Lacombe
HHT Center Paris, APHP; Neuroradiology-CHU Bicêtre; Consultation Multidisciplinaire-CHU Ambroise Paré; Oncogenetics and Angiogenesis Laboratory-CHU Pitié Salpétriére, Paris, France

(C55) Cognitive functions in patients with hereditary hemorrhagic telangiectasia
MF de Caro, M Mitolo, P Suppressa, L Castorani, C Sabbá, C Logroscino
Department of Neurologic and Psychiatric Sciences, Department of Internal Medicine and Public Health, Interdepartmental HHT Centre, University of Bari, Policlinico, Bari, Italy

(C34) Genetic HHT1 or HHT2 diagnosis in pediatric central nervous system arteriovenous shunts: a prospective cohort
A Ozanne, F Coulet, J Roume, I Bourgault-Villada, S Blivet, JP Pelage, C Fagnou, G Lesur, P Lasjaunias, F Toulgoat, G Saliou, D Ducreux, B Raffestin, T Chinet, F Soubrier, P Lacombe
HHT Center Paris, APHP; Neuroradiology-CHU Bicêtre; Consultation Multidisciplinaire-CHU Ambroise Paré; Oncogenetics and Angiogenesis Laboratory-CHU Pitié Salpétriére, Paris, France

(PC9) Detection of cerebral arteriovenous malformations with magnetic resonance imaging in patients with HHT (Osler Rendu Weber disease)
A Massman, P Fries, M Wirth, R Seidel, UW Geisthoff, A Buecker, GK Schneider
Saarland University Hospital Homburg/Saar; Clinics of City Cologne/Holweide, Germany

17:00-19:00 **Patients' Associations Committee Workshop (2nd part)** (Magdalena Palace)
Chairs: Michael Nolan and Santiago de la Riva

19:30-21:00 **GRMAB meeting** (Magdalena Palace)

19:30-20:30 Guided visit to the Magdalena Palace

Friday May 29th

8:20-10:00 **Session VII: Antiangiogenic approaches in HHT** (Paraninfo Hall)
Chairs: Karen Swanson and Christine Mummery

8:25-8:40 Introduction:

Searching for the magic bullet for bleeding in HHT, "Pros and cons"
Robert I White Jr.
Yale HHT Center, New Haven, CT, USA

8:40-9:10 Lecture:

Antiangiogenic drugs in clinical management
Christianne Bruns
University of Munich, Germany

9:10-10:00 Oral presentations:

(C16) Efficacy and safety of Bevacizumab in the treatment of hemorrhagic heredi tary telangiectasia associated with severe hepatic vascular malformations. A phase II study.
S Dupuis Girod, I Ginon, D Marion, F Faure, E Decullier, PJ Valette, E Guillot, D Revel, D Gamondes, S Bailly, E Babin, MF Carette, R Corre, B Gilbert, JH Harle, PY Hatron, P Kaminsky, P Lacombe, B Lorcerie, P Magro, S Riviere, JF Viallard, F Chapuis, H Plauchu, JC Saurin
Hospices Civils de Lyon: Hôpital de l'Hôtel Dieu, Service de Génétique et centre de référence pour la maladie de Rendu Osler; CH Lyon Sud, Service de Cardiologie; Hôpital de l'Hôtel Dieu, Service de Radiologie; Hôpital E. Herriot, Service d'ORL; pôle IMER; CH Lyon Sud, Service de Radiologie; INSERM U878, CEA-Grenoble; French HHT Network, centres de compétence pour la maladie de Rendu-Osler; CH Lyon Sud, Service d'Hépato-gastroentérologie, France

(C31) Thalidomide for treatment of chronic severe bleeding in hereditary hemorrhagic telangiectasia
E Buscarini, G Manfredi, P gazzaniga, L Reduzzi, C Danesino, Olivieri, F Pagella, M Grosso, G Pongiglione, E Boccardi, on behalf of HHT-NET
Departments of Gastroenterology, Cardiology, Radiology, Maggiore Hospital, Crema; Genetic Institute and ENT Institute, University of Pavia; Radiology department, Ospedale S Croce, Cuneo; Paediatric Cardiology Department, Ospedale Gaslini, Genova; Interventional Neuroradiology Unit, Niguarda Hospital, Milan, Italy

(PC10) An interim report of thalidomide for treatment of recurrent angioectasia related gastrointestinal bleeding
J Gossage, SM Chamberlain, S Sridhar, A Kumar
Medical College of Georgia, Augusta; Stony Brook University, NY, USA

(B13) Thalidomide stimulates vessel maturation and prevents nosebleeds in hereditary haemorrhagic telangiectasia patients
F Lebrin, S Brun, S Martin, S van den Brink, HM Arthur, CJJ Westermann, JJ Mager, F Dish, RJ Snijder, A Eichmann, CL Mummery
INSERM U833, Paris, France; College de France, Paris, France; Hubrecht Laboratory, Netherlands Institute for Developmental Biology, Utrecht, Netherlands; Institute of Human Genetics, International Centre for Life, University of Newcastle, UK; St Antonius Hospital, Nieuweigen, The Netherlands; Dept. of Anatomy and Embriology, Leiden University Medical Center, Leiden, The Netherlands

10:00-11:10 **Session VIII: Hepatic involvement in HHT** (Paraninfo Hall)
Chairs: Elizabetta Buscarini and Lawrence Young

Oral presentations:

(C11) Heart failure in hereditary hemorrhagic telangiectasia: clinical, echocardio graphic features and natriuretic peptides in patients with hepatic involvement
I Ginon, S Dupuis-Girod, G Rioufol, G Finet, C Khouatra, JF Cordier, M Barthelet, D Marion, PJ Valette, S Giraud, JC Saurin, H Plauchu, M Ovize
Hospices Civils de Lyon: CH Lyon Sud, Service d'Explorations Cardiologiques, Pierre-Bénite; Hôpital de l'Hôtel Dieu, Service de Génétique et Centre de référence pour la maladie de Rendu-Osler; Hôpital Louis Pradel, Service d'Hémodynamique, Lyon-Bron; Hôpital Louis Pradel, Service de Pneumologie et Centre de référence des maladies orphelines pulmonaires, Lyon-Bron; Hôpital Louis Pradel, Service d'Explorations fonctionnelles cardiovasculaires; Hôpital de l'Hôtel Dieu, Service de Radiologie, Lyon; CH Lyon Sud, Service de Radiologie, Pierre-Bénite; Hôpital Edouard Herriot, Laboratoire de Génétique moléculaire, Lyon; CH Lyon Sud, Service d'Hépato-gastroentérologie, Pierre-Bénite, France

(C41) Treatment for heart failure in HHT patients with symptomatic liver disease
LH Young, G Garcia-Tsao, K Henderson, RI White Jr
Yale University School of Medicine, New Haven, CT, USA

(C49) Non invasive determination of portal vein to right heart shunting: quantifying shunts in HHT liver AVMs
M Kuo, C Oh, TB Kinney, FJ Miller
Institutions UCSD Medical Center, San Diego, California, USA

(C30) How many HHT patients will require invasive treatments for symptomatic hepatic vascular malformations (HAVMs) along follow up?
E Buscarini, G Manfredi, P Gazzaniga, L Reducci, C Danesino,
C Olivieri, F Pagella, M Grosso, G Pongiglione, E Boccardi, on behalf of HHT-NET
Departments of Gastroenterology, Cardiology and Radiology, Maggiore Hospital, Crema; Genetic Institute and ENT Institute, University of Pavia; Radiology Dept, Ospedale S Croce, Cuneo; Paediatric Cardiology Dept, Ospedale Gaslini, Genova; Interventional Neuroradiology Unit, Niguarda Hospital, Milan, Italy

(C17) Does liver transplantation improve HHT patients with severe liver involvement?
AL Chesnais, S Dupuis-Girod, I Ginon, J Dumortier, JC Saurin, G Rioufol, G Finet, E Decullier, S Giraud, F Faure, O Merrot, D Marion, JY Scoazec, H Plauchu, O Boillot
Hospices Civils de Lyon: Hôpital de l'Hôtel Dieu, Service de Génétique et Centre de référence pour la maladie de Rendu-Osler; CH Lyon Sud, Service de Cardiologie, Pierre-Bénite; Hôpital E. Herriot, Service d'Hépato-gastroentérologie; Hôpital Louis Pradel, Service de Cardiologie, Bron; pôle IMER, Université de Lyon; Hôpital E. Herriot, Laboratoire de Génétique moleculaire; Hôpital E. Herriot, Service d'ORL ; Hôpital de la Croix Rousse, Service d'ORL, Lyon; Hôpital de l'Hôtel Dieu, Service de Radiologie; Hôpital E. Herriot, Service d'anatomo-pathologie; Hôpital E. Herriot, Service de transplantation hépatique, France

(C39) Magnetic resonance imaging and magnetic resonance angiography of the liver and hepatic vasculature in patients with hereditary hemorrhagic telangiectasia (Rendu Olser Weber disease)
GK Shneider, A Massmann, P Fries, M Wirth, UW Geisthoff, A Buecker
Saarland University Hospital Homburg/Saar; Clinics of City Cologne/Holweide, Germany

11:10-11:40 Coffee break and poster viewing (Paraninfo gardens)

11:40-13:15 **Session IX: Management and outcomes of PAVMs in HHT** (Paraninfo Hall)
Chairs: Hans-Jurgen Mager and Mark Chesnut

Oral presentations:

(C5) New approach to management of patients with diffuse pulmonary arteriovenous malformations
J Pollak, RI White, J Fahey, J Murphy, P Pierucci, D Chyun, K Henderson
Yale University School of Medicine, New Haven, CT, USA

(C7) Pulmonary arteriovenous malformations associated with migraine with aura: a large prospective study
MC Post, MWF van Gent, HWM Plokker, CJJ Westermann, JC Kelder, JJ Mager, TT Overtoom, WJ Schonewille, V Thijs, RJ Snijder
Department of Cardiology, Pulmonology, Radiology and Neurology, St Antonius Hospital, Nieuwegein, The Netherlands; Department of Neurology, University Hospital Gasthuisberg, Leuven, Belgium

(C19) Embolization of ruptured pulmonary arteriovenous malformations in HHT patients
JP Pelage, S Blivet, JH Blondel, I Bourgault, Th Chinet, G Lesur, A Ozanne, B Raffestin, J Roume, F Soubrier, E Kuhl, P Lacombe
Consultation pluridisciplinaire Rendu Osler, APHP, Boulogne, France

(C20) Embolization of pulmonary arteriovenous malformations in 70 consecutive patients over a 3-year period: results with the use of multidetector computed tomography
P Lacombe, S Blivet, JH Blondel, I Bourgault, Th Chinet, G Lesur, A Ozanne, B Raffestin, J Roume, F Soubrier, L cellerin, R Corre, JP Pelage
Consultation pluridisciplinaire Rendu Osler, APHP, Boulogne, France

(C50) Outcomes of isolated intrapulmonary shunt in HHT
HH Wong, H Leong-Poi, V Prabhudesai, R Bijarchi, ME Faughnan
Departments of Medicine and medical Imaging, St Michael's Hospital and Li Ka Shing Knowledge Institute, University of Toronto, Canada

(C44) To embolise or not to embolise pulmonary arteriovenous malformations in the presence of severe pulmonary hypertension
C Shovlin, JSR Gibbs, JE Jackson
Imperial College London and Hammersmith Hospital, Imperial College Healthcare, NHS Trust, UK

13:15-14:30 Working lunch and poster viewing (Paraninfo gardens)

14:00-14:30 Evaluation of posters candidates for Best Junior Award (Committee)

14:30-16:30 **Session X (simultaneous): Epistaxis management in HHT** (Paraninfo Hall)
Chairs: Douglas Ross and Urban Geisthoff

14:30-15:00 Lecture:

Designing a grading system for epistaxis
Jeffrey Hoag
Drexel University College of Medicine, Philadelphia, USA

15:00-16:30 Oral presentations:

(C47) The effect of epistaxis on health related quality of life (Hr-Qol) in patients with hereditary hemorrhagic telangiectasia (HHT)
J Hoag, D Reh, D Boyce, S Mitchell, P Terry, C Merlo
Drexel University College of Medicine, Philadelphia; Johns Hopkins University School of Medicine, Baltimore, USA

(C32) Quality of life in individuals affected of hereditary hemorrhagic telangiectasia
AO Geirdal, S Al-Deen, G Bachmann-Haristad, K Heimdal
Oslo University College, Department of Medical Genetics and Department of ENT, Oslo University Hospital, Rikshospitalet, Norway

(C3) A grading scale for epistaxis in hereditary hemorrhagic telangiectasia
S Al-Deen, G Bachmann-Haristad
Rikshospitalet, Oslo, Norway

(C46) Anti estrogen therapy for hereditary hemorrhagic telangiectasia-a double blind placebo control clinical trial
E Yaniv, M Price, M Haddad
Rabin Medical Center, Israel

(C15) Closure of the nasal cavity according to Young for the treatment of recurrent epistaxis in HHT
U Geisthoff, A Mainka
Department of Otolaryngology, Hospitals of the City of Cologne; Department of Otolaryngology, Hospital Dresden Friedrichstadt, Dresden, Germany

(PC1) Extended experience with Young's procedure for the management of epistaxis and hereditary hemorrhagic telangiectasia
LP Johnson, F Miller, TM Davidson
Departments of Otolaryngology-Head and Neck Surgery and Radiology, University of Utah Health Sciences Center, Salt Lake City; Department of Radiology and Division of Otolaryngology-Head and Neck Surgery, University of California, San Diego, USA

(C14) Treatment of epistaxis with an angled 980 nm diode laser in patients with HHT
G Bachman-Haristad, S Al-Deen
Rikshospitalet, Oslo, Norway

14:30-16:30 **Session XI (simultaneous): Endoglin, ALK1 and Smad4 in TGF-β and BMP pathways** (C1 Hall)
Chairs: Gerard Blobe and Sabine Bailly

Oral presentations:

(B2) BMP9 responses mediated via ALK1 rely on different inputs from type II receptors in human pulmonary artery endothelial cells
P Upton, RJ Davies, RC Trembath, NW Morrell
Department of Medicine, University of Cambridge School of Clinical Medicine, Addenbrooke's and Papworth Hospitals, Cambridge; King's College, London; Department of Medical and Molecular Genetics, Guy's Hospital, London, UK

(B5) The ALK1 ligand, BMP9, is a plasmatic vascular quiescence factor
L David, M Bidart, C Mallet, N Ricard, M Keramidas, N Lamandé, S Dupuis Girod, H Plauchu, JJ Feige, S Bailly
INSERM U878 iRTSV/LAPV; CEA Grenoble; INSERM U833, Collége de France, Paris; Hôpital Hôtel-Dieu, Lyon, France

(B4) Functional analysis of the BMP9 response of ALK1 mutants from HHT2 patients
N Ricard, G Lesca, C Mallet, S Giraud, A Calender, JJ Feige, S Bailly
INSERM U878 iRTSV/LAPV, CEA, Grenoble; Service de Génétique Moléculaire et Clinique, Hôpital Edouard Herriot, Lyon, France

(B6) A new role for TGFβ in vascular system: TGFβ1 induces podosome formation in aortic endothelial cells in an ALK1/Smad1/5 dependent manner
P Rottiers, C Billottet, F Saltel, V Tridon, E Reuzeau, E Genot
IECB/INSERM U889, France

(B34) CK2β as a novel activator/mediator of ALK1 signaling
JC Haney, J Sogani, G Blobe
Duke University, Durham, North Carolina, USA

(B35) ALK5 phosphorylation of the endoglin cytoplasmic domain regulates Smad 1/5/8 signaling and endothelial cell migration
BN Ray, NY Lee, T How, GC Blobe
Duke University, Durham, North Carolina, USA

(B20) Endoglins differentially modulate TGFβ1 signalling
S Velasco, M Pericacho, C Bernabéu, JM López Novoa, A Rodríguez Barbero
Instituto "Reina Sofía" de Investigación Nefrológica. Departamento de Fisiología y Farmacología. Universidad de Salamanca, Spain

(B21) Network analysis suggest several novel proteins shared by ALK1, TβRII and endoglin: implications for HHT
M Letarte, G Xu, M Barrios-Rodiles, D Voulgaraki, E Cheng, Z Jawed, R Nadon, JL Wrana
Molecular Structure and Function Program, The Hospital for Sick Children, Heart and Stroke Richard Lewar Center of Excellence and Department of Immunology, University of Toronto; Centre for Systems Biology, Samuel Lunenfeld Research Institute, Mount Sinai Hospital, Toronto; Department of Human Genetics, McGill University, Montreal, Canada

(B29) TGF-β signaling in endothelial cells plays a temporal and spatial role during cerebral vascular development
HL Nguyen, YJ Lee, E Lee, SO Park, SP Oh
Department of Physiology anf Functional Genomics, University of Florida, Gainesville, Florida, USA

14:30-16:30 **Session XII (simultaneous): Screening for PAVMs** (C2 Hall)
Chairs: Claire Shovlin and José Antonio Parra

Oral presentations:

(C48) Considerations for pediatric screening and treatment programmes in families with hereditary hemorrhagic telangiectasia
C Shovlin, A Bush, D Edwards, JE Jackson, N Coote
NHLI Cardiovascular Sciences and Pediatrics, Imperial College London; Royal Brompton Campus; Hammersmith Campus; Respiratory Medicine, Imaging and Pediatrics, Hammersmith Hospital, Imperial College Healthcare Trust, London, United Kingdom

(C9) Screening for pulmonary arteriovenous malformations using transthoracic contrast echocardiography
MWF van gent, MC Post, JGLM Luermans, RJ Snijder, CJJ Westermann, HWT Plokker, TT Overtoom, JJ Mager
Department of Cardiology, Pulmonology and Radiology, St Antonius Hospital, Nieuwegein, The Netherlands

(C26) Contrast echocardiography or CT scan for the detection of pulmonary arteriovenous malformations (PAVMs) in patients with hereditary hemorrhagic telangiectasia
S Blivet, TH Chinet, JH Blondel, I Bourgault-Villada, C Fagnou, G Lesur, A Ozanne, JP Pelage, B Raffestin, F Soubrier, J Roume, P Lacombe
HHT Center of Paris, APHP; Ambroise Paré, Bicêtre, Pitié-Salpêtriere, France

(C28) Complications to contrast echocardiography (CE) for screening of pulmonary arteriovenous malformations (PAVMs): a prospective survey
P Gazzaniga, E Buscarini, G Manfredi, L Reduzzi, C Danesino, C Olivieri, F Pagella, M Grosso, G Pongiglione, E Boccardi, on behalf of HHT-NET
Cardiology and Gastroenterology Dept, Maggiore Hospital, Crema; Genetic Institute and ENT Institute, University of Pavia; Radiology Dept, Ospedale S Croce, Cuneo; Paediatric Cardiology Dept, Ospedale Gaslini, Genova; Interventional Neuroradiology Unit, Niguarda Hospital, Milan, Italy

(C18) Utility of transcranial doppler contrast study in pulmonary arteriovenous malformation assesment in hereditary hemorrhagic telangiectasia
D Manawadu, D Vethanayagan, M Saqqur, C Derksen, J Choy, K Khan
Department of Medicine and Edmonton HHT Center, University of Alberta, Edmonton, Alberta, Canada

(C36) Detection of reperfused pulmonary arteriovenous malformations with contrast-enhanced magnetic resonance angiography in patients with hereditary hemorrhagic telangiectasia (Osler-Rendu-Weber disease)
GK Schneider, A Opitz, UW Geisthoff, M Katoh, A Buecker, A Massmann
Saarland University Hospital Homburg/Saar, Clinics of City Cologne/Holweide, Germany

(C43) Post 2007-2008 Guidelines: should antibiotic profilaxis be given prior to dental procedures for patients with pulmonary arteriovenous malformations and hereditary hemorrhagic telangiectasia?
C Shovlin, KB Bamford, D Wray
Imperial College London and University of Glasgow, UK

16:30-17:00 Coffee break and poster viewing (Paraninfo gardens)

17:00-18:30 **Workshop (simultaneous): Toronto Guidelines and beyond** (Paraninfo Hall)
Chairs: Marie Faughnan and Carlo Sabba

17:00-18:30 **Workshop (simultaneous): New trends in HHT research** (C2 Hall)
Chairs: Michelle Letarte and José Miguel López Novoa

17:00-18:30 **Workshop (simultaneous): Outcomes with new devices in the management of PAVMs** (C1 Hall)
Chairs: Robert I White Jr and Pascal Lacombe

Oral presentations:

(C35) Occlusion of pulmonary arteriovenous malformations with Amplatzer vascular plug II - preliminary results
R Andersen, E Dorenberg, P Giaevert, K Heimdal, G Hafsahl
Departments of Interventional Radiology, Pulmonary Medicine and Medical Genetics, Oslo University Hospital, Rikshospitalet, Oslo, Norway

(C37) Embolotherapy of pulmonary arteriovenous malformations with Amplatzer plugs: long term results
E de Gussem, J Sala, M van Leersum, CJJ Westermann, TT Overtoom, JJ Mager
Department of Pulmonology and Radiology, St Antonius Hospital, Nieuwegein, The Netherlands

(C54) Medium term results of use of Amplatzer vascular plugs in treating pulmonary arteriovenous malformations
G Robinson, DF Ettles, PM Scott, R Lakshminarian, AH Morice
Hull Royal Infirmary, Hull, East Yorkshire, United Kingdom

(C1) Does use of coils in addition to Amplatzer vascular plugs prevent recanalization?
S Trerotola, R Pyeritz
Hospital of the University of Pennsylvania, USA

19:00-20:00 Leisure program

21:00-23:00 Gala dinner (Gran Casino de El Sardinero)

Saturday May 30th

8:30-10:30 **Session XIII: What can we learn from other Rare Diseases?** (Paraninfo Hall)
Chairs: Roberto Zarrabeitia and Francesc Palau

8:30-9:00 Lecture:

Policies for the benefit of patients with Rare Diseases: lessons to be applied
Segolene Ayme
Director of ORPHANET, President of the European DG Sanco Task Force in Rare Diseases

9:00-9:30 Lecture:

The Spanish Research Center for Rare Diseases (CIBERER)
Francesc Palau
Director of Center for Biomedical Research on Rare Diseases (CIBERER), ISCIII, Valencia. Spain

9:30-10:00 Lecture:

Genetics of human vascular malformations
Mikka Vikkula
Université Catholique de Louvain, Brussels. Belgium

10:00-10:30 Round Table Discussion

10:30-11:00 Coffee break (Paraninfo gardens)

11:00-12:00	**Session XIV: Summing up: brief summaries, updates and future directions in clinical research, basic research, clinical trials and genetics on HHT** (Paraninfo Hall) Chairs: Claire Shovlin, Carmelo Bernabeu, James Gossage and Reed Pyeritz
12:00-12:30	Closing ceremony (Paraninfo Hall)
12:30-14:00	Working lunch (Paraninfo gardens)
14:00-16:00	Specific meetings: **European Union HHT Network meeting** (C2 Hall) Chair: Luisa M. Botella Rooms available for specific interviews/meetings
16:00-20:00	Leisure program

Sunday May 31st

8:30-11:30	Rooms available for specific interviews/meetings

ORAL COMMUNICATIONS

ENERCA 3: EUROPEAN REFERENCE NETWORK OF EXPERT CENTERS IN RARE ANAEMIAS

JL Vives Corrons and M del Mar Mañu Pereira (on behalf of ENERCA consortium)

Red Cell Pathology Unit. Hospital Clínic i Provincial. University of Barcelona, Spain; enerca@enerca.org

Background. ENERCA "European network for Rare and Congenital Anaemias" is co-funded by the European Commission (Public Health and Consumer Protection Directorate). Its website www.enerca.org is functional since 2001. The purpose of ENERCA is to improve the quality of life of patients with rare anaemia (RA) by increasing the efficacy of diagnosis, treatment and follow up. *Objective.* The main objective of ENERCA 3 is the establishment of a European Reference Network (ERN) of Expert Centres (EC) in Rare Anaemias (RA). The ERN for RA will serve as a platform for the provision of high quality information and services to health professionals, patients and other stakeholders such as health authorities and pharmaceutical industry. *Methods.* The partners involved in the Project are 48 in total: 24 Associated and 24 Collaborating, covering the vast majority of Member States (MS). Most of the partners have been working together since 2002, and all are well known and recognized experts in their respective field. General methodology is designed on the basis of three transversal Work packages (WPs): WP1 "Networking of expert centres"; WP2 "Quality of patient care" and WP3 "Education and training" and three specific WP devoted to the public health issues and management of patients with RA: WP4 "Sickle Cell Disorders"; WP5: "Thalassaemia"; and WP6 "Very rare Anaemias". Three additional WP have been also included for Project management: WP7 "Evaluation", WP8 "Dissemination" and WP9 "Coordination". The methods are mainly focused on the establishment of the consensus criteria necessary to become an Expert Centre in the ERN for RA, the analysis of the legal framework existing between MS for patients and blood samples referral with the aim of overcome the administrative barriers created by the different national rules and laws, the establishment of close links between experts in order to gather epidemiological data and create a Epidemiological European Registry for patients with Rare Anaemias, elaboration of standardized guidelines for clinical practice in RA, and the development of educational and training activities for improving the knowledge on RA. Continuous medical education will be assured by the celebration of courses, workshops and symposiums on RA. Moreover, continuous e-learning and educational material will be periodically launched for the dissemination of knowledge in RA among patients and patient's associations. *Results.* Project outcomes will include a) the consolidation of the European Reference Network of Expert Centres in RA, b) the promotion of the harmonization of diagnostic procedures by preparation of a comprehensive catalogue of External Quality Assessment Schemes (EQAS) in RA, c) the improvement of clinical care of patients with RA by preparation of standardized guidelines for diagnosis and treatment, d) to facilitate comparable epidemiological data and the better knowledge of RA situation in and between MS by establishment of a Epidemiological Registry for RA en Europe and e) the increase of knowledge and awareness on RA among health professionals, patients patient's associations and public in general, by the preparation of training and educational material distributed by printing (in different languages) and/or by the ENERCA Web site. *Conclusions.* The achievement of the Project's objectives and outcomes will contribute to the improvement of health and quality of life of patients with RA by increasing the efficacy of patient's diagnosis, treatment and follow up.

SESSION I: ARTERIOVENOUS MALFORMATIONS AND ANIMAL MODELS. ANGIOGENESIS AND VASCULAR DEVELOPMENT

NOTCH SIGNALING DURING VASCULAR DEVELOPMENT

T Gridley

The Jackson Laboratory, Bar Harbor, Maine, USA

The Notch signaling pathway is an evolutionarily conserved, intercellular signaling mechanism. Mutations in Notch pathway components disrupt embryonic development in diverse organisms and cause inherited disease syndromes and cancers in humans. We have been performing a comprehensive genetic analysis of the requirements for Notch pathway components in mice, as well as developing mouse models of inherited disease syndromes caused by mutations of Notch pathway ligands and receptors. The Notch pathway is critically important for vascular development and physiology in vertebrates. Notch signaling is required for regulation of artery/vein differentiation in endothelial and vascular smooth muscle cells, regulation of blood vessel sprouting and branching during both normal development and tumor angiogenesis by controlling differentiation of endothelial tip cells, and the differentiation and physiological responses of vascular smooth muscle cells. For example, mouse embryos heterozygous for a targeted mutation in the gene encoding the DLL4 ligand exhibit haploinsufficient lethality due to vascular defects. This haploinsufficient lethality is dependent on genetic background, and we have been studying the nature of these genetic background-dependent defects. We have also been studying the multiple roles played by the JAG1 ligand during blood vessel and cardiovascular development, including its roles in both the endothelial and vascular smooth muscle cell lineages. Our current work on analysis of the functional roles of the Notch pathway during blood vessel and cardiovascular development will be described.

B11 CORRELATION OF HHT TYPE AND CHARACTERISTICS OF PULMONARY AVMS BY CT

J Carlisle, J McDonald, P Bayrak-Toydemir, K Whitehead

University of Utah, USA

It has been reported that pulmonary AVMs are more common in individuals with HHT1 than HHT2 (Bayrak-Toydemir, 2006; Letteboer, 2006). It has also been suggested that symptomatic PAVMs are more frequent in HHT1 than HHT2 (Sabba, 2007; Lesca, 2007). However, the natural history and morphology of PAVM in HHT1 versus HHT2 is largely unknown. Identifying correlations between genotype and clinical findings related to pulmonary AVMs may aid in clinical management of these disorders as well as provide clues regarding the pathogenesis of each. Chest CT images on 115 HHT patients (52 ACVRL1 and 63 ENG) diagnosed with pulmonary AVM by CT, or with evidence of a pulmonary shunt by contrast echocardiography, were reviewed for size, location, and structure of individual AVMs as well as overall number. Preliminary analysis indicates the following: In patients with ENG vs ACVRL1 mutations, findings of PAVM by CT were *definite* in 63% vs 32%, *equivocal* in 13% vs 12% and *absent* in 25% vs 56% respectively. In ENG vs ACVRL1 patients PAVM were more likely to be bilateral (55% vs 10%), more than 1-2 in number (53% vs 8%), and have larger pedicle diameter (average 3mm vs 1.3mm). Definite PAVMs had multiple feeders in 15% of ENG vs. 22% of ACVRL1 patients. PAVM were saccular/lobular in 78% vs 88% as opposed to "reticular or lace like" in 22% vs 12%. There appear to be distinct differences between the number, size and possibly characteristics of PAVMs in patients with HHT1 vs HHT2. Detailed findings will be presented.

B14 CELLULAR CHANGES DURING FORMATION OF ARTERIOVENOUS MALFORMATIONS IN A MOUSE MODEL OF HHT1

M Mahmoud, K Allinson, ZH Zhai, R Oakenfull, M Fruttiger[1] and HM Arthur

Institute of Human Genetics, Newcastle University, UK; [1]Institute of Ophthalmology, University College London, UK

Background. HHT1 patients carry mutations in the Endoglin gene. We have developed a reproducible mouse model of HHT1 in order to investigate the aberrant molecular and cellular events that occur in this disease.The endoglin gene is efficiently inactivated at a time of choice by tamoxifen treatment of mice carrying floxed endoglin and VEcadherin-Cre-ERT2 alleles. We have investigated the consequences of endoglin depletion in adult quiescent blood vessels as well as during angiogenesis. *Methods*. A local angiogenic stimulus was applied to adult mice using a subdermal matrigel implant and vascular responses were examined local to, and distant from, the implant. We also examined angiogenesis in the neonatal retina, which has well characterised stages of physiological angiogenesis in a two dimensional plane. *Results.* Endoglin deficiency leads to reduced neovascularisation of the matrigel plug. In addition; significant local venous enlargement occurs close to, but not distant from, the matrigel, a response that is not seen in control mice. The venous enlargement involves a large increase in cellularity that cannot be explained by vasodilation alone. In the neonatal retina, endoglin deficiency leads to arteriovenous malformations (AVMs). Abnormally large calibre interconnecting vessels in the AVM exhibit increased cellularity and develop venous identity. At the retinal periphery there is delayed progression of the capillary plexus consistent with the angiogenesis defects previously observed. *Conclusion*. An angiogenic stimulus is required for vascular malformations to occur and a dominant feature is disorganised endothelial cell proliferation. We are now investigating anomalous cell signalling events that may be responsible.

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B19
REPETITIVE MECHANICAL STRESS ON SKIN OF HHT MODEL MICE INDUCES TORTUOUS BLOOD VESSELS

Y Yonenaga, R Suzuki, F Lan, T Seki

Medical College of Georgia, Augusta, GA, USA

Pathogenesis of hereditary hemorrhagic telangiectasia (HHT) has not been fully elucidated. In HHT patients, only select blood vessels develop telangiectases, although all vasculature has a genetic mutation. Therefore, it has been proposed that there are genetic, environmental, and/or physiological stimuli, so-called "second-hits," which initiate development of the lesions. Several candidates for such stimuli have been proposed including an additional genetic mutation in the remaining healthy copy of the gene, repetitive mechanical stress, hypoxia, ultraviolet (UV) ray exposure, local inflammation, and infection. In this study, we utilized a set of magnets to repeatedly compress skin of HHT model mice, *Alk1(+/lacZ)*, and observed whether this repetitive mechanical stress provokes telangiectases. One month of repetitive compression caused a significantly higher number of new blood vessels in the *Alk1(+/lacZ)* mice than wild type littermates. Black ink perfusion revealed that the new vessels in the *Alk1(+/lacZ)* were tortuous and irregular in diameter. Histologically, these new blood vessels showed no obvious difference in their structure compared to the wild type and had proper smooth muscle cell lining. The lacZ staining showed no positive staining in the skin, indicating that *Alk1* expression is not induced in these blood vessels. This magnet compression model showed that the repetitive mechanical stress induces defective blood vessels in HHT mouse skin. More frequent or extended stress may cause telangiectasis in this model.

B22
ANGIOGENIC STIMULI ARE REQUIRED FOR DEVELOPMENT OF DE NOVO ARTERIOVENOUS MALFORMATIONS IN ALK1-DEFICIENT ADULT MICE

SO Park,[1] M Wankhede,[2] E Choi, YJ Lee,[1] B Sorg,[2] SP Oh[1]

[1]Department of Physiology and Functional Genomics, College of Medicine, University of Florida, Gainesville, FL; [2]Department of Biomedical Engineering, College of Engineering, University of Florida, Gainesville, FL, USA

Hereditary hemorrhagic telangiectasia (HHT) is a vascular dysplasia, characterized by recurrent nosebleeds, mucocutaneous telangiectasias, and arteriovenous malformations (AVMs) in the brain, lung, liver and gastrointestinal tract. While reduced expression of either Endoglin (ENG) or Activin receptor-like kinase 1 (ALK1) has shown to be associated with HHT, the precise pathogenetic mechanisms underlying HHT remain elusive. It remains unknown why selective blood vessels prone to develop vascular lesions. It is also unclear whether AVMs form only during development or can form *de novo* in adult stages. We show here that mice with ALK1 deficiency in vascular endothelial cells develop vascular malformations in the brain, lung, and small intestines. When Alk1 was deleted in adult mice by an inducible cre line (Alk1-iKO), the mutant mice die within 2 weeks with severe hemorrhages and AVMs in the lungs and gastrointestinal tract. Subdermal blood vessels of the Alk1-iKO mice appeared to be normal. However, when skin wound was inflicted in the Alk1-iKO mice, AVMs were developed in the subdermal vessels surrounding the wound. This result indicated that ALK1-deficiency and angiogenic stimuli are two crucial elements necessary and sufficient for development of *de novo* AVMs in adult mice. Using skin fold window chamber model with intravital imaging system, we could monitor *de novo* AVM formation in these mutant mice. Arterial blood flow through AV fistulas creates turbulent flow at the receiving veins. Such abnormal hemodynamic conditions are correlated with dilatation and tortuosity of veins in the AVM lesions. These novel animal models provide novel insights on HHT pathogenesis.

B27
ALK1 REGULATES BLOOD VESSEL CALIBER IN RESPONSE TO FLOW

PA Corti, SA Young, DW Laux, BL Roman

Department of Biological Sciences, University of Pittsburgh, OH, USA

To understand the mechanism underlying development of telangiectases and arteriovenous malformations in HHT patients, we are studying vascular development in the zebrafish *alk1* mutant, *violet beauregarde* (*vbg*). Previously, we demonstrated that *vbg* mutant embryos develop enlarged cranial arteries that aberrantly connect to neighboring veins, forming lethal arteriovenous shunts. Confocal imaging demonstrates that these shunts are actually vein-derived angiogenic sprouts that contribute to cranial artery development. In wild type embryos, these connections are transient, whereas in *vbg* embryos, one of these connections fails to regress. Detailed analysis of ontogeny of this lesion demonstrates that it initiates around 32 hours post-fertilization, manifesting as an increase in caliber of and cell number within *alk1*-expressing arteries. Further increases in arterial caliber and cell number, as well as arteriovenous shunts, develop as heartbeat strengthens and blood flow increases. Interestingly, evidence from embryos that lack heartbeat suggests that later defects, including arteriovenous shunts, are not genetically programmed, but represent an adaptive response to increased blood flow. Blood flow plays a critical role not only in manifestation of the *vbg* phenotype, but also in regulation of *alk1* expression: in the absence of blood flow, *alk1* is not expressed. We have identified several flow-responsive genes that are dysregulated in *vbg* embryos, suggesting that Alk1 might be important in flow-induced signaling. These results suggest that blood flow induces *alk1*, which is necessary to stabilize arterial caliber. In the absence of *alk1*, arterial caliber increases, triggering retention of normally transient arteriovenous connections to accommodate increased flow.

B7
THE ANTIOXIDANT TEMPOL PREVENTS ONSET OF PULMONARY ARTERIAL HYPERTENSION IN ENDOGLIN AND ALK1 HETEROZYGOUS MICE

M Jerkic,[1,2,3] MG Kabir,[2] A Davis,[1] J Leen,[1] B McIntyre,[4] N Husain,[1] J Belik,[4,5] M Husain,[2,6] M Toporsian,[1,2,7] M Letarte[1,2,3]

[1]Molecular structure and function Program, Hospital for Sick Children, Toronto, [2]Heart and Stroke Richard Lewar Center of Excellence, University of Toronto, [3]Immunology Department, University of Toronto, [4]Physiology and Experimental Medicine Program, Hospital for Sick Children, Toronto, [5]Departments of Pediatrics, University of Toronto, [6]Toronto General Hospital Research Institute, Toronto, [7]Beth Israel Deaconess Medical Center, Boston, MA, USA

As mutations in the *ALK1* gene have been reported in patients presenting with pulmonary arterial hypertension (PAH), we examined *Alk1* heterozygous (*Alk1*$^{+/-}$) C57Bl/6 mice for signs of PAH. The right ventricular (RV) systolic pressure (RVSP) measured using a Millar Mikro-tip transducer was found to be significantly elevated in 8-12 week-old mice compared to littermate controls. Other signs of PAH included RV hypertrophy, increased muscularization and outward remodeling of small peripheral pulmonary arterioles, as well as reduced vascular density. Signs of PAH were also observed in *Endoglin* heterozygous (*Eng*$^{+/-}$) mice. Levels of reactive oxygen species (ROS) in lung tissue of both *Eng* and *Alk1* heterozygous mice were higher than in control mice, in agreement with our eNOS uncoupling model. We therefore tested if administration of antioxidant may prevent the appearance of PAH in both *Eng*$^{+/-}$ and *Alk1*$^{+/-}$ mice. 3-week old mice, which show a normal vasculature, were treated with Tempol (1mM) in the drinking water for 6 weeks. This treatment prevented the rise in RVSP, the muscularization of small peripheral pulmonary arterioles and the reduction in vascular density observed in untreated *Eng*$^{+/-}$ and *Alk1*$^{+/-}$ mice. Moreover, Tempol prevented the RV hypertrophy present in untreated *Alk1*$^{+/-}$ mice. Our results strongly suggest that ROS play an important role in the pathogenesis of PAH, as observed in our mouse models of HHT, and that anti-oxidant treatment can alleviate onset of disease and may be of benefit to patients.

SESSION II: GENETICS AND GENOTYPE/PHENOTYPE IN HHT

C12
INFLUENCE OF HHT STATUS ON RADIOLOGICAL ASPECT OF PULMONARY ARTERIO-VENOUS MALFORMATIONS

MF Carette,[1,3,5] F Coulet,[4,5] A Lavolé,[2,5] B Monod,[1,5] J Cadrane[1,2,3,5] A Khalil[1,5]

[1]Departments, of Interventional Radiology, and [2]Pneumology, Tenon hospital; [3]Pierre and Marie Curie University, [4]Molecular Genetic department, Pitié Salpêtrière hospital; [5]Competent Center for HHT in Ile de France, Paris, France

Objective: To compare the radiological findings of pulmonary arteriovenous malformations (PAVMs) in hereditary hemorrhagic telangiectasia (HHT) patients and non HHT patients. Materials and Methods: Fifty seven consecutive patients with PAVMs identified from a prospective register (March 1993 to December 2009) including all patients referred for PAVMs' vaso-occlusion or evaluated for HHT in Tenon hospital, a recognized Competent Center for HHT in Paris (France), were included in this study. HHT were selected on Curacao criteria. We analyzed the distribution and the architecture of PAVMs (431) according to findings at multidetector or helical monodetector CT-scan or pulmonary angiography. Result: Genetics, age, gender, and PAVM number of 38 HHT patients and 19 non-HHT patients (11 with negative research for mutation) are reported in the Table 1.

Table 1. Genetics, number of patients, gender, age and number of PAVMs in HHT patients and non-HHT patients.

Group	*Genetic mutation*	*Number (sex)*	*Age*	*PAVM number (mean)*
HHT patients				
		38 (23F, 15M)	14.5-72 (41,8yrs)	396 (10.4)*
	Endoglin	21 (11F, 10M)	14.5-62 (37.25 yrs)	310 (14.7)
	ALK1	4 (3F, 1M)	27-71 (46.4 yrs)	6 (1.5)
	SMAD4	2 (1F, 1M)	20 and 32 yrs	19 (9.5)
	Not explored or in attempt	7 (5F, 2M)	14.5-72 (51.6 yrs)	37 (5.9)
	Negative research	4 (3F, 1M)	19.5-65.5(50 yrs)	24 (6)
Non-HHT patients				
		19 (13F, 6M)	14.5-78 (45.3 yrs)	35 (1.24)*

**the difference is very statistically significant for the number of PAVM reporting to each patient (p=0.0062).*

Small and tiny PAVMs are more frequent in HHT patients than in non-HHT patients (278/396 versus 10/35: $p<0.001$). Telangiectasis and diffuse disease (8 patients) were only visible in HHT patients. Isolated complex PAVM are more frequent in non-HHT patients (7/9

patients versus 3/21 patients: p=0.0017). In non-HHT patients, 2 patients with hepato-pulmonary syndrome with 14 PAVMs create 3 large flat fistulas abutting pleura; Latero-lateral fistulas (n=3) were only seen in non-HHT patients including one patient having history of gunshot. Conclusion: Telangiectasis, diffuse PAVMs, very small and numerous PAVMs are more significantly seen in HHT patients. At the opposite, unique complex PAVMs are more significantly related to non-HHT patients.

C23
PREVALENCE OF PULMONARY RIGHT-TO-LEFT SHUNT IN HEREDITARY HAEMORRHAGIC TELANGIECTASIA: ASSESSMENT OF DIFFERENCES BETWEEN HHT 1 AND 2

WFM van Gent,[1] MC Post,[1] RJ Snijder,[2]
CJJ Westermann,[2] HWM Plokker,[1] JH Mager[2]

Department of [1]Cardiology and [2]Pulmonology St. Antonius Hospital, Nieuwegein, The Netherlands

Rationale. Transthoracic contrast echocardiography (TTCE) can effectively detect pulmonary right-to-left shunting (RLS) and might be used as a screening method for pulmonary arteriovenous malformations (PAVMs) in patients with hereditary hemorrhagic telangiectasia (HHT). *Objectives*. To study TTCE results in HHT subtypes (HHT1 and HHT2) and a HHT negative control group. *Methods*. In 320 persons, referred for possible HHT as first degree family members of index HHT patients, a clinical screening program including TTCE with pulmonary RLS grading was performed. All persons were offered genetic analysis. *Results*. Genetic analysis was performed in 234 persons, and those were included in the study. HHT1 was diagnosed in 83 patients (58% female; mean age 41±15 years) and HHT2 in 91 patients (50% female; mean age 47±13 years). In patients with HHT1 and HHT2, TTCE was positive for the presence of a pulmonary shunt in 70 (84%) and 32 (35%) patients, respectively. TTCE shunt grades 1, 2 and 3 were present in 10 (14%), 21 (30%) and 39 (56%) patients with HHT1 and in 20 (63%), 5 (16%) and 7 (21%) patients with HHT2 and positive TTCE studies, respectively (p<0.0001). TTCE was positive for the presence of a pulmonary RLS in 4 (7%) persons with negative genetic test results. *Conclusion*. A pulmonary shunt on TTCE is more prevalent and tends to be larger in patients with HHT1, as compared to HHT2. TTCE is also positive in a small fraction of a control group of patients without HHT.

B28
BEYOND GENOTYPE-PHENOTYPE CORRELATIONS IN HEREDITARY HAEMORRHAGIC TELANGIECTASIA

CL Shovlin,[1] E Kulinskaya[2]

[1]NHLI Cardiovascular Sciences and [2]Statistical Advisory Service, Imperial College, London, UK

Introduction. Locus heterogeneity has provided important genotype-phenotype correlations into relative frequencies of AVM distribution, and other HHT complications. The most striking HHT heterogeneity however, is the variation between different members of the same family who have an identical HHT mutation. *Methods.* To better understand the phenotypic diversity between HHT-affected relatives, a generic model was developed whereby inherited gene mutations raise the predisposition of a phenotype towards, but not necessarily to the measurable disease threshold [Shovlin, Haslett and Lamb 1999]. This concept allowed a focus on non-genetic factors that modified clinical disease presentation, and was translated to two sequential prospective HHT series. Power calculations (necessitating >300 HHT; >200 PAVM patients) and referral rates determined the series lengths of six (1999-2005) and three (2005-2008) years respectively. *Results.* In the first series, time-to-event analysis (Anderson-Gill model) was used to investigate effects of 30 time-dependent patient variables, as well as catheter-measured pulmonary artery pressure and plasma FVIII on the time to binary events of venous thromboembolic disease; paradoxical embolic stroke, and brain abscess. Primary data are reported for all endpoints [Shovlin et al Thromb Haemost 07; Thorax 08; ERJ 08]. The power of the series was shown by the unanticipated association of low pulmonary artery pressure and stroke risk [p=6.2x10^{-5}]. Analysis of the second series in which novel biomarkers for clinical endpoints are allowing serial interrogation of environmental risk modifiers, are ongoing. *Conclusions*. Precision-phenotyping of HHT cohorts, utilising within-family variation is identifying biomarkers that assist in individualised risk predictions, and are potential fruitful avenues for novel non-genetic therapeutic modalities.

B3
FAMILY MEMBERS OF PATIENTS WITH HEREDITARY HEMORRHAGIC TELANGIECTASIA: HHT CENTER PARIS EXPERIENCE IN 217 RELATIVES FROM 80 FAMILIES WITH GENOTYPING

J Roume,[1] F Coulet,[3] I Bourgault-Villada,[1] JH Blondel,[1]
S Blivet,[1] JP Pelage,[1] A Ozanne,[2] C Fagnou,[1] G Lesur,[1]
P Lasjaunias,[2] B Raffestin,[1] T Chinet,[1] F Soubrier,[3]
P Lacombe[1]

HHT Center Paris, AP-HP; [1]CHU Ambroise Paré, [2]CHU Kremlin Bicêtre, [3]CHU Pitié Salpétrière, Paris, France

Objective. To assess the clinical and genetic characteristics of family members of patients with hereditary hemorrhagic telangiectasia (HHT). *Setting.* HHT Center in Paris. *Participants.* 217 members family of 80 genotyping HHT patients screened from January 2004, through December 2008. *Interventions.* volunteers previously well informed directly by means of the educational course of the proband about the intrafamilial variability of symptoms and potential severe visceral complications; screened one half a day by mean of a stepped multidisciplinary clinical screening protocol based upon Curaçao criteria and genetic screening systematically proposed. *Main outcome measures.* Age, sex, prevalence of cutaneo mucous telangiectases, visceral Arterio Venous Malformations (AVMs), genetic characteristics and proposed therapeutics. *Results.* 123 relatives were found with manifestations of HHT. Below twenty years old: 38%, between twenty and forty: 27%, over forty: 35%. Sex Ratio: 0.78. All four Curaçao criteria were present for 56 cases, three criteria for 21 cases, two criteria for 12 cases

and 34 cases (27,6%) were asymptomatic with only the familial criteria and found by mean of the genetic focused screening .79 were relatives of the 47 HHT1 probands. 21of them were referred for embolization of large pulmonary arterio venous malformations (PAVMs); 44 were of the 33 HHT2 probands, one of them, proposed for cerebral AVMs embolization. .Antibioprophylaxy.was proposed for 40 patients with small PAVMs. *Conclusions.* More half of HHT members familly present visceral AVMs and can to life-threatening events. They should be encouraged to engage in a screening program, from earliest age,since the prevalence of potentially serious localizations is higher than previously thought.

B37
PULMONARY ARTERIOVENOUS SHUNTING IS MORE SEVERE IN HHT2

K Whitehead, J McDonald, J Carlisle

University of Utah HHT Center, USA

Numerous differences between HHT1 and HHT2 have been described. Several studies using CT scanning have identified more severe pulmonary AVMs in HHT1. Saline contrast echocardiography has been used as a screening modality for PAVM. The amount of contrast in the left ventricle correlates with the severity of PAVM. We hypothesize that HHT1 will have more severe shunt physiology. We defined shunt severity on a five point scale, using refinements of a previously described severity scale (5= most severe). All patients with known genotype and a reported positive contrast echo were re-evaluated on this semi-quantitative scale by a reviewer blinded to genotype and CT scan results. The severity of shunt by genotype was compared by two-tailed T-test. In contrast to previous reports using only CT scanning to describe PAVM, we found that among patients with a positive screening echo study, HHT2 patients had a more severe shunt score than HHT1. The mean score was 2.8 in HHT2 and 2.1 in HHT1 (p<0.03). In HHT2 9/29 (31%) patients had a shunt severity score in the most severe 2 categories, whereas only 3/23 (13%) HHT1 patients were similar. Conversely, 13/29 (45%) HHT2 patients had a shunt severity score in the least severe two categories, whereas 17/23 (74%) HHT1 patients were similar. In contrast to studies which have looked only at imaging characteristics of PAVM, patients with HHT2 have more severe shunts by contrast echocardiography suggesting more frequent diffuse small lesions not detected by CT imaging.

B9
IN SILICO EVALUATION OF SPLICE-SITE MUTATIONS OF ENG AND ACVRL1 GENES

C Olivieri,[1] L Boeri,[1] A Colombo,[2] E Matti,[2] F Chu,[2] M Perego,[3] A Minelli,[1] C Canzonieri,[1,3] F Ornati[1] and on behalf of the HHT-NET (C Danesino, E Buscarini, G Manfredi, P Gazzaniga, L Reduzzi, F Pagella, M Grosso, G Pongiglione, E Boccardi)

[1]Medical Genetics -University of Pavia, Pavia, Italy; [2]ENT Unit - IRCCS Policlinico San Matteo, Pavia, Italy; [3]GI Endoscopy Unit, IRCCS Policlinico San Matteo, Pavia, Italy

Splice Site Mutations alter or abolish the specific sequence denoting the site at which the splicing of an intron takes place and is often difficult to determine, by sequence only, if the change observed is pathogenetic. It is difficult to have proper HHT endothelial cells for expression studies. We have studied 46 Splice Site mutations reported in the HHT Mutation Database (*www.hhtmutation.org*), and added 2 new ones recently found by our group at 5' splice-site. The Splice Site Mutations found were 35 in the *ENG* gene and 11 in the *ACVRL1* gene, respectively 9,8% of all *ENG* mutations and 3,7% of all *ACVRL1* mutations collected in the HHT Mutation Database. All the mutations were analysed through 3 informatic tools to predict the strength and recognition of splice site (Splice-Site Analyzer Tool; Splice Site Score Calculation; MaxEntScan: score5ss for human 5' splice sites and MaxEntScan: score3ss for human 3' splice sites). The first method gives data about Splice-Site Score, number of hydrogen bonds between U1 snRNP and the 5' splice-site, and the ΔG of U1/5' splice site. The second one calculates MaxEntScan scoresplice. The last software provides Maxent, MDD, MM and WMM scores. The results obtained show that Splice-Site Score is reduced of about 22% in 5' splice-site at p.+1 and +2. A higher loss of strenght of splice-site is observed when in the same positions an insertion is found. As far as 3' splice-site is concerned Splice-Site Score is reduced about 20 % in p.-1 and -2.

B15
ROLE OF NONCODING REGION MUTATIONS OF ACVRL1 AND ENG IN THE PATHOGENESIS OF HEREDITARY HEMORRHAGIC TELANGIECTASIA

K Damjanovich,[1] H Escobar,[2] J McDonald,[1,3] F Gedge,[1] L.-S Chou,[1] P Bayrak-Toydemir[1,4]

[1]ARUP Institute for Clinical and Experimental Pathology, [2]DNA Sequencing and Genomics Core Facility, University of Utah, [3]Department of Radiology, University of Utah, [4]Department of Pathology, University of Utah, USA

Hereditary Hemorrhagic Telangiectasia (HHT) is known to be caused by mutations in activin A receptor type II-like 1 (*ACVRL1*) and endoglin (*ENG*) genes. However, approximately 20% of the HHT patients do not have mutations in the coding regions of either gene that can be detected by sequencing or deletion/duplication testing. We hypothesized that sequence alterations in noncoding regions of the HHT genes could have a role in disease pathogenesis. We selected 16 unrelated, clinically affected HHT patients in whom we were unable to find the causative mutations in the coding regions of *ACVRL1* and *ENG*. Family members of 3 of these 16 patients were available for linkage studies. Two of these families suggest linkage to *ACVRL1*, and the other family *ENG* locus. We sequenced the regulatory regions of the 5' and 3' untranslated regions (*UTRs*), and introns, of both genes in all 16 patients. We found 48 variants in *ACVRL1* and 52 variants in *ENG* which have not been previously reported as polymorphisms. For every unreported sequence variant found, we sequenced the available family members to determine the segregation with the disease. We analyzed the effects of these variants on evolutionary

conserved regions and transcription factor binding sites and splice site enhancers or repressors through a bioinformatics approach. In this presentation, we will present our findings and discuss the disease causing potential of these variants.

B17
MISSENSE AND INTRONIC VARIANTS IN ENG AND ALK1 GENES: IDENTIFICATION OF PATHOGENIC MUTATIONS MAY BE DIFFICULT

S Giraud,[1] S Dupuis-Girod,[2] G Lesca,[1] C Gressier,[1] C Chretien,[1] O Boute,[3] P Kaminsky,[4] B Leheup,[5] H Plauchu,[2] A Calender[1]

[1]Hospices Civils de Lyon, Hôpital E. Herriot, Service de Génétique moléculaire et clinique, Lyon; [2]Hospices Civils de Lyon, Hôpital de l'Hôtel Dieu, Service de Génétique et centre de référence pour la maladie de Rendu-Osler, Lyon; [3]Centre Hospitalier Régional Universitaire de Lille, Hôpital Jeanne de Flandres, Service de Génétique clinique, Lille; [4]Centre Hospitalier Universitaire de Nancy, Hôpitaux de Brabois, Service de Médecine interne, Vandoeuvre; [5]Centre Hospitalier Universitaire de Nancy, Hôpitaux de Brabois, Service de Médecine infantile et de Génétique clinique, Vandoeuvre, France

Introduction. Genetic analysis has become essential in HHT patients diagnosis and it is primordial to know the familial causal mutation. It is easy to predict truncating or splicing mutations are deleterious; it is more difficult for missense or intronic mutations located outside consensus splicing sites. We reported here troubles in interpretation of molecular diagnosis for carriers of double mutations. *Methods.* We analysed HHT index cases by dPHLC and sequencing of *ENG* and *ALK1*. When we identified a missense or intronic variant not reported in HHT mutation database we completed analysis by segregation study in relatives when available. *Results*. We detected in 3 patients the association of two different unknown variants, in 4 patients the association of two different deleterious mutations and in 12 patients the association of one mutation and one unknown variant. Segregation study could be done in 9 families: it excluded causal effects for 4 unknown variants and confirmed one *ALK1* intronic variant was a neomutation. Three index cases carried one *ENG* mutation reported as deleterious in HHT mutation database (V504M and S615L) and another variant or mutation, but in their families ENG mutation did not segregate with the phenotype. *Conclusion.* Genetic analysis in HHT index cases should explore the entire coding sequence of *ENG* and *ALK1* systematically. For unknown variants, segregation study must be performed for correct biological interpretation and results noticed in HHT mutation database. Nevertheless it may be difficult to conclude about the significance of one variant and functional analysis should be useful.

SESSION III: CELLULAR AND MOLECULAR INVOLVEMENT IN HEREDITARY HEMORRHAGIC TELANGIECTASIA AND RELATED PATHOLOGIES

B12
IMPAIRED RECRUITMENT OF HHT-1 MONONUCLEAR CELLS TO THE ISCHEMIC HEART IS DUE TO AN ALTERED CXCR4/CD26 BALANCE

S Post, A Smits, A vdn Broek, J Sluijter, I Hoefer, B Janssen, R Snijder, J Mager, G Pasterkamp, C Mummery, P Doevendans, M-J Goumans

Leiden University Medical Center, The Netherlands

Aim. Mononuclear cells (MNCs) from patients with hereditary hemorrhagic telangiectasia type 1 (HHT1), a genetic disorder caused by mutations in endoglin, show a reduced ability to home to infarcted mouse myocardium. Stromal-cell derived factor-1α (SDF-1α) and its receptor CXCR4 are crucial for homing and negatively influenced by CD26. The aim of this study was to gain insight into the impaired homing of HHT1-MNCs. *Methods*. CXCR4 and CD26 expression on MNCs was determined by flow cytometry. Transwell migration to SDF-1α was used to analyze in vitro migration. Experimentally induced myocardial infarction in mice, followed by tail vein injection of MNCs, was used to study homing in vivo. *Results*. Although HHT1-MNCs express elevated levels of CXCR4, this was counterbalanced by high levels of CD26, resulting in decreased migration towards a SDF-1α gradient in vitro. Their migration was enhanced by inhibiting CD26 with Diprotin A. Furthermore, while MNCs from healthy controls responded to TGFβ stimulation by increasing CXCR4 and lowering CD26 expression levels, HHT1-MNCs did not react as efficiently. In particular, CD26 expression remained high. Interestingly, homing of HHT1-MNCs to the infarcted region of the murine heart was restored by pre-incubating the HHT1-MNCs with Diprotin A before injection into the tail vein. Conclusions We show that impaired homing of HHT1-MNCs is caused by an impaired ability of the cells to respond to SDF-1α. Our results suggest that modulating CD26 levels using inhibitors like Diprotin A can restore homing in cases where increased CD26 contributes to the underlying pathological mechanism.

B16
AGE-DEPENDENT CHANGES IN PULMONARY VASCULAR REACTIVITY AND SUPEROXIDE PRODUCTION IN ENDOGLIN AND ALK1 HETEROZYGOUS MICE

M Jerkic,[1,2] B McIntyre,[3] J Pan,[3] J Leen,[1] D Li,[3] M Toporsian,[1,2,4] J Belik,[3,5] M Letarte[1,2]

[1]Molecular Structure and Function Program, Hospital for Sick Children, Toronto; [2]Heart and Stroke Richard Lewar Center of Excellence and Immunology Department, University of Toronto; [3]Physiology and Experimental Medicine Program, Hospital for Sick

Children, Toronto; [4]Beth Israel Deaconess Medical Center, Boston; [5]Departments of Pediatrics, University of Toronto, Canada

Our previous studies suggest that HHT is associated with impaired vascular tone due to higher production of endothelial nitric oxide synthase (eNOS)-derived reactive oxygen species (ROS), which may lead to abnormal vascular remodeling in the systemic circulation. However little is known about potential changes in the pulmonary vasculature and their time-course. Newborn (4-7 day-old) and adult (8-12 week old) *Endoglin* (*Eng*) and *Alk1* heterozygous mice were studied with respect to pulmonary vascular reactivity and the contribution of ROS to this response. Intrapulmonary arteries from newborn and adult mice were pre-contracted, and relaxation to acetylcholine (Ach) was measured. While newborn $Eng^{+/-}$ and $Alk1^{+/-}$ vessels showed similar contraction and relaxation, the ACh-induced vasorelaxation was significantly higher in adult $Eng^{+/-}$ and $Alk1^{+/-}$ vessels relative to littermate controls. This vasodilatory response was inhibited to a large degree by L-NAME in both adult and newborn mice suggesting eNOS-dependence. In all groups of newborn mice, no differences in either ROS or H_2O_2 production were observed. However, adult $Eng^{+/-}$ and $Alk1^{+/-}$ lungs showed increased ROS and H_2O_2 generation, relative to controls. We observed no difference in lung NADPH oxidase 2 and 4 expression levels in the lung tissue between adult heterozygous and control mice. The levels of the ROS scavenging superoxide dismutase (SOD) enzymes were also unchanged. eNOS uncoupling was observed in lung tissues of adult but not newborn heterozygous mice. Our data suggest that increased eNOS dependent-ROS production develops with age in the lungs and accounts for the heightened pulmonary vasorelaxation in adult $Eng^{+/-}$ and $Alk1^{+/-}$ mice.

B23
IMMUNOLOGICAL PROFILE IN 42 PATIENTS WITH HHT: ARE THEY IMMUNOCOMPROMISED?

CH Malcus,[1] S Dupuis-Girod,[2] F Poitevin,[1] S Giraud,[3] H Plauchu,[1] F Touraine-Moulin[1]

[1]Hospices Civils de Lyon, Hôpital E. Herriot, Service d'Immunologie, Lyon; [2]Hospices Civils de Lyon, Hôpital de l'Hôtel Dieu, Service de Génétique et centre de référence pour la maladie de Rendu-Osler, Lyon; [3]Hospices Civils de Lyon, Hôpital E. Herriot, Laboratoire de Génétique moléculaire, Lyon, France

Introduction. HHT is associated with a high frequency of bacterial infectious diseases. Few studies argue for an immune dysfunction in HHT that may explain this high rate of infections. To try to clarify this issue, we studied adaptative and innate immunity in HHT patients. *Methods*. 42 HHT Patients (23F, 19M) were prospectively included. *ACVRL1*, *ENG* and *MADH4* gene were mutated in 21, 11, 1 cases respectively. In 9 cases, gene analysis is on going. We analysed serum immunoglobulin levels, lymphocytes, CD3, CD4 and CD8 cells were enumerated by flow cytometry (FC500, Beckman-Coulter) and chemotaxis, phagocytosis and oxidative burst of phagocytic cells were evaluated with Migratest, Phagotest and Burstest (Orpegen) in 36 patients. Results were compared with our laboratory normal values. *Results*. Immunoglobulin serum level mean values were normal but 24% of patients showed an isolated increase of IgA. IgG and/or IgA and/or IgM were elevated in 26% of the patients. 43% were lymphopenic (min-max values: 369/µL - 1152/µL). 45%, 31% and 69% present respectively a decrease of CD3, CD4 and CD8 cells (respectively min-max values: 203/µL - 892/µL, 151/µL - 446/µL, 44/µL - 327/µL). The neutrophils chemotaxis, monocytes and neutrophils phagocytosis and oxidative burst were normal. *Conclusion*. Our study showed a normal humoral and innate immunity but a selective adaptative immune deficiency. However, since these infections are mainly related to innate immunity defect, other associated factors may explain the frequent occurrence of bacterial infections in HHT patients.

B24
A ROLE FOR ENDOGLIN AS A MODULATOR OF TUMOR PROGRESSION

E Pérez-Gómez,[1] G Del Castillo,[1] M Villa-Morales,[2] J Santos,[2] J Fernández-Piqueras,[2] C Gamallo,[3] C Bernabéu,[4] M Quintanilla[1]

[1]Instituto de Investigaciones Biomédicas Alberto Sols, Consejo Superior de Investigaciones Científicas (CSIC)-Universidad Autónoma de Madrid (UAM), Madrid, Spain; [2]Laboratorio de Genética Molecular Humana, Departamento de Biología, UAM, Madrid, Spain; [3]Departamento de Anatomía Patológica, Hospital Universitario de la Princesa, UAM, Madrid, Spain; [4]Centro de Investigaciones Biológicas, CSIC, Madrid, Spain

Our finding that endoglin is expressed both in epidermal basal keratinocytes and in their appendages (hair follicles and sweat glands), led us to study the expression of L- and S-endoglin during the different stages of chemical mouse skin carcinogenesis: benign papilloma, squamous cell carcinoma (SCC), and spindle cell carcinoma (SpCC). While the expression of S-endoglin both in normal epidermis and in tumours is irrelevant, L-endoglin undergoes a proteolitic cleavage (shedding) during the SCC to SpCC progression, resulting in the inactivation of membrane associated endoglin (mEng) and the release of soluble endoglin (sEng) in the stroma. Both the reduction of mEng expression in SCC cells through the use of siRNA, and the expression of L- and S-endoglin in SpCC cells, demonstrate that L-endoglin, but not S-endoglin, attenuates the TGF-β_1/Smad2/3 signalling, and that L-endoglin modulates cellular growth and invasiveness. Loss of mEng in SCC cells activates the TGF-β_1/Smad2/3 signalling, which promotes an epithelial-mesenchymal transition and a progression from SCC to SpCC. Loss of mEng also leads to the inhibition of cellular growth, both *in vitro* and *in vivo*. These observations explain our results obtained after the chemical carcinogenesis treatment in mice heterozygous for endoglin ($Eng^{+/-}$); this endoglin haploinsuficiency led to a reduction in the number of papilloma as compared to control mice ($Eng^{+/+}$), as well as to a dramatic acceleration of malign progression to spindle cell carcinoma.

B25
S-ENDOGLIN UPREGULATION AS A SENESCENCE MARKER OF ENDOTHELIAL CELLS AND ITS ROLE IN VASCULAR PATHOLOGY

FJ Blanco,[1] MT Grande,[2] C Langa,[1] B Oujo,[2] S Velasco,[2] A Rodriguez-Barbero,[2] E Perez-Gomez,[3] M Quintanilla,[3] JM López-Novoa,[2] C Bernabeu[1]

[1]Centro de Investigaciones Biológicas (CSIC) and CIBER de Enfermedades Raras (ISCIII), Madrid, Spain; [2]Instituto Reina Sofía *de Investigación Nefrológica, Departamento de Fisiología y Farmacología, Universidad de Salamanca, and Red de Investigacion Renal, Salamanca, Spain; [3]Instituto de Investigaciones Biomédicas Alberto Sols (CSIC-UAM), Madrid, Spain*

The lifespan ending of endothelial cells (ECs) is a stage termed replicative senescence. At this point, ECs enter in a gene reprogramming that contributes to age-associated cardiovascular disorders, such as atherosclerosis and hypertension. One of the genes differentially expressed by senescent ECs is the short isoform of endoglin (referred as S-endoglin, in counterpart to the mainly expressed long, L-, endoglin). As evidenced by RT-PCR, the S/L ratio of endoglin isoforms was increased during senescence of human ECs *in vitro*, as well as during aging of mice in vascularized tissues. Thus, the effect of S-endoglin protein on the TGF-β receptor complex was studied. As revealed by co-immunoprecipitation assays, S-endoglin was able to interact with both TGF-β type I receptors, ALK5 and ALK1, although the interaction with ALK5 was stronger than with ALK1. S-endoglin conferred a lower proliferation rate to ECs and behaved differently from L-endoglin in relation to TGF-β-responsive reporters with ALK1 or ALK5 specificities, mimicking the behaviour of the endothelial senescence markers Id1 and plasminogen activator inhibitor-1. *In situ* hybridization studies demonstrated the expression of S-endoglin in the endothelium from human arteries and veins. Furthermore, transgenic mice overexpressing S-endoglin in ECs showed hypertension, decreased hypertensive response to NO inhibition, decreased vasodilatory response to TGF-β1 administration, and decreased endothelial nitric oxide synthase expression in lungs and kidneys, supporting the involvement of S-endoglin in the NO-dependent vascular homeostasis. Taken together, these results suggest that S-endoglin is induced during endothelial senescence and may contribute to age-dependent vascular pathology. Studying the molecular mechanisms that regulate the endoglin alternative splicing will provide us a better understanding of the role of this receptor in the physiology of ECs.

B31
ENDOGLIN PROMOTES ENDOTHELIAL TUBULE STABILITY AND SURVIVAL

NY Lee and GC Blobe

Duke University, Durham, NC, USA

Endoglin is a co-receptor for transforming growth factor-β (TGF-β) superfamily signaling vital for proper vascular development, as evidenced by the embryonic lethal phenotype observed in endoglin-null mice, as well as loss-of-function mutations in the human endoglin gene in hereditary hemorrhagic telangiectasisa (HHT1) patients. However, how endoglin participates in vascular remodeling and angiogenesis at the molecular level has remained elusive. Here, we compared the ability of endoglin-expressing (*Endo*$^{+/+}$) and endoglin-null (*Endo*$^{-/-}$) mouse embryonic endothelial cells (MEECs) to form tubules on Matrigel. *Endo*$^{+/+}$ MEECs formed more steady state tubules with a robust branching network (2-3 fold greater number of tubules and branching networks) when compared to *Endo*$^{-/-}$MEECs. Ectopic expression of endoglin in *Endo*$^{-/-}$ MEECs enhanced network formation, supporting an endoglin-specific effect. Interestingly, time-course studies revealed comparable tubule formation between *Endo*$^{+/+}$ and *Endo*$^{-/-}$ MEECs at early time points, suggesting that endoglin primarily functions to maintain tubule stability. Treatment of *Endo*$^{+/+}$ MEECs with TGF-β1 antagonized while BMP-9 accentuated tubule formation in a dose-dependent manner. Neither ligand significantly altered tubule formation in *Endo*$^{-/-}$ MEECs. *Endo*$^{+/+}$ MEECs grown on Matrigel had higher basal Akt activation relative to *Endo*$^{-/-}$ MEECs. In parallel to inhibiting tubule formation in *Endo*$^{+/+}$ MEECs, TGF-β1 inhibited Akt activation and stimulated apoptosis, as demonstrated by increased caspase-3 activation. Taken together, these results suggest a role for endoglin in regulating neo-vasculature stability and cell survival.

B1
REDUCED PLASMA LEVELS OF ANG-2, s-ENG and sFlt1 AS NOVEL BIOMARKERS IN HHT

L Ojeda-Fernandez,[1] L Barrios,[2] A Rodriguez-Barbero,[3] C Bernabéu,[1] LM Botella[1]

[1]Centro de Investigaciones Biológicas, CSIC and Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER). Madrid. [2]Centro Técnico de Informática CSIC. Madrid. [3]Depatamento de Fisiología y Farmacología. Universidad de Salamanca and Red de Investigación Renal, Salamanca, Spain

Hereditary Hemorrhagic Telangiectasia (HHT) or Osler–Weber–Rendu syndrome is normally diagnosed by clinical criteria. Patients with the clinical HHT diagnosis may undergo molecular diagnosis for the mutation origin of the disease, made by PCR and DNA sequencing of *Endoglin*, ACVLR1, and *Smad4*, the known affected genes. The sequencing process, assisted by DHPLC (Denaturing High Pressure liquid Chromatography) or completed by MLPA (Multiplex Ligation-dependent Probe Amplification) is normally a long, and very expensive procedure. Although, the search for HHT biomarkers has been tried, up to date, there is not a reliable biomarker for the disease. We have tried to identify some soluble components differentially expressed in the plasma of HHT patients. For this purpose we have chosen Angiopoietin-2 (Ang-2), downregulated in a microarray analysis of HHT endothelial cells (Fernandez-L *et al.*, 2007), soluble endoglin (sEng) since total amount of ENG is downregulated in HHT endothelial cells (Fernández-L *et al.*, 2007), and VEGF-RI (sFlt1), increased in preeclampsia together with sENG (Venkatesha *et al.*, 2006). The analysis of Ang-2, sEng and sFlt-1, was

carried out by ELISA (R&D Systems). As a result of this analyisis Ang-2, sEng and sFlt1 levels were found significantly reduced in plasma of HHT patients compared to control individuals. We propose that down regulated protein levels of Ang-2, sEng and sFlt1 in plasma represent novel HHT biomarkers that could be useful in the biochemical diagnosis of HHT facilitating the rapid identification of potential HHT patients.

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SESSION IV: CLINICAL MANAGEMENT AND OUTCOMES IN HHT

C53
OUTCOMES OF PREGNANCY IN HEREDITARY HEMORRHAGIC TELANGIECTASIA

EM de Gussem,[1] AY Lausman,[3] AJ Beder,[2] CP Edwards,[2] JJ Mager,[1] ME Faughnan[2]

[1]Department of Respirology, St Antonius Hospital, Netherlands; [2]Department of Medicine and Li Ka Shing Knowledge Institute, St Michael's Hospital, University of Toronto, Canada; [3]Department of Obstetrics & Gynaecology, St Michael's Hospital, University of Toronto, Canada

Objective. To study pregnancy outcomes in women with HHT. *Methods.* Retrospective study of women (18-55 years) from Toronto HHT Database, using telephone questionnaire regarding pregnancy, delivery, epidural anesthesia and fetal outcomes. Women were categorized as non-HHT (0-1criterion) or HHT (≥3 criteria). *Results*. Previous pregnancy was reported in 185/217 (86%) recruited women. Eighty-seven women with HHT and 41 non-HHT women had 245 and 114 pregnancies, respectively. Miscarriages occurred in 21% of pregnancies, with no difference between groups. HHT-related complications included minor hemoptysis during 2 (1.1%) pregnancies, hemothorax during four (2.2%) and right heart failure during one (0.5%), all in women previously unscreened or treated for AVMs. Pre-eclampsia occurred in 6.6 % of pregnancies in HHT women versus 3.7% in non-HHT (p=NS), with no significant difference in rates of other pregnancy complications between groups (36.3% versus 35.4%, p=NS), of delivery complications (3.3% versus 4.9%, p=NS, of post-partum complications (5.5% versus 3.7%, p=NS) or of congenital defects (3.2% versus 4.8%, p=NS). Epidural/spinal anesthesia was performed in 93/184 (50.5%) deliveries in HHT women, without spinal screening and without major complications. There was a trend towards more pre-term delivery in HHT versus non-HHT (13.4% versus 6%, p=0.07). *Conclusions*. Women with HHT have pregnancy, delivery, post-partum and epidural complication rates similar to women without HHT. Major complications from AVMs occurred in 3% of pregnancies, most preventable by pre-pregnancy screening. There was a trend towards more pre-term delivery in women with HHT.

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C58
ESTIMATES OF MATERNAL RISKS OF PREGNANCY FOR WOMEN WITH HEREDITARY HAEMORRHAGIC TELANGIECTASIA (HHT, OSLER-WEBER-RENDU SYNDROME): SUGGESTED APPROACH FOR OBSTETRIC SERVICES

CL Shovlin,[1,2] V Sodhi,[3] A McCarthy,[4] P Lasjaunias,[5] JE Jackson,[6] MN Sheppard[7]

[1]NHLI Cardiovascular Sciences, Imperial College London; [2]Respiratory Medicine and [6]Department of Imaging, Hammersmith Hospital, [3]Anaesthetics and [4]Obstetrics, Queen Charlotte's Hospital, London, UK, [7]Histopathogy, Royal Brompton Hospital, London. [5]Neuroradiologie, Bicêtre Hospital, Kremlin Bicetre, France

Introduction. Pregnancy outcomes are rarely reported in hereditary haemorrhagic telangiectasia. Maternal death due to pulmonary AVM haemorrhage is a recognised complication. Our aim was to estimate rates and types of major complications of HHT in pregnancy, to guide management decisions. *Methods.* With ethical approval, outcomes of 262 pregnancies in 111 women with HHT and pulmonary arteriovenous malformations (PAVMs) were studied. In addition, outcomes of 222 pregnancies in 86 HHT-affected first degree relatives were analysed. *Results*. 1.02% (95% confidence intervals 0.13, 1.92%) resulted in a major PAVM bleed; 1.24% (0.25, 2.23%) in stroke (not all were HHT-related); and 1.00% (0.13, 1.92%) in maternal death. All deaths occurred in women previously considered well. Prior awareness of HHT or PAVM diagnosis was associated with improved survival in women experiencing a life-threatening event (p=0.041, Fisher's exact test). The data for and against screening asymptomatic women during pregnancy for pulmonary, cerebral or spinal AVMs were discussed in detail. *Conclusions.* Most HHT pregnancies proceed normally. Rare major complications, and improved survival outcome following prior recognition, means that in British obstetric terminology, HHT pregnancies should be considered high risk, for greater obstetric medical review than recommended for low risk pregnancies. In the absence of symptoms, recommendations were to defer pulmonary AVM screens, only perform cerebral imaging if warranted by family history, and to consider spinal MRI where the possibility of spinal AVMs would lead obstetric anaesthetists to withhold epidural analgesia.

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C38
MANAGEMENT OF VENOUS THROMBOEMBOLISM IN HEREDITARY HEMORRHAGIC TELANGIECTASIA

D Goodenberger, M Chakinala, D Picus

Washington University HHT Center, St. Louis, Missouri, USA; Dallas Veterans Affairs Medical Center, Dallas, Texas, USA; and University of Texas Southwestern Medical School, Dallas, Texas, USA

Venous thromboembolism has been reported to occur in 6.5% of patients with hereditary hemorrhagic telangiectasia (HHT). This may be a consequence of prothrombotic and antifibrinolytic therapy, recurrent hospitalization, and increased factor 8.[1] Little guidance exists for treatment of these individuals with a vascular bleeding diathesis,[2,3] although experienced individuals regularly discuss individual cases among themselves. We reviewed the records of 346 patients with HHT seen at our center between 1999 and 2006. Gender distribution was 36% male, 64% female. Mean age at presentation was 41 (range 10 months to 83 years). From among that group, 13 (3.4%) were identified with deep venous thrombosis (DVT) and/or pulmonary embolism (PE). Mean age at diagnosis was 48 (range 26-75). 31% were male, 69% female. All had definite HHT by Curacao criteria. 5 of 13 had DVT, 4 of 13 PE, and 4 of 13 both. Risks for DVT were identified in 9 of 13 (69%), including surgery, hormonal therapy, cancer, anti-cardiolipin antibody, and protein C deficiency. Factor 8 levels were not measured. 8 of 13 were managed successfully with anticoagulation. 1 received heparin subcutaneously for one year. 3 were treated with warfarin for a defined period of six months. 4 were treated with warfarin indefinitely, with durations ranging from six to ten years at the time of data collection. None had significant increases in bleeding, and none required transfusions. None had more than moderate epistaxis pretreatment, none more than minimal gastrointestinal (GI) blood loss, and only one had required transfusion in the past (treated with heparin). Of the remaining 5, one was not treated due to remote occurrence. 2 were treated with inferior vena cava (IVC) filters initially, one because of a concomitant duodenal ulcer and recent transfusion requirement, and one because of brain metastases from lung cancer. 2 were treated initially with warfarin, but required discontinuation and IVC filter because of increased bleeding. 1 had significant pretreatment significant nasal and GI bleeding and had required transfusions in the past. The other had pretreatment moderate GI and nasal bleeding. In summary, selected patients with HHT and venous thromboembolism may be managed effectively and safely with anticoagulation. Factors predicting success include mild epistaxis or less, absence of GI bleeding, and no prior requirements for transfusion.

C42
LIFE-EXPECTANCY OF PARENTS WITH HEREDITARY HEMORRHAGIC TELANGIECTASIA

EM de Gussem,[1] CP Edwards,[2] CJJ Westermann,[1] ME Faughnan,[2,3] JJ Mager[1]

[1]Department of Pulmonology, St Antonius Hospital, Nieuwegein, The Netherlands; [2]Department of Medicine, Division of Respirology, St Michael's Hospital, University of Toronto, Canada; [3]Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, Canada

Objective. Persons affected by HHT are at risk of life-threatening hemorrhage, stroke and heart failure, most can be prevented with screening and treatment. We hypothesize that people with HHT have a shorter life expectancy if not screened, compared to people without HHT. *Methods.* A self-administered questionnaire was

sent to the most senior generation followed at the HHT Centers in Toronto and The Netherlands, regarding the mortal status of their parents and if deceased: age at death, cause of death and whether the parent with HHT had been screened/treated for arteriovenous malformations. Patients were selected if they had a definite diagnosis of HHT. *Results.* 300/574 (52%) completed questionnaires were returned. Two-hundred-twenty-four reported both parents had died. Overall mean age at death for parents with HHT and without HHT was 70.5 years (range 20.7-97.3, SD 13.6) and 74.2 years (range 27.0-103.0, SD 13.5) respectively (p-value<0.01). In female parents, mean age at death was 70.5 years (20.7-97.3, SD 15.0) with HHT versus 77.0 years (31.7-103.0, SD 14.2) without HHT (p-value<0.01). In male parents, mean age at death was 70.4 years (30.0-91.7, SD 12.1) with HHT versus 72.1 years (26.9-99.8, SD 12.6) without HHT respectively (p-value=0.3). Less than 20% of HHT parents were known to have been screened and treated for pulmonary or cerebral AVMs. *Conclusion.* Life expectancy is reduced in largely unscreened and untreated HHT parents, most significantly in women.
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C51
SURVIVAL IN HEREDITARY HEMORRHAGIC TELANGIECTASIA

J Goodwin,[1] R Nisenbaum,[2] C Edwards,[1] ME Faughnan[1]

[1]Department of Medicine and Li Ka Shing Knowledge Institute, St. Michael's Hospital, University of Toronto, Canada; [2]Centre for Research in Inner City Health and Applied Health Research Centre, The Keenan Research Centre, Li Ka Shing Knowledge Institute, St. Michael's Hospital, Dalla Lana School of Public Health, University of Toronto, Canada

Hereditary Hemorrhagic Telangiectasia (HHT) causes significant morbidity and mortality, but survival rates are unknown. Our aim was to report survival in HHT patients, and predictors of survival, from time of first assessment at an HHT Centre. We included all HHT patients (definite or possible diagnosis) assessed at the Toronto HHT Centre (1997-2008). We collected data from chart/database review and telephone follow-up. Survival curves, 5- and 10-year survival rates and 95% confidence intervals were estimated using Kaplan-Meier methods, overall, and stratified by gender, genetic mutation, HHT diagnosis (definite vs likely), PAVMs, CAVMs, Liver VMs, and GI bleeding. Survival curves were compared using log-rank tests. A P value of less than .05 was considered statistically significant. Analyses were performed using SAS. Of 588 patients, 34 were lost to follow up. Of the remaining 554 patients, 415 were diagnosed as *definite HHT* and 139 as *likely HHT*. Sixty percent were female; mean age was 43.9 years (range 14-88). Five-year survival was 95.9% (95% CI= 93.4% - 97.4%) and 10-year survival was 90.7% (95% CI=86.6% – 93.7%). Survival was significantly lower in patients with CAVMs (p<0.0001) and GI bleeding (p<0.0001). There was no significant difference in survival by gender, HHT diagnosis (definite vs likely), PAVMs, liver VMs or genetic mutation results. We conclude that HHT patients, cared for at an HHT Centre, have excellent 5-year and 10-year survival rates. However, survival is significantly reduced in patients with CAVMs or GI bleeding.
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C52
PRE-VISIT NURSING ASSESSMENT EDUCATES HHT PATIENTS AND PREPARES PHYSICIANS

R Pantalone, E Leek, S Gupta, ME Faughnan

Department of Medicine and Li Ka Shing Knowledge Institute, St. Michael's Hospital, University of Toronto, Toronto, Canada

Initial clinical assessment of an HHT patient is complex and time consuming, given multi-system symptoms, multiple tests performed, the importance of obtaining family history and the extensive patient education required. The Toronto HHT Centre uses a pre-visit telephone Nursing Assessment, for new patients, to obtain preliminary patient and family history information and to educate patients. We aimed to measure the effectiveness of the Nursing Assessment for patient education and physician preparation. We therefore administered a questionnaire to 11 consecutive new HHT patients, and another questionnaire to their HHT-physician. Subjects answered yes/no questions and used a Likert scale to rate effectiveness of the Assessment for pre-visit education. The physician used a Likert scale to evaluate the accuracy and usefulness of the Assessment. Six/11 patients (55%) had no prior knowledge of HHT. Ten/11 (91%) patients reported that the Assessment prepared and educated them for their first visit. Nine/11 (82 %) reported the length of the Assessment to be appropriate. Ten/11 (91%) stated that they would recommend the Assessment to other HHT Centres. The physician reported 10/11 (91%) of patients to be well prepared and informed. In 10/11 (91%) cases, the physician reported that the Assessment was helpful in triaging and determining initial testing. The physician reported, in all cases, that the Assessment information helped optimize physician time with the patient. The preclinic Nursing Assessment is an effective tool in the HHT Centre, educating patients in advance of their first clinic visit and optimizing physician time with patients.
Funding (M.E.F.): Nelson Arthur Hyland Foundation

C2
TRANSILLUMINATION OF THE FINGERS FOR VASCULAR ANOMALIES

ER Mohler III, V Doriswamy, A Sibley, BA Bernhardt, RE Pyeritz

University of Pennsylvania School of Medicine, Philadelphia, PA, USA

Hereditary hemorrhagic telangiectasia (HHT) is a common, pleiotropic, autosomal dominant disorder of vascular development. Diagnosis is established largely on clinical grounds, with emphasis on epistaxis, mucocutaneous telangiectases, visceral arteriovenous malformations, and family history. Because all of the features are

age-dependent, establishing the diagnosis can be difficult, especially in young people. Cutaneous telangiectases most frequently occur on the digits, but are often not evident on visual inspection. We describe a novel approach for detecting vascular abnormalities deep in the digits by means of a hand-held illuminator. Ten patients with HHT and without evident cutaneous digital telangiectases were compared to 10 controls for telangiectases in the fingers using a handheld otoscope in a darkened room. To assess blood flow in the fingers, Duplex ultrasound was performed with an 8 MHz transducer. A sagittal view of each finger was examined using color and power Doppler. Transillumination revealed round, dark lesions along blood vessels in 9 of 10 patients with HHT and none in age-matched healthy controls. Power Doppler show increased blood flow in fingers of HHT patients when compared to normal controls. Color Doppler showed dilated veins and arteries in close proximity in the region of the lesions seen on transillumination, consistent with the dark spots being small arteriovenous malformations. Transillumination with an otoscope identifies vascular abnormalities in the fingers of patients with HHT. Further studies are needed to determine the prevalence of telangiectases in the fingers of HHT patients and controls and whether this finding is present in other vascular diseases.

C25
DIAGNOSTIC CURAÇAO CRITERIA FOR HHT; ARE THEY STILL VALID?

MWF van Gent,[1] MC Post,[1] JJ Mager,[2] HWM Plokker,[1] TGW Letteboer,[3] H Kelder,[1] CJJ Westermann[2]

[1]Department of Cardiology, [2]Pulmonology, St Antonius Hospital, Nieuwegein; [3]Department of Medical Genetics, University Medical Center Utrecht, Utrecht, The Netherlands

Background. In 2000 the consensus clinical diagnostic criteria for HHT were drawn up. These Curaçao criteria have never been validated. We studied these criteria (epistaxis, telangiectases, and visceral AVMs), as compared to genetic test results as the gold standard. *Method*. We included all consecutive patients with known genetic test results, who were screened for HHT as first degree relatives of index patients. Screening for PAVMs was routinely performed using chest HRCT.,. Screening for HAVMs and gastro-intestinal telangiectasia was only performed when clinically suspected and screening for CAVM was offered to all patients. *Results*. We included 606 and 304 patients of families with the HHT1 and HHT2 genotype, of whom 409 (67.5%) and 208 (68.4%) patients displayed a mutation, respectively. In univariate analysis, epistaxis was the strongest independent predictor for HHT1 (OR 69; 95%CI 39.7-120.0) and HHT2 (OR 38.3;95% CI 39.3-76.0). The presence of visceral AVMs in HHT2 did not improve diagnostic accuracy. In multivariate analysis the OR for epistaxis, telangiectases, and visceral AVMs in HHT1 were 20.3 (95% CI 9.7-42.6), 16.9 (95%CI 8.2-34.7, and 39.0 (95%CI 8.3-183.5; p<0,0001 for all criteria), respectively. In HHT2 the multivariate OR for epistaxis, telangiectases and visceral AVMs were 11.3 (95%CI 5.1-24.8; p<0.0001), 9.8 (95%CI 4.2-22.6; p<0.0001), and 6,9 (95%CI 0,8-63,4; p=0,09) respectively. *Conclusion*. In HHT1, the current Curaçao criteria are all valuable for correct clinical diagnosis. However, in HHT2 the use of visceral AVMs, as superimposed on epistaxis and telangiectases, does not improve clinical diagnosis, however no routine screening for HAVMs was done.

SESSION V: MOLECULAR DIAGNOSTICS FOR HHT

B36
WILL GENETIC TESTING AID DIAGNOSING RELATIVES AT-RISK? AN EXPLORATORY STUDY

B Bernhardt, C Zayac, S Keddem, R Pyeritz

HHT Center, Hospital at the University of Pennsylvania and Penn Center for the Integration of Genetic Healthcare Technologies (CIGHT), USA

Clinical genetic testing for HHT has been available in the USA since 2003. Our study assesses the utility of genetic testing from the perspective of various stakeholders. We interviewed 20 adults with HHT who had complete gene sequencing about their diagnostic and genetic testing experiences. Average age was 54 years, 55% were female, and 55% were college graduates. Most interviewees reported that their diagnosis was made only after seeing many physicians and experiencing a variety of symptoms and complications. This lag in diagnosis was attributed to physician unfamiliarity with HHT. The presence of symptomatic family members did not lead to quicker diagnoses. Although most of the interviewees had a good understanding of their DNA test results, those testing negative or with a variant of uncertain significance were sometimes confused. Most participants discussed their results with many family members, and urged that they get genetic testing. Participants felt a particular responsibility toward their children and grandchildren. Relatives often declined genetic testing for reasons including: fear of not being able to get or keep insurance if testing positive; an assumption that they would test negative because they were asymptomatic; lack of insurance coverage for genetic testing; or fear of learning that they had HHT. Therefore, there are important barriers to being correctly diagnosed with HHT. Most HHT patients who have sequencing to identify the family mutation do discuss their result with family members and urge that they be tested, but are often met with resistance. Patient and provider education is needed about the role of genetic testing in either diagnosing or excluding the diagnosis in relatives.

B8
ASSESSING THE IMPACT OF MOLECULAR GENETIC TESTING FOR HEREDITARY HEMORRHAGIC TELANGIECTASIA

K Hart, L Ellington, A Brothman, P Bayrak-Toydemir, J McDonald

University of Utah, USA

Introduction. Genetic testing for hereditary hemorrhagic telangiectasia (HHT) is performed to confirm diagnoses in symptomatic individuals and to identify presymptomatic affected individuals for optimal clinical managment. However, little is known regarding the social and psychological impacts of genetic testing for HHT. *Methods.* Ninety adult individuals from the University of Utah HHT Clinic with genetic testing prior to one year were invited to complete a questionnaire based survey. Participants were categorized into three groups: 1) index cases in whom the family's mutation was identified, 2) individuals who tested positive for a familial mutation and, 3) individuals who tested negative for their family's specific mutation. The questionnaire was adapted from the Multidimensional Impact of Cancer Risk Assessment study to capture participants' psychosocial responses to HHT testing. The assessment included responses regarding distress about test results, regrets of getting testing, test impacts, insurance related concerns, comprension about results, screening and treatment options, worries about children's risk, and family communications and conflicts. Questions were classified into distress, uncertainty, experience, or comprension categories. *Results.* Preliminary analyses suggest that those tested did not have regrets about being tested, had sought additional medical information, consultation and/or screening since learning of their results, and experienced no significant adverse social or psychological effects. One interesting observation is that although all individuals who tested negative reported relief about their results, some nonetheless reported anxiousness and worries about potential medical risks for themselves and their children. Detailed response data and analyses will be presented.

B10
ALK1 AND ENG-MUTATIONS IN NORWEGIAN PATIENTS WITH HEREDITARY HEMORRHAGIC TELANGIECTASIA: RECURRENT MUTATIONS AND A PROBABLE FOUNDER EFFECT

K Heimdal,[1] S Al-Deen,[2] G Bachmann-Harildstad,[2] M Kroken,[3] K Eidlid[3]

[1]Department of Medical Genetics and [2]Department of ENT, Oslo University Hospital Rikshospitalet.
[3]Department of medical genetics, Oslo University Hospital Ullevål, Norway

Purpose. To report mutation data from the Norwegian HHT-centre. *Patients and methods.* Patients with suspected HHT were offered mutation analyses with sequencing of all exons of the ENG and ALK1 genes followed by MLPA. Haplotype analyses are ongoing. *Results.* Thirty-five different mutations were detected in 64 independently ascertained families (Table). Seventeen mutations have been reported previously. Eighteen mutations were novel, eleven in ENG and seven in ALK1. The mutations ENG p.R93X, ALK1 p.W217X and ALK1 p.R484W (on two different haplotypes), previously reported in several studies were found in five families each and may represent hotspots for mutation in HHT. The novel mutation ALK1 p.T277K was detected in 14 families all originating from a limited geographical area in Northern Norway probably representing a Norwegian founder mutation. Three out of the five families with ALK1 p.R484W originated from the same geographical area and together these mutations were responsible for the fact that there was a very uneven distribution of HHT in Norway with close to 1/3 of the patients living in a limited, sparsely populated geographical area in Northern Norway. *Conclusion.* The Norwegian data support the notion that the HHT-related mutation spectrum is influenced by a mixture of recurrent and founder muta-

tions. Local founder mutations may influence local disease prevalence to a high degree.

Table.

	ENG	*ALK1*	*SUM*
Number of mutations	*19 (54.3 %)*	*16 (45.7 %)*	*35 (100 %)*
Number of families	*27 (42.2 %)*	*37 (57.8 %)*	*64 (100 %)*
Recurrent mutations	*5 (14.3 %)*	*2 (5.7 %)*	*7 (20 %)*
Missense mutations	*5 (26,3 %)*	*9 (56,3 %)*	*14 (40,0 %)*

LINKAGE ANALYSIS ON FOUR LARGE HEREDITARY HEMORRHAGIC TELANGIECTASIA FAMILIES

CJ Bukjiok,[1] J McDonald,[1,2] K Damjanovich,[1] F Gedge,[1] P Bayrak-Toydemir[1,3]

[1]ARUP Institute for Clinical and Experimental Pathology, [2]Department of Radiology, University of Utah, [3]Department of Pathology, University of Utah, USA

Hereditary hemorrhagic telangiectasia (HHT) is a multisystem vascular dysplasia which shows locus heterogeneity. In addition to mutations of *ENG* (chromosome 9q34), *ACVRL1* (chromosome 12q13), and *SMAD4* (chromosome 18q21) which cause HHT1, HHT2, and Juvenile Polyposis/HHT syndrome, respectively, mutations of two yet-to-be-identified genes on chromosome 5q31 (HHT3) and chromosome 7p14 (HHT4) are the cause of this disorder in two unrelated families. We performed linkage analysis on 3 additional families which were negative for mutations in the coding regions of *ENG*, *ACVRL1* and *SMAD4*. There were 13, 17, and 22 family members respectively available for our study. We performed locus specific linkage analysis with short tandem repeat markers located in the 5 known HHT loci. Results for one family suggest linkage to 9q34. A second family appears linked to the HHT4 locus on chromosome 7p14. A third family was not linked to any of these loci. Our findings further support the locus heterogeneity observed in HHT. Studies are underway to narrow the critical region on chromosome 7p. In addition, we have an ongoing study to analyze the noncoding regions of ENG and ACVRL1 genes (see abstract by Damjanovich K, *et al*.).

B32
COMPARISSON BETWEEN DIFFERENT MUTATION DETECTION METHODS IN HHT, AND SOME NEW MUTATIONS

K Brusgaard, P Tørring, AD Kjeldsen[1]

Department of Clinical Biochemistry and Molecular Genetics; [1]Department of Otorhinolaryngology, Odense University Hospital, Odense C, Denmark

Introduction. Clinical genetics has established it self as a valuable tool in HHT diagnostics. Molecular genetic test results are based on different approaches. In this regard the applications selected in the lab may be more or less adequate. Sensitivity, specificity, hands on requirement, pricing and turn-around-time all become important parameters. We have been comparing direct sequencing to prescreening protocols utilizing DHPLC and TGCE. For larger rearrangements we have been comparing the use of long-PCR/RFLP analysis and MLPA. Our aim has been to establishing a fast reliable mutation screening procedure for the ENG and ACVLR1 loci. Additionally, we present some new mutations in either loci. *Materials and methods.* PCR primers were constructed to harbour exons and exon/intron boundaries. D-HPLC gradients were calculated using the Wavemaker software. TGCE gradients were empirical determined. Long-PCR/RFLP design was made in-house, MLPA reagents was purchased from MRCHolland. *Results.* Usually, DNA sequencing is taken as the gold standard and all prescreening procedures compared to this. This is not a strictly fair comparison as our lab has found deviation in both DHPLC and TGCE profiles that can not be resolved by bi-directional sequencing. Small deviations between DHPLC and TGCE performance was detected with TGCE being by several measures the fastest and cheapest method. Additionally, TGCE requires less and hands-on-time. Compared to direct sequencing both DHPLC and TGCE are considerably labor-saving. When comparing L-PCR combined with RFLP to a commercial MLPA protocol the results points in favor of the MLPA procedure. The methods described allowed the characterization of several new mutations. *Conclusion.* In establishing a routine procedure for a clinical genetic routine procedure it is important to compare alternative analysis procedures. The methods all show different advantages on disadvantaged that all has to be considered in the final choice of protocol. Cost, time consumption and the specificity of the method should all be considered.

B33
HOMOZYGOSITY FOR A NOVEL MUTATION IN ENG DISCOVERED IN A PATIENT WITH HEREDITARY HEMORRHAGIC TELANGIECTASIA (HHT)

P Torring, AD Kjeldsen, K Brusgaard

Odense Universityhospital, Department of Clinical Genetics and Department of Otorhinolaryngology, Denmark

Background. HHT is an autosomal dominant disorder, meaning that normally the affected individuals are heterozygous for the involved mutation. In analyzing a HHT family we discovered a female family member homozygous for a point mutation (c.817-3T>G) in *ENG*. Such an occurance has, to our knowledge, never been published before. Homozygosity for HHT-causing mutations is believed to be lethal in utero. c.817-3T>G has not previously been described, but is predicted to be disease-causing, based on mutation prediction analysis and the fact that the mutation segregates with HHT in the family. The 48 year old female homozygous for c.817-3T>G was in good health, but diagnosed with HHT. *Aim.* To verify and explore the status of the mutation as disease-causing, and the homozygous state in

the female HHT patient. *Methods.* Mutation analysis of additional family members (*n*=9) with clinically diagnosed HHT and non-HHT. Mutation analysis on epithelial tissue, from the study subject, was performed to test for the presence of tissue mosaicism. Functional study of the *ENG* mRNA are being carried out. *Results and conclusion.* We discovered a 48 year old female HHT patient homozygous for a novel mutation in *ENG*. Mutation analysis of epithelial tissue confirmed the homozygosity. The mutation segregates with the disease status in the affected individuals. A daughter showed no mutation, thus suggesting germline mosaicism of the study subject. Further results and conclusions to be presented.

SESSION VI: CENTRAL NERVOUS SYSTEM INVOLVEMENT AND TREATMENT IN HHT

C4
THE SPECTRUM OF PHENOTYPES IN CAVMS; IS THERE A DIFFERENCE BETWEEN MICRO ARTERIOVENOUS MALFORMATIONS (AVMS) AND MICRO CAPILLARY VASCULAR MALFORMATIONS (CVMS)?

K ter Brugge, T Krings, R Willinsky, R Agid

Toronto Western Hospital, University of Toronto, Canada

Cerebral Vascular Malformations in HHT patients can represent a variety of phenotypes. These phenotypes are not definitively linked to the various genotypes. While certain phenotypes appear to represent an early expression of the disorder others appear to occur at any age. Among the group of HHT cerebral vascular malformations that are small in size (<1 cm) a new entity of capillary vascular malformation can be proposed. This new entity, which has specific angiographic and MRI imaging characteristics, should be distinguished from the so-called micro AVM phenotype as it appears to have a different clinical natural history. In our experience about 15 % of HHT patients who have CVMs will have this type of vascular malformation. In our experience none of these lesions has been symptomatic or presented subsequently with hemorrhage. This is in contra-distinction to small size CAVMs in HHT patients, which can be associated with hemorrhagic presentation and likely will have increased risk for future hemorrhage . It is therefore in our opinion important to recognize the difference between these two types of micro lesions as they will require different management strategies. High resolution MRI (3 Tesla) and detailed angiographic examination are required to identify and distinguish CCVMs from CAVMs in the HHT population.

C33
BRAIN and SPINAL ARTERIOVENOUS SHUNTS IN HEREDITARY HEMORRHAGIC TELANGIECTASIA TYPE 1 or 2: ANGIOGRAPHY AND GENETICS RESULTS

A Ozanne,[1,2] J Roume,[2] F Coulet,[3] I Bourgault-Villada,[2] S Blivet,[2] JP Pelage,[2] C Fagnou,[2] G Lesur,[2] P Lasjaunias,[1] F Toulgoat,[2] G Saliou,[2] D Ducreux,[2] B Raffestin,[2] T Chinet,[2] F Soubrier,[3] P Lacombe[2]

HHT Center Paris, APHP; [1]Neuroradiology, CHU Bicêtre; [2]Consultation Multidisciplinaire, CHU Ambroise Paré; [3]Oncogenetics and Angiogenetics Laboratory, CHU Pitié Salpétrière, Paris, France

Background and purpose. Variable phenotypic expression of central nervous arteriovenous malformation have already been described in HHT. The aim of this study is to review them regarding their genotype HHT1 versus HHT2. *Material and methods.* Nine patients refered for embolization of a cerebral or spinal arteriovenous malformation had a genetic analysis with a diagnosis of HHT1

or HHT2. We reviewed the angiographic and clinical charts of these patients. Cerebral arteriovenous fistula (CAVF), cerebral micro arteriovenous malformation (microCAVM) of nidus type, cerebral AVM larger than 1 cm, spinal arteriovenous fistula (SAVF) and cerebral dural arteriovenous shunt (CDAVS) were the different neurovascular phenotypes held up. *Results.* Six patients were HHT1, from 13 months to 27 years at presentation: CAVF, CAVM, microCAVM, SAVF and CDAVS were identified. Three patients were HHT2, from 8 months to 32 years at presentation : SAVF and CAVM were identified. *Conclusion.* nor HHT1 nor HHT2 is specifically dealing with one of the neurovascular lesion type. Moreover both HHT1 and HHT2 patients, children and adults, may present symptomatic CNS arteriovenous malformations which need to be treated by embolization.

C55
COGNITIVE FUNCTIONS IN PATIENTS WITH HEREDITARY HEMORRHAGIC TELANGIECTASIA

MF De Caro,[1] M Mitolo,[1] P Suppressa,[2] L Castorani,[2] C Sabbà,[2] G Logroscino[1]

[1]Department of Neurologic and Psychiatric Sciences; [2]Department of Internal Medicine and Public Health, Interdepartmental HHT Centre, University of Bari, Policlinico, Bari, Italy

Background. Visceral arteriovenous malformations (VAM) may determine brain damage which may depend on several mechanisms including bleeding. As yet, there is no existing data assessing cognition in HHT patients without history of CNS disorders. *Objective.* To evaluate the influence of HHT on cognitive functions in patients with no history of CNS (central nervous system) disorders. *Methods.* Subjects were taken from patients referring to our University Interdepartmental HHT Center (Department of Internal Medicine and Public Health) and were subjected to the following standardized neuropsychological tests: Mini Mental State Examination (MMSE), Frontal Assessment Battery (FAB), Raven-Coloured Progressive Matrices, Rey Auditory Verbal Learning Test, Digit Span (forward and backward), Rey-Osterrieth Complex Figure, Digit Cancellation Test, Trail Making Test A and B, Verbal Associative Fluency Test, and Stroop Test. *Results.* Sixteen patients were enrolled in the study (50% males; age 46.8±15.32 yrs; education 10.2±4.61). Neuropsychological tests showed the following score percentages which were below the normal range: 18.8% for the FAB (μ=15.88), Rey Auditory Verbal Learning Test (μ=7.87) and Rey-Osterrieth Complex Figure (μ=12.48) tests; 62.5% for Backward Digit Span (μ=3.18), 25% for Stroop Test (μ =27.18), 12.5% for FAS (μ=26.69); 6.3% for Forward Digit Span (μ=4.53) and the Trail Making Test A (μ=41.37). *Conclusion.* This pilot study shows that cognitive functions may be impaired in asymptomatic HHT patients (working memory, executive functions, verbal and visual-spatial long term memory). These results should be considered cautiously. Future larger studies are warranted.

C34
GENETIC HHT1 OR HHT2 DIAGNOSIS IN PEDIATRIC CENTRAL NERVOUS SYSTEM ARTERIOVENOUS SHUNTS: A PROSPECTIVE COHORT

A Ozanne,[1,2] F Coulet,[3] J Roume,[2] I Bourgault-Villada,[2] S Blivet,[2] JP Pelage,[2] C Fagnou,[2] G Lesur,[2] P Lasjaunias,[1] F Toulgoat,[1] G Saliou,[1] D Ducreux,[1] B Raffestin,[2] T Chinet,[2] F Soubrier,[3] P Lacombe[2]

HHT Center Paris, APHP; [1]Neuroradiology, CHU Bicêtre; [2]Consultation Multidisciplinaire, CHU Ambroise Paré; [3]Oncogenetics and Angiogenetics Laboratory, CHU Pitié Salpétrière, Paris, France

Background and purpose. Curaçao criteria may not be all present in HHT pediatric cases. The aim of the study was to test HHT diagnosis by genetic analysis in cases of central nervous system arteriovenous malformation in children. *Materials and methods.* Between february 2006 and june 2008, 30 patients were prospectively screened as they were presenting central nervous system arteriovenous shunt diagnosed at the pediatric age, either High Flow ArterioVenous Fistula (AVF) or Multiple Cerebral Arteriovenous Malformations (mCAVM). All were less than 7 years of age. Both the endoglin and the ALK1 genes were anlayzed by sequencing of the coding sequence and search for large gene rearrangements by MLPA. Clinical charts with Curaçao criteria and revealing symptoms were reviewed. *Results.* 3 cases were including multiple CAVM (13 months and 19 months, 6 years), two were single spinal AVF (8 months and 4 years). None was a single cerebral AVF. Three were HHT1, two were HHT2. These all 5 cases revealed HHT in the case and in the family. One of them had no other Curaçao criteria. Two had Family History as only associated criteria. Two had two other criteria including Family History. 25 cases were negative. *Conclusion.* 5/30 (17%) of these pediatric cases had a genetic diagnosis of HHT1 or HHT2. This incidence is lower than expected regarding previous litterature. Nevertheless, all were revealing HHT disease; this brings to recommand screening HHT in children presenting with cerebral or spinal AVF, even more with multiple CAVM.

PC9
DETECTION OF CEREBRAL ARTERIOVENOUS MALFORMATIONS WITH MAGNETIC RESONANCE IMAGING IN PATIENTS WITH HEREDITARY HEMORRHAGIC TELANGIECTASIA (OSLER-RENDU-WEBER DISEASE)

A Massmann, P Fries, M Wirth, R Seidel, UW Geisthoff, A Buecker, GK Schneider

Saarland University Hospital Homburg/Saar, Germany; Clinics of City Cologne/Holweide, Germany

Purpose. To evaluate cerebral arteriovenous malformations in patients with hereditary hemorrhagic telangiectasia (HHT). *Methods and Materials.* 207/249 patients (mean age 46.5; male 103; female 146) with confirmed HHT according to Curacao criteria underwent screening cerebral MRI (cMRI) for the presence of CAVMs with

high-resolution non-contrast-enhanced T1-, T2-weighted, STIR and FLAIR sequences. CAVM presence was scored as *0* (=none present), *1* (=definitely present) or *2* (=uncertain) and was evaluated by patient gender, age and size. Patients with a definitely present or possible CAVM were referred for additional non-contrast and contrast-enhanced MRA to exactly characterize the angioarchitecture of malformations for evaluation of embolization therapy or surgical treatment. *Results.* MRI revealed 11/207 (5.3%) patients (mean age: 48.2; male 6; female 5) with possible or definite arteriovenous malformations. 5/11 (male 3; female 2) patients showed a definite CAVM related to HHT (size: 8 mm-20 mm). 2 patients with former resection of CAVMs in childhood showed no relapse. Further evaluation of patients classified as possible CAVM (*2*) (6 patients) in screening cMRI revealed other pathologies like small cavernomas (*n*=2, size<3 mm), or hypo- to hyperintense signal variability of cerebral nuclei without apparent clinical consequence. *Conclusion.* Compared to the literature, our results reveal a very rare frequency of cerebral arteriovenous malformations related to HHT. For screening purpose a high-resolution MRI without contrast media is suitable to identify clinically relevant CAVMs. A further characterization of angioarchitecture with contrast-enhanced MRA techniques completes the diagnostic work-up for therapy planning and monitoring.

SESSION VII: ANTIANGIOGENIC APPROACHES IN HHT

CONTROLLING HEMORRHAGE IN HHT – SEARCH FOR THE "MAGIC BULLET": REFLECTIONS FROM THE YALE HHT CENTER

RI White Jr. for Drs. Ross, Proctor, Young, Garcia, Pollak, and Henderson

Yale University School of Medicine, New Haven, CT, USA

Many of the patients referred to our multidiscipline team are thought to have gastrointestinal bleeding (GIB) in addition to epistaxis, by the referring doctor. Most will not have had a nasal exam, performed by an otolaryngologist, familiar with HHT, nor will they have had "expert" diagnosis and management by a team familiar with HHT. Empirically, at our center, if we can control epistaxis and replace body stores of iron, most iron deficiency anemia is controlled. Studies by Dr. Proctor and Dr. Ross have shown many patients have not received first line therapy for epistaxis and all patients whether bleeding or not, undergoing endoscopy and small bowel exam (capsule or push enteroscopy), have telangiectases diffusely throughout the gastrointestinal tract. What is the magnitude of the problem defined: as continued blood loss after maximum control of epistaxis due to GIB? Over the last 6 years from a cohort of 1600 patients we have encountered 16 patients with recalcitrant GIB after control of nosebleeds and management of anemia with established therapies. Among this small subgroup are 8 with diffuse oozing from gastrointestinal telangiectases associated with ALK-1 HHT and severe high output liver disease. The remaining 8 patients have had not had significant liver disease. The few placebo-controlled trials, the ethinyl estradiol and norethrindone studies by Van Cutsem and antifibrinolytic trials in small groups of patients by Morales et al., have shown significant improvement in GIB and epistaxis respectively. Despite this, there have been no multicenter trials substantiating these results although we have also published successful observational studies over extended time, with good results. How about some of the potent anti-VEGF medications? In earlier work from our center with interferon we were not able to control gastrointestinal bleeding in 2 of the 8 patients with high output liver disease. (unreported Yale HHT Center results) The Mayo Clinic has had an ongoing study with interferon and we have not as yet seen their published data on its efficacy. Thalidomide was considered early on but after consideration of toxicity and the limited numbers of refractory GIB, we never embarked on study of this medication. Avastin is also undergoing consideration by some. Limited experience in a patient with uncontrolled GI bleeding and trachealbronchial telangiectases using Avastin in doses similar to the single Australian patient failed. (Frank Miller from UCSD Center and Yale Center) Fortunately, mice models are being studied by Oh et al, so that we will have some knowledge about Avastin's properties before embarking on studies with this medication clinically. A warning, published by Buscarini about use of Avastin, should also

be considered. Are we at a "crossroads", weighing the balance of using these anti VEGF medications as experimental or "first line therapy"? What is required is a sensible approach, agreed upon as part of the Toronto Consensus Guidelines, before embarking on new promising agents but with significant toxicity.

Approach to GI Bleeding – Toronto Consensus Conference Guidelines

↓

Annual hemoglobin/hematocrit >35 y/o

↓

Endoscopy if anemia out of proportion to epistaxis

↓

In patients with suspected GI bleeding – upper endoscopy as first diagnostic test

↓

Diagnosis of GI bleeding: presence of anemia out of proportion to epistaxis + endoscopic visualization of GI telangiectasia + clinical judgment

↓

Oral and/or IV iron supplementation as first therapy

↓

Multiple attempts at local endoscopic therapy not recommended (because of additive risk of adverse events without corresponding benefits)

↓

Systemic hormonal and/or antifibrinolytic therapy in selected patients

We are hopeful that management of epistaxis by experienced otolaryngologists in conjunction with medical approaches will be maximized before any consideration of newer agents with more significant toxicity. If additional medication is required to control GIB, trials of the Van Cutsem regimen of hormonal therapies along with some of the antifibrinolytics should be studied in well controlled multi center studies. Animal model studies of the more potent and more toxic anti-VEGF medications, should be published as well as their compassionate use in patients with GIB failing less toxic medicines, before launching into more extensive clinical application of anti-VEGF medicines.

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ANTIANGIOGENIC DRUGS IN CLINICAL MANAGMENT

CJ Bruns

Department of Surgery, University of Munich, Klinikum Großhadern, LMU, Munich, Germany

By definition, angiogenesis is the establishment of a neovascular blood supply derived from pre-existing blood vessels. Newly derived blood vessels are derived from post-capillary venules. Recently, it has become apparent that the process of tumor angiogenesis is, in reality, a combination of the above; i.e. the main blood supply to a tumor is derived from pre-existing blood vessels, but circulating endothelial cell precursors may contribute to the growing endothelial cell mass. Pioneering work from the laboratory of Folkman and colleagues over the last thirty years has established that exponential growth of a tumor does not occur until neovascularization occurs since growth of tumors in organs where blood vessels do not proliferate is limited to the distance of oxygen diffusion (1-2 mm). Angiogenesis is driven by the production of angiogenic factors by the host, the tumor cells, or both.
Antiangiogenic therapy is an area of active basic-science and clinical research. Since primary tumor growth is often controlled with surgery or irradiation, anti-angiogenic agents may be most beneficial in the treatment of widespread metastatic disease. Several principles must be considered, however, if this therapy is to be effective. First, because anti-angiogenic agents are not tumoricidal but rather tumoristatic, this type of therapy may need to be delivered chronically. Thus the agent must be well tolerated with minimal untoward side effects. Second, the

endpoint of anti-angiogenic therapy would not be tumor shrinkage but rather tumor stabilization. Third, since anti-angiogenic therapy may be chronic, normal physiologic processes that require angiogenesis may be impaired.
Most relevant antiangiogenic inhibitors block VEGF mediated endothelial cell functions during angiogenesis thus inhibiting endothelial proliferation, migration or survival. Vascular endothelial growth factor isoforms and their receptors (VEGFR-1/Flt1, VEGFR-2/Flk1/KDR and VEGFR-3/Flt4) play a crucial role in the regulation of angiogenesis in the majority of tumor entities. Prominent substances inhibiting VEGF-signalling are monoclonal antibodies against VEGF protein or receptors: Bevacizumab (Avastin) is a humanized monoclonal VEGF-antibody against soluble VEGF and has been investigated in numerous preclinical studies. Further advances in this field include the development of a soluble decoy receptor incorporating both VEGFR-1 and VEGFR-2 domains (VEGF-Trap), binding VEGF with significantly higher affinity than previously reported VEGF antagonists. Small molecule VEGF receptor tyrosine kinase inhibitors are a second leading class of antiangiogenic drugs: SU5416, SU6668 with additional inhibitory effects on bFGF and PDGF receptor tyrosine kinase, PTK787/ZK22854, a VEGFR-1 and VEGFR–2 tyrosine kinase inhibitor. SU11248/ sunitinib (Sutent), a broad spectrum orally available tyrosine kinase inhibitor of VEGF, PDGF, c-kit and Flt-3 kinase activity as well as BAY-43-9006/sorafenib (Nexavar), an orally available small-molecule inhibitor of VEGFR-2 and 3, PDGF receptor β and Raf-1 kinase have proven significant improvement of progression free survival in metastatic renal cell cancer in clinical phase III studies. With anti-VEGF being nowadays the standard of current anti-angiogenic therapeutic strategies, additional targets need to be validated whose therapeutic exploitation combines well with anti-VEGF therapies and alternative strategies need to be advanced for anti-VEGF resistant or VEGF-independent tumor growth.

C16
EFFICACY AND SAFETY OF BEVACIZUMAB IN THE TREATMENT OF HEMORRHAGIC HEREDITARY TELANGIECTASIA ASSOCIATED WITH SEVERE HEPATIC VASCULAR MALFORMATIONS. A PHASE II STUDY

S Dupuis-Girod,[1] I Ginon,[2] D Marion,[3] F Faure,[4] E Decullier,[5] PJ Valette,[6] E Guillot,[6] D Revel,[7] D Gamondes,[7] S Bailly,[8] E Babin,[9] MF Carette,[9] R Corre,[9] B Gilbert,[9] JR Harle,[9] PY Hatron,[9] P Kaminsky,[9] P Lacombe,[9] B Lorcerie,[9] P Magro,[9] S Rivière,[9] JF Viallard,[9] F Chapuis,[5] H Plauchu,[1] JC Saurin[10]

[1]Hospices Civils de Lyon, Hôpital de l'Hôtel Dieu, Service de Génétique et centre de référence pour la maladie de Rendu-Osler, Lyon; [2]Hospices Civils de Lyon, CH Lyon Sud, Service de Cardiologie, Pierre-Bénite; [3]Hospices Civils de Lyon, Hôpital de l'Hôtel Dieu, Service de Radiologie, Lyon; [4]Hospices Civils de Lyon, Hôpital E. Herriot, Service d'ORL, Lyon; [5]Hospices Civils de Lyon, pôle IMER, Lyon; [6]Hospices Civils de Lyon, CH Lyon Sud, Service de radiologie, Pierre-Bénite; [7]Hospices Civils de Lyon, CH Lyon Sud, Service de radiologie, Pierre-Bénite; [8]INSERM U878, CEA-Grenoble; [9]French HHT Network, centres de compétence pour la maladie de Rendu-Osler; [10]Hospices Civils de Lyon, CH Lyon Sud, Service d'Hépato-gastroentérologie, Pierre-Bénite, France

Introduction. The efficacy of anti-VEGF treatments such as Bevacizumab in cases of HHT can be considered because of the molecular mechanisms implied in angiogenesis and HHT, as well as the mechanisms of action of this type of treatment. Two articles that have recently reported spectacular improvement thanks to Bevacizumab in patients with HHT complicated with severe liver involvement and cardiac effects support us in this sense. Up to now, the only treatment recommended in the severe hepatic forms of HHT is a liver transplant, the disadvantages of which are both multiple and well known: long waiting lists, surgical morbidity and mortality, immunosuppressive treatment for life. Furthermore, treatment with Bevacizumab is not a contraindication, should the drug be ineffective, for a subsequent liver transplant if necessary. *Trial design.* Single centre phase II trial. Using a Gehan design, 7 patients will be included in the first phase and 18 additional patients will enter the second phase. *Target population.* Patients aged between 18 and 70 years, monitored for confirmed HHT disease and with severe liver and cardiac involvement related to HHT. *Drug and Dose.* Bevacizumab, 5 mg/kg every 14 days with a total of 6 injections. *Primary objective.* To test the efficacy of Bevacizumab in the severe hepatic forms of HHT. The efficacy of the treatment on cardiac output. Efficacy is defined as a decrease in cardiac output, 3 months after the first injection, in relation to the initial value at the start of the trial. *Methodology.* A two-phase Gehan method will be used with a first phase designed to eliminate a non effective treatment quickly and a second phase allowing assessment of efficacy. *Results.* On going

C31
THALIDOMIDE FOR TREATMENT OF CHRONIC SEVERE BLEEDING IN HEREDITARY HEMORRHAGIC TELANGIECTASIA

E Buscarini,[1] G Manfredi,[1] P Gazzaniga,[2] L Reduzzi,[3] C Danesino,[4] C Olivieri,[4] F Pagella,[5] M Grosso,[6] G Pongiglione,[7] E Boccardi,[8] on behalf of HHT-NET

[1]Gastroenterology Dept, [2]Cardiology Dept, [3]Radiology Dept, Maggiore Hospital, Crema; [4]Genetic Institute, University of Pavia; [5]ENT Institute, University of Pavia; [6]Radiology Dept, Ospedale S Croce, Cuneo; [7]Paediatric Cardiology Dept, Ospedale Gaslini, Genova; [8]Interventional Neuroradiology Unit, Niguarda Hospital, Milan; Italy

Aims. Preliminary reports on the effectiveness of thalidomide in treating nose or GI bleeding from angiodysplasia prompted us to initiate a treatment protocol to evaluate thalidomide results. *Methods*. The treatment protocol, approved by our Institutional Review Board, dealt with HHT patients with severe chronic anaemia, from epistaxis or GI bleeding, requiring more than 1 blood unit transfusion/month and refractory to standard therapies.

Pregnant females, pre-menopausal females and sexually active males rejecting contraceptive measures were excluded. The initial thalidomide dosage of 100 mg/day was to be increased to 200 and 300 mg/day after 4 and 6 weeks, respectively, in case of partial/no response. We checked blood cell count, iron deficiency , liver and kidney function, ECG, echocardiogram and electromiography before, during and after treatment. Treatment-related side effects were recorded. *Results*. We treated eight patients (age 57-69, 6 m), with severe epistaxis (3), GI bleeding (4), or both (1); 7 were able to complete the six month treatment, in 1 treatment was interrupted after 4 months because of poor response and side effects. Average hemoglobin value in the 6 months preceding treatment was 6.1 gr/dl (range 4.8-7.7); during treatment it was 9.0 gr/dL (range 6.2-12.2); blood transfusion requirements are shown in Figure 1.

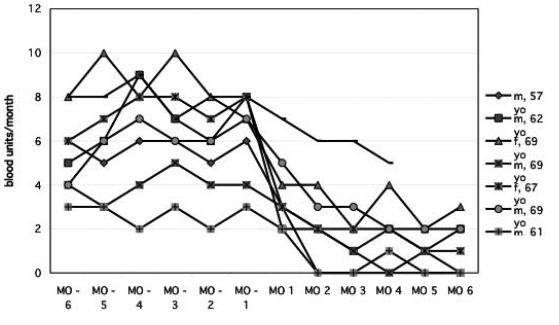

Figure 1.

The maximum thalidomide dose used was 200 mg/day. No major side effects were observed; minor side effects included constipation and vertigo which improved spontaneously after the first month in 4 patients, but in one prevented any increase in dosage beyond 100 mg; lower limb edema in 2. *Conclusions*. The treatment seems a reasonable option for HHT patients with severe chronic bleeding; further clinical trials are warranted.

PC10
AN INTERIM REPORT OF THALIDOMIDE FOR TREATMENT OF RECURRENT ANGIOECTASIA RELATED GASTROINTESTINAL BLEEDING

JR Gossage, SM Chamberlain, S Sridhar, A Kumar

Medical College of Georgia, Augusta, GA, USA; Stony Brook University, NY, USA

Rationale. Patients with HHT and acquired angiodysplasias are frequently affected by gastrointestinal bleeding related to vascular malformations. Vascular endothelial growth factor (VEGF) is a potential mediator of the development of vascular malformations in these disorders. We studied whether the VEGF inhibitor thalidomide would reduce GI bleeding in these disorders. *Methods.* Patients with recurrent GI bleeding due to HHT or acquired angiodysplasias, and who required at least 4 units of blood in the past 2 years, were enrolled in an open label study of thalidomide. Patients were treated with 50-200 mg of thalidomide daily for 24 wk and then followed off of thalidomide for 24 wks. Capsule endoscopy was performed at baseline, 24 wks, and 48 wks. Hemoglobin level, transfusion need, and frequency of GI bleeding and epistaxis were monitored. Results. 3 patients with HHT and 1 with acquired angiodysplasias have been enrolled so far and 3 have completed at least 24 weeks of treatment. In the 24 wks prior to enrollment, patients required an average of 51 units of PRBC. During treatment with thalidomide patients experienced a 19-57% decrease in transfusions. 2 patients with recurrent epistaxis experienced a 54 and 89% decrease in epistaxis and 2 noted a decrease in cutaneous telangiectases. Their were no serious complications and drowsiness was the most frequent side effect. Repeat capsule endoscopy at 24 wks was normal in 1 patient and unchanged in another. *Conclusions.* Thalidomide may decrease the incidence of GI bleeding and other vascular complications in patients with HHT and acquired angiodysplasias.

B13
THALIDOMIDE STIMULATES VESSEL MATURATION AND PREVENTS NOSEBLEEDS IN HEREDITARY HAEMORRHAGIC TELENGIECTASIA PATIENTS

F Lebrin,[1,2,3] S Srun,[1,2] S Martin,[1,2] S van den Brink,[3] HM Arthur,[4] CJJ Westermann,[5] JJ Mager,[5] F Dish,[5] RJ Snijder,[5] A Eichmann,[1,2] CL Mummery[3,6]

[1]INSERM U833, Paris, France. [2]Collège de France, Paris, France; [3]Hubrecht Laboratory, Netherlands Institute for Developmental Biology, Utrecht, Netherlands; [4]Institute of Human Genetics, International Centre for Life, University of Newcastle, UK; [5]St Antonius Hospital, Nieuwegein, The Netherlands; [6]Dept. of Anatomy and Embryology, Leiden University Medical Center, Leiden, The Netherlands

Hereditary Haemorrhagic Telangiectasia is an autosomal dominant disorder of vascular dysplasia that affects many organs. Although not life threatening, a major quality of life issue is frequent and severe nosebleeds that pose a major therapeutic challenge. Anti-angiogenic substances may represent long-awaited specific drugs for the treatment of vascular malformations in HHT. However, these molecules display significant different actions and differential/cautious evaluation of this therapeutic strategy is necessary. Our clinical collaborators have recently reported that nosebleeds were dramatically reduced in a small group of 6 HHT patients daily treated by thalidomide. To investigate its effects *in vivo*, we first focussed on developmental retinal angiogenesis in *Endoglin*$^{+/-}$ or *ALK1*$^{+/-}$ mice that are predisposed to develop HHT-like vascular abnormalities. Mutant mice showed increased vascular density associated with elevated number of vessel sprouts in the peripheral part of the vascular plexus when compared to controls. Interestingly, thalidomide was able to normalize the excessive vessel branching phenotype and importantly to enhance vessel maturation. Furthermore, vessel coverage defects observed in ear and in the subcutis area of skin of mutant mice were rescued by thalidomide injections, although vessel density was unchanged. Whilst

the precise mechanisms underlying thalidomide-induced vessel maturation are unknown, thalidomide seems to target both pericytes and endothelial cells. Finally, preliminary evidences indicate that similar mechanisms might occur in human. Taken together, we demonstrate that thalidomide may prevent epistaxis in HHT patients by stimulating pericyte/vSMC recruitment. Moreover, an understanding of the mechanisms underlying thalidomide action may lead to new strategies for novel drug design to treat HHT patients.

SESSION VIII: HEPATIC INVOLVEMENT IN HHT

C11
HEART FAILURE IN HEREDITARY HEMORRAGIC TELANGIECTASIA: CLINICAL, ECHOCARDIOGRAPHIC FEATURES AND NATRIURETIC PEPTIDES IN PATIENTS WITH HEPATIC INVOLVEMENT

I Ginon,[1] S Dupuis-Girod,[2] G Rioufol,[3] G Finet,[3] C Khouatra,[4] JF Cordier,[4] M Barthelet,[5] D Marion,[6] PJ Valette,[7] S Giraud,[8] JC Saurin,[9] H Plauchu,[2] M Ovize[5]

[1]Hospices Civils de Lyon, CH Lyon Sud, Service d'Explorations Cardiologiques, Pierre-Bénite, F-69495; [2]Hospices Civils de Lyon, Hôpital de l'Hôtel Dieu, Service de Génétique et Centre de référence pour la maladie de Rendu-Osler, Lyon F-69288; [3]Hospices Civils de Lyon, Hôpital Louis Pradel, Service d'Hémodynamique, Lyon-Bron, F-69677; [4]Hospices Civils de Lyon, Hôpital Louis Pradel, Service de Pneumologie et Centre de référence des maladies orphelines pulmonaires, Lyon-Bron, F-69677; [5]Hospices Civils de Lyon, Hôpital Louis Pradel, Service d'Explorations fonctionnelles cardiovasculaires, Lyon-Bron, F-69677; [6]Hospices Civils de Lyon, Hôpital de l'Hôtel Dieu, Service de Radiologie, Lyon F-69288; [7]Hospices Civils de Lyon, CH Lyon Sud, Service de Radiologie, Pierre-Bénite, F-69495; [8]Hospices Civils de Lyon, Hôpital Edouard Herriot, Laboratoire de Génétique moléculaire, Lyon, F-69437; [9]Hospices Civils de Lyon, CH Lyon Sud, Service d'Hépato-gastroentérologie, Pierre-Bénite, F-69495, France

Introduction. Although HHT hepatic arteriovenous malformations (HAM) are rarely associated with hepatic complications, they may lead to a progressive high-output cardiac failure. Little knowledge is available about this particular pattern and evolutivity of heart failure (HF). Symptomatic and poorly-evaluated treatments may be proposed, whereas liver transplantation has been considered the only curative treatment. *Methods.* 36 HHT patients with HAM were investigated. Clinical signs of HF were recorded. Left ventricular (LV) function, cardiac output (CO), LV filling-pressures and pulmonary artery pressure (PAP) were analyzed by echocardiography. Blood samples were collected, for hemoglobin and BNP assessment. *Results.* Mean age was 58.7±12.2 years (33F, 3M). When identified, mutation was predominantly ALK1 (28/31). Nine patients had associated pulmonary arteriovenous malformations. Mean cardiac output was 6.44±1.13 $l.min^{-1}$ (3.97 to 9.87 $l.min^{-1}$), mean cardiac index was 3.97±0.73 $l.min^{-1}.m^{-2}$. Patients could be classified in 4 groups: 7 patients with normal CO and pressures (G1), 18 patients with high CO but preserved LV-filling pressures (G2), 6 patients with high CO and mildly elevated LV-filling pressures (G3) and 5 patients with elevated LV-filling pressures and/or PAP and/or complications (G4). BNP levels increased from 51.6±3.2 $pg.ml^{-1}$ in G1 to 748.8±657.1 $pg.ml^{-1}$ in G4. Epistaxis and need for tran-

sfusion were higher in G4. *Conclusion.* Clinical exam, echocardiography and BNP level, allowed a better characterization of cardiac manifestations in HHT patients with HAM: half of them had high CO alone, 6 exhibited mildly elevated LV pressure and 5 worsened HF. Careful cardiac evaluation is necessary to select candidates for treatments and transplantation.

C41
TREATMENT FOR HEART FAILURE IN HHT PATIENTS WITH SYMPTOMATIC LIVER DISEASE

LH Young, G Garcia-Tsao, K Henderson, RI White Jr

Yale University School of Medicine, New Haven, CT, USA

Background. High output heart failure is the most frequent symptomatic manifestation of liver vascular malformations in hereditary hemorrhagic telangiectasia (HHT), but the risk factors for poor outcome are not well understood. *Methods.* At the Yale HHT Center, 39/47 patients with symptomatic liver HHT had heart failure. Genotyping of 16 patients revealed 14 ALK1 mutations, one ALK1 variant of uncertain significance, and one endoglin mutation. A chart review was conducted with Human Investigations Committee approval to identify clinical features that portended poor outcomes. *Results.* Heart failure was treated with intensive diuretic therapy and treatment of anemia. Moderate left atrial enlargement was common, leading to atrial fibrillation (n=8), which typically worsened dyspnea. Atrial fibrillation was treated with pharmacologic therapy and cardioversion to maintain sinus rhythm. Heart failure patients *crossed over*, developing symptomatic biliary ischemia (n=4), which carried a poor prognosis. A separate group of patients developed encephalopathy with high plasma ammonia (n=7), late in the course of disease, in part from portal vein-to-hepatic vein shunting without evidence of cirrhosis or portal hypertensión. Symptomatic encephalopathy was often precipitated by gastrointestinal bleeding and responded to lactulose. However, encephalopathy, like biliary ischemia, conferred a high-risk for early mortality in heart failure patients. *Conclusions.* Symptomatic heart failure in patients with liver vascular malformations can be conservatively managed with intensive treatment of epistaxis, iron-deficiency anemia, volue overload and atrial fibrillation. The development of symptomatic biliary ischemia or encephalopathy are features that predispose to early mortality and should trigger consideration for liver transplantation when feasible.

C49
NON-INVASIVE DETERMINATION OF PORTAL VEIN TO RIGHT HEART SHUNTING: QUANTIFYING SHUNTS IN HHT LIVER AVM'S

M Kuo, C Oh, TB Kinney, FJ Miller

Institutions UCSD Medical Center, San Diego, CA, USA

Introduction. Quantifying portal shunts has not been used frequently because of its invasiveness. We recently used a nuclide technique involving the rectal administration of 99m technetium to determine the shunt index (SI) to potentially detect patients in whom embolization might be possible without significant morbidity and no mortality. A technique we used was from a little known publication from Osaka Japan written in 1988 which allowed us to quantitate these shunts and may also be helpful in some patients where the presence of liver disease is difficult to determine (J.Nuclear Medicine 1988, 29:460-465). *Method.* Five patients with HHT liver disease were studied; 10mcuries of 99m technetium pertechnitate were injected rectally and time activity curves were generated using a gamma camera centered over the liver, spleen and heart. The details of the technique will be described. *Results.* All 5 patients had abnormal SI values (normal less than 5.9%) with values ranging from 29-49%; the patient with the value of 29% has HPS with no avm but has hyperplasia on biopsy. The ammonia level was 2x normal otherwise all other laboratory values were normal. Medical therapy is continuing in 3 patients with avm's another died of lymphoma and the 5th is being evaluated for liver transplant. *Conclusion*. Nuclide shunt index using the rectal route is a simple method to quantify the portal to right heart shunts in patients with HHT liver disease and may be helpful in the diagnosis of the rare patient with HPS and normal CTA/MRI findings and HHT.

C30
HOW MANY HHT PATIENTS WILL REQUIRE INVASIVE TREATMENTS FOR SYMPTOMATIC HEPATIC VASCULAR MALFORMATIONS (HAVMS) ALONG FOLLOW-UP?

E Buscarini,[1] G Manfredi,[1] P Gazzaniga,[2] L Reduzzi,[3] C Danesino,[4] C Olivieri,[4] F Pagella,[5] M Grosso,[6] G Pongiglione,[7] E Boccardi,[8] on behalf of HHT-NET

[1]Gastroenterology Dept, [2]Cardiology Dept, [3]Radiology Dept, Maggiore Hospital, Crema; [4]Genetic Institute, University of Pavia; [5]ENT Institute, University of Pavia; [6]Radiology Dept, Ospedale S Croce, Cuneo; [7]Paediatric Cardiology Dept, Ospedale Gaslini, Genova; [8]Interventional Neuroradiology Unit, Niguarda Hospital, Milan, Italy

Aims. To evaluate the number of HHT patients with HAVMs requiring invasive treatments (hepatic artery embolization, liver transplantation (OLT)) during follow-up. *Methods*. Patients at risk of HHT across Italy were referred for a multidisciplinary HHT family screening protocol aimed to establish the HHT affection status. From April 1992 to April 2007 502 consecutive subjects (231 males, mean age 38.7, median 41, range 3-88) at risk for HHT were examined. Inclusion criteria were a diagnosis of HHT, either clinical or genetic; presence of liver VMs on Doppler US. Clinical and instrumental follow up of liver VMs has been recommended to all patients with liver VMs found at initial screening with a schedule depending on liver VMs severity; follow-up records til October 2008 concerning this patient cohort were reviewed.The need for transarterial embolization of HAVMs or for OLT were considered as end-points in the study. *Results.* In 502 subjects a clinical diagnosis of HHT was definite, possible and unlikely in 272 (54.1 %), 80 (15.9 %) and 150 (30%) patients; 154 (43.7% of affected) subjects (47 males, mean age 48 (range 7-82) had HAVMs at baseline evaluation. Mean follow-up was 60

months (range 12-181). Five (3%) of patients with HAVMs underwent invasive treatments during follow-up: 3 patients (1m, 2 f, mean age 54) underwent transarterial embolization of HAVMs; 2 female, mean age 43, underwent OLT. *Conclusions.* During follow-up a non negligible rate of HHT patients with HAVMS can require invasive treatments, which are currently recommended only for non responders to intensive medical treatments.

C17
DOES LIVER TRANSPLANTATION IMPROVE HHT PATIENTS WITH SEVERE LIVER INVOLVEMENT?

AL Chesnais,[1] S Dupuis-Girod,[1] I Ginon,[2] J Dumortier,[3] JC Saurin,[4] G Rioufol,[5] G Finet,[5] E Decullier,[6] S Giraud,[7] F Faure,[8] O Merrot,[9] D Marion,[10] JY Scoazec,[11] H Plauchu,[1] O Boillot[12]

[1]Hospices Civils de Lyon, Hôpital de l'Hôtel Dieu, Service de Génétique et centre de référence pour la maladie de Rendu-Osler, Lyon; [2]Hospices Civils de Lyon, CH Lyon Sud, Service de Cardiologie, Pierre-Bénite; [3]Hospices Civils de Lyon, Hôpital E. Herriot, Service d'Hépato-gastroentérologie, Lyon; [4]Hospices Civils de Lyon, CH Lyon Sud, Service d'Hépato-gastroentérologie, Pierre-Bénite; [5]Hospices Civils de Lyon, Hôpital Louis Pradel, Service de Cardiologie, Bron; [6]Hospices Civils de Lyon, pôle IMER, Lyon, Université de Lyon; [7]Hospices Civils de Lyon, Hôpital E. Herriot, Laboratoire de Génétique moléculaire, Lyon; [8]Hospices Civils de Lyon, Hôpital E. Herriot, Service d'ORL, Lyon; [9]Hospices Civils de Lyon, Hôpital de la Croix Rousse, Service d'ORL, Lyon; [10]Hospices Civils de Lyon, Hôpital de l'Hôtel Dieu, Service de Radiologie, Lyon; [11]Hospices Civils de Lyon, Hôpital E. Herriot, Service d'anatomo-pathologie, Lyon; [12]Hospices Civils de Lyon, Hôpital E. Herriot, Service de transplantation hépatique, Lyon, France

Introduction. Hepatic involvement is observed in up to 50% of HHT patients and is defined by a range of arterio-veinous malformations. Three different types of intrahepatic shunting can be observed: hepatic artery to hepatic veins, hepatic artery to portal vein and portal vein to hepatic vein. This involvement may lead to biliary ischemia, portal hypertension or high-output cardiac failure. Orthotopic liver transplantation has been proposed as the only definitive curative action. The aim of this study was to evaluate patients' improvement after liver transplantation according to mortality, cardiac and hepatic features, epistaxis and quality of life. *Methods.* Patients who underwent liver transplant for HHT in the Lyon liver transplant Unit from 1993 to 2007 were followed prospectively at this centre and in the French reference centre for HHT. Quality of life was evaluated using the SF-36 questionnaire. *Results.* 13 patients were included in this study (12 women and 1 man). Mean age at transplant was 51.8 years. Indications for liver transplantation were isolated cardiac failure (n=9), biliary necrosis (n=2), both (n=1) and hemobilia (n=1). Twelve patients are still alive (92.3%) with a mean time from transplant of 82.5 months. For the 9 patients with *cardiac heart failure*, mean cardiac output failed from 9.56 to 5.01 L/min respectively (p=0.001). No severe hepatic complications were observed. 9 patients out of 12 (75%) also experienced a dramatic improvement in epistaxis and quality of life allowing increased physical activities. *Conclusion.* Liver transplant is a successful option for the treatment of severe hepatic HHT with low mortality in this cohort. Further studies are needed to define the optimal timing and prognosis factors.

C39
MAGNETIC RESONANCE IMAGING AND MAGNETIC RESONANCE ANGIOGRAPHY OF THE LIVER AND HEPATIC VASCULATURE IN PATIENTS WITH HEREDITARY HEMORRHAGIC TELANGIECTASIA (RENDU-OSLER-WEBER DISEASE)

GK Schneider, A Massmann, P Fries, M Wirth, UW Geisthoff, A Buecker

Saarland University Hospital Homburg/Saar, Germany; Clinics of City Cologne/Holweide, Germany

Purpose. To evaluate liver involvement in patients with hereditary hemorrhagic telangiectasia (HHT). *Methods and Materials.* 230 patients (mean age: 46.9; male 96; female 134) with proven HHT according to Curacao criteria, or first-degree relatives, underwent non-contrast and contrast-enhanced (Gd-BOPTA 0.05 mmol/kg bodyweight) MRI of the liver for detection of hepatic manifestations of HHT. *Results.* RI revealed 38/230 patients (mean age: 57; male 8; female 30) with hepatic and vascular pathologies related to HHT. Hepatomegalia and hepatic arterio-venous malformations (HAVM) were found in 28/38 and 21/38 patients, respectively. Right-heart-insufficiency (RHI), due to HAVM, was present in 9 patients, who did not suffer from hemodynamically relevant pulmonary AVM (PAVM). An enlarged diameter of the hepatic artery (HA) correlated with increased nodular hyperplastic changes of the liver (19 patients), a lower RHI-rate, and inversely with the diameter of the portal vein. *Conclusion.* HHT-patients with a hepatomegaly and nodular hyperplastic changes of the liver most likely have shunts at the sinusoidal level. Direct arterio-venous and arterio-portal shunts are associated with an almost normal liver size without hyperplastic changes. The increased arterial blood supply to the liver could explain the nodular hyperplastic changes similar to the mechanism of focal overgrowth of liver tissue discussed in the development of FNH. HAVM causing hyperplastic nodules do not result in direct hemodynamical left-to-right-shunts, while HAVM without hyperplastic nodules is likely to cause RHI.

SESSION IX: MANAGEMENT AND OUTCOMES OF PAVMs IN HHT

C5
NEW APPROACH TO MANAGEMENT OF PATIENTS WITH DIFFUSE PULMONARY ARTERIOVENOUS MALFORMATIONS

J Pollak, RI White Jr, J Fahey, J Murphy, P Pierucci, D Chyun, K Henderson

Yale University School of Medicine, New Haven, CT, USA

Purpose. To present the results of our new approach for management of patients with diffuse pulmonary arteriovenous malformations (PAVM) using exercise stress testing (EST). *Materials and Methods.* Twenty patients from a cohort of 35 with diffuse PAVM have undergone EST using a standard cycle ergometer test. All patients had previously undergone pulmonary angiography, chest computed tomography, and repair of large focal PAVM. Mean room air oxygen saturation at baseline and at maximum exercise (85% of maximum heart rate) were tabulated. Serial studies in 6 children and young adults were plotted by year (2003-08) and compared using the patient as their own control. *Results.* Fourteen females and 6 males ranged in age from 4 to 50 years (mean 22 years). Baseline mean oxygen saturation was 84% and fell to 73% at maximum exercise. There was no significant difference between those with unilateral and bilateral involvement (p=.09). In the 6 patients with serial EST, the baseline and exercise oxygen saturations were quite stable. In patients who became symptomatic, with age, growth and more activity, complete embolization of one or more segments of the lung improved their EST and functionality. *Conclusions*. Based on our previous work and the results of EST, we believe that this test should be a component of follow-up after thorough anatomical assessment and occlusion of focal PAVM. Serial EST is non-invasive and safe. Pending further validation, exercise testing may become the most valuable way of following patients with diffuse PAVM.

C7
PULMONARY ARTERIOVENOUS MALFORMATIONS ASSOCIATED WITH MIGRAINE WITH AURA: A LARGE PROSPECTIVE STUDY

MC Post,[1] MWF van Gent,[1] HWM Plokker,[1] CJJ Westermann,[2] JC Kelder,[1] JJ Mager,[2] TT Overtoom,[3] WJ Schonewille,[4] V Thijs,[5] RJ Snijder[2]

Department of [1]Cardiology, [2]Pulmonology, [3]Radiology, and [4]Neurology, St Antonius Hospital, Nieuwegein, The Netherlands, and [5]Department of Neurology, University Hospital Gasthuisberg, Leuven, Belguim

Background. Migraine with aura (MA) is associated with a cardiac right-to-left shunt. In retrospective studies, a high prevalence of migraine has also been reported in the presence of a pulmonary right-to-left shunt, a pulmonary arteriovenous malformation (PAVM). *Methods.* We prospectively studied the association between the presence of a PAVM and MA in consecutive persons referred for hereditary hemorrhagic teleangiectasia (HHT) screening between May 2004 and April 2008. A high resolution computed tomography of the chest for PAVM detection was made in 387 out of 417 consecutive persons (93%). Prior to screening a structured validated headache questionnaire was completed by 357 out of these 387 persons (92%). Two independent neurologists diagnosed migraine according to the International Headache Society Criteria. *Results.* A PAVM was present in 76 (21%) out of the 357 included persons (61% female, mean age 43±16 years). The prevalence of MA was 24% in the presence of a PAVM compared to 6% in the absence of a PAVM (OR 4.2: 95% CI 2.1-8.6; p<0.001). In a multivariate analysis model MA was an independent predictor for the presence of a PAVM (OR 4.1: 95% CI 2.0-8.6; p<0.001). A PAVM was present in 50% of the patients with MA compared to 19% in the non-migraine controls (OR 4.2: 95% CI 2.1-8.6; p<0.001). The presence of a PAVM was an independent predictor for MA in a multivariate analysis model (OR 3.9: 95% CI 1.9-8.2; p<0.001). *Conclusion.* Pulmonary arteriovenous malformations are associated with migraine with aura in patients screened for hereditary hemorrhagic telangiectasia.

C19
EMBOLIZATION OF RUPTURED PULMONARY ARTERIOVENOUS MALFORMATIONS IN HHT PATIENTS

JP Pelage, S Blivet, JH Blondel, I Bourgault, Th Chinet, G Lesur, A Ozanne, B Raffestin, J Roume, F Soubrier, E Kuhl, P Lacombe

Consultation pluridisciplinaire Rendu-Osler, APHP, Boulogne, France

Purpose. To describe clinical presentation, imaging findings and therapeutic options in patients with spontaneously ruptured pulmonary arteriovenous malformations (PAVMs). *Materials and methods.* All consecutive patients with ruptured PAVMs treated with embolized during a 4-year period were recorded from our database. The following criteria were analyzed: age at presentation, clinical presentation, imaging findings using multidetector computed tomography (MDCT). The technique of embolization and its results were also analyzed. *Results.* From a database of 92 patients with PAVMs treated with embolization, 4 (3 male and 1 woman) were identified to have a spontaneous rupture PAVM. Three of them were adults (mean age 56 years) and one was a child (10 y.o.). Two of them were already diagnosed with hereditary hemorrhagic telangiectasia whereas the diagnosis was subsequently made after embolization of the ruptured PAVM in 2 patients. In 3 patients, endoglin mutation was identified. Two patients presented with diffuse PAVMs, 1 with multiple PAVMs and 1 with a single large PAVM. Two patients presented hemoptysis related to pulmonary hemorrhage and 2 had massive hemothorax. In 2 patients, the rupture of PAVM occurred during air travel. Emergent embolization of the ruptured PAVM located in the lower pulmonary lobe in 3 cases and the lingula in 1 case was successfully performed using coils. Bleeding cessation

was observed in all patients who made a full recovery. *Conclusion.* Pulmonary hemorrhage or hemothorax due to spontaneous rupture of PAVM is a potentially life-threatening complication that should be treated aggressively with embolization. Early diagnosis is the key to life-saving treatement.

C20
EMBOLIZATION OF PULMONARY ARTERIOVENOUS MALFORMATIONS IN 70 CONSECUTIVE PATIENTS OVER A 3-YEAR PERIOD: RESULTS WITH THE USE OF MULTIDETECTOR COMPUTED TOMOGRAPHY

P Lacombe, S Blivet, JH Blondel, I Bourgault, TH Chinet, G Lesur, A Ozanne, B Raffestin, J Roume, F Soubrier, L Cellerin, R Corre, JP Pelage

Consultation pluridisciplinaire Rendu-Osler, APHP, Boulogne, France

Purpose. To evaluate the results of embolization of pulmonary arteriovenous malformations (PAVMs) using multidetector computed tomography (MDCT). *Material and methods*. All consecutive patients with PAVMs embolized during a 3-year period were evaluated using MDCT. The following criteria were analyzed on MDCT: retraction and contrast enhancement of the embolized aneurysmal sac, recanalization or persistent perfusion of the PAVMs, pulmonary-to-pulmonary anastomoses or reperfusion through arterial side branches, diameter of bronchial and non bronchial systemic arteries and evolution of non embolized PAVMs. A successful treatment was defined as a complete retraction of the PAVMs. *Results.* Post embolisation MDCT was obtained in 58/70 patients. A total of 100 embolized PAVMs was analyzed. A successful treatment was observed in 62% of patients. Complete retraction of the aneurysmal sac was present in 71/100 PAVMs. Contrast-enhancement was identified in 30 PAVMs (42%) and recanalization in 11 PAVMs (mean diameter 1.3 mm). The remaining 29 PAVMs had incomplete retraction. Contrast enhancement was present in 27 PAVMs (93%) and recanalization in 19 PAVMs (mean diameter 2.0 mm). Enlarged systemic arteries were detected in 43/71 retracted PAVMs and 15/29 non retracted PAVMs respectively. Enlargement of non embolized PAVMs was detected in 14% of patients. *Conclusion.* Complete retraction of the aneurismal sac has been identified in 71% of cases. Surprisingly, contrast-enhancement of embolized PAVMs was present in 42% of retracted PAVMs and 93% of incompletely retracted PAVMs. Bronchial or non-bronchial systemic artery supply was also frequently seen.

C50
OUTCOMES OF ISOLATED INTRAPULMONARY SHUNT IN HHT

HH Wong, H Leong-Poi, V Prabhudesai, R Bijarchi, ME Faughnan

Departments of Medicine and Medical Imaging, St. Michael's Hospital and Li Ka Shing KnowledgeInstitute, University of Toronto, Toronto, Canada

Pulmonary arteriovenous malformations (PAVMs) occur in 30-50% of HHT patients. In addition, some patients have intrapulmonary shunt (IPS) on contrast echocardiography (CE) but no CT-detectable PAVMs. We aimed to describe their clinical presentation and outcomes. We identified patients with IPS on CE but negative CT scan for PAVMs, from the Toronto HHT Database (1998-2008), and definite HHT diagnosis. Retrospective chart and imaging review was performed. Of 74 patients with isolated IPS, 43/74(58%) were female; mean age was 43 years (range:21-73). ALK1 mutation was detected in 30/74 (41%), endoglin mutation in 13/74 (18%), VOUS in 4/74 (5%) and no detected mutation in 8/74 (11%). At initial assessment, dyspnea was reported in 25/74 (34%), migraine in 17/74(23%), previous minor hemoptysis in 10/74 (14%) and previous stroke in 3/74 (4%), though the strokes occurred at ages 59-65 years and with multiple non-HHT risk factors. In 3/74 (4%) patients, significant PAVMs were detected on immediate pulmonary angiography, following initial negative CT (all pre-helical CT use). Mean follow-up was 48 months (range: 0–120). During follow-up, there were 2 deaths (ages 69 and 70 years), neither related to PAVMs, and there were no hemorrhagic or neurologic PAVM complications. In two/74 (3%), PAVMs (one significant) were detected on follow-up CT and confirmed retrospectively on initial CT. As we observed no PAVM complications, we conclude that the risk of complications from isolated IPS must be very low. Follow-up is important however, allowing detection of small missed PAVMs and potential new PAVMs.

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C44
TO EMBOLISE OR NOT TO EMBOLISE PULMONARY ARTERIOVENOUS MALFORMATIONS IN THE PRESENCE OF SEVERE PULMONARY HYPERTENSION

CL Shovlin, JSR Gibbs, JE Jackson

Imperial College London and and Hammersmith Hospital, Imperial College Healthcare NHS Trust, UK

Introduction. Pulmonary arteriovenous malformations carry significant risks which can be reduced by embolisation. A small group of patients have PAVMs and severe pulmonary hypertension. Should the recommendations regarding PAVM treatment be modified for this group? *Methods.* We reviewed published data to evaluate whether pulmonary hypertension modifies the natural history or treatment related risks for PAVMs. Risk-benefit considerations were then re-evaluated. *Results*. i) In the setting of pulmonary hypertension, dyspnoea is usual. PAVM haemorrhage may be increased. Ischaemic stroke risk is lower in patients with higher mean pulmonary artery pressures (PAP: HR 0.89 (95% CI 0.83, 0.95)/mmHg, p=6.2x10^{5}). Brain abscess risks are unchanged. ii) PAVM patients differ in their haemodynamic responses to embolisation. Isolated case reports, including fatalities, highlight the risk of increased PAP post embolisation. Such a response is unusual and not necessarily predicted by test balloon occlusion. *Interpretation.* In general, for patients with severe pulmonary hypertension, we would not interpret risk-benefit considerations in

favour of PAVM embolisation. The most difficult judgements relate to management of active major haemoptysis or haemothorax. In such emergency settings, the risk of precipitating a further increase in PAP may be considered justifiable. In our opinion, even if test balloon occlusion appears satisfactory, patients should be warned of a potential fatal increase in PAP. Further data are required to assess whether particular categories of pulmonary hypertension carry lower risks.

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SESSION X: EPISTAXIS MANAGEMENT IN HHT

DEVELOPMENT OF A HEREDITARY HEMORRHAGIC TELANGIECTASIA EPISTAXIS SEVERITY SCORING (HHT-ESS) SYSTEM

J Hoag,[1] D Reh,[2] S Mitchell,[2] P Terry,[2] C Merlo[2]

[1]Drexel University College of Medicine, Philadelphia, PA; [2]Johns Hopkins University School of Medicine, Baltimore, MD, USA

Introduction. Hereditary Hemorrhagic Telangiectasia-related epistaxis leads to dramatic alterations in social functioning and quality of life. Although more than 95% of patients experience epistaxis, there is considerable heterogeneity in the severity of epistaxis experienced between individuals. Several methods to categorize epistaxis severity have been utilized by care centers; however, little uniformity currently exists among different centers. Because no standardized method exists to categorize epistaxis severity, the purpose of this study was to determine factors associated with patient reported severity in order to develop an epistaxis severity score (HHT-ESS). *Methods.* In order to determine factors believed to be associated with epistaxis, HHT care providers and a focused group of patients were interviewed to determine a comprehensive list of possibly associated factors. From this list, an electronic survey was developed and administered to patients with HHT. Descriptive analyses were performed with calculations of means and medians for continuous variables and proportions for categorical variables. Multiple ordinal logistic models were developed to determine risk factors for epistaxis severity. Subsequently, multiple linear regression models were created to develop the HHT-ESS. Finally, boot-strap sampling methods were employed to assist with model estimation. *Results.* 914 respondents from 21 countries completed the electronic survey. From this, a cohort of 877 (96%) subjects reported epistaxis. The mean (SD) age was 52.8 (12.9) years and 61.2% were female. Independently associated risk factors for self reported epistaxis severity included frequency of epistaxis (OR 1.56), average duration of bleeding episodes (OR 2.20), intensity of bleeding (OR 2.26), having sought medical attention for epistaxis (OR 2.34), need for epistaxis-specific blood transfusion (OR 3.06), and presence of anemia (OR 1.50, $p<0.001$ for all). Using multiple linear regressions, predictors of self reported epistaxis severity are shown in the Table 1. Using the coefficients from the linear regression model, the HHT-ESS was generated. For ease of use, the raw score was normalized to a range of 0 (none) to 10 (most severe). *Conclusion.* Through evaluation of a comprehensive list of possibly related predictors of epistaxis severity obtained from patients and care providers, six factors were utilized to develop an epistaxis severity score. These include: frequency of bleeding episodes, average bleeding duration, intensity of average bleeding episodes, seeking medical attention for nose bleeding, the presence of anemia, and the need for blood transfusion specifically related to epistaxis. We believe that this HHT-ESS may serve as an outcome measure for

assessing clinical status and therapeutic efficacy.
Funding. This project was supported through a grant from the HHT Foundation International, Inc.

Table 1.

Variable	*Coefficient*	*Standard Error*	p-*value*
Intensity	*0.26*	*0.07*	*< 0.001*
Frequency	*0.15*	*0.02*	*< 0.001*
Duration	*0.25*	*0.02*	*< 0.001*
Medical Attention	*0.32*	*0.07*	*< 0.001*
Transfusion	*0.35*	*0.06*	*< 0.001*
Anemia	*0.13*	*0.03*	*< 0.001*

C47
THE EFFECT OF EPISTAXIS ON HEALTH RELATED QUALITY OF LIFE (HR-QoL) IN PATIENTS WITH HEREDITARY HEMORRHAGIC TELANGIECTASIA (HHT)

J Hoag,[1] D Reh,[2] D Boyce,[2] S Mitchell,[2] P Terry,[2] C Merlo[2]

[1]Drexel University College of Medicine, Philadelphia, PA; [2]Johns Hopkins University School of Medicine, Baltimore, MD, USA

Introduction. Epistaxis is the most common manifestation of HHT affecting more than 96% of patients with the disease. Quality of life in patients with HHT has previously been shown to be lower than national averages in most domains; however, these studies are limited by small sample size. The purpose of this study was to determine HR-QoL in a large diverse group of patients with HHT and correlate these findings with patterns of disease. *Methods.* A standardized quality of life questionairre (SF-36, v.1) was administered to people with HHT through the use of an internet based survey program from April through August 2008. Demographic information, location of visceral AVMs, information related to epistaxis including severity and treatments received, and aspects of life affected by the disease were also collected. Descriptive analyses were performed with calculations of means and medians for continuous and proportions for categorical variables. HHT HR-QoL domains were compared with a reference population and analyzed with respect to self reported epistaxis severity. *Results.* 690 HR-QoL responses were collected. Scores for each domain were significantly lower than the reference population ($p<0.001$ for all) including both Physical and Mental Component Summaries. Reduced HR-QoL was also noted with increasing patient reported epistaxis severity across all domains ($p<0.001$). *Conclusion.* HR-QoL in HHT patients are lower than a reference population across all domains measured by SF-36. Formation of an HHT-specific HR-QoL tool may be helpful for evaluation of future therapeutics.
Funding. This project was supported through a grant from the HHT Foundation International, Inc

C3
A GRADING SCALE FOR EPISTAXIS IN HEREDITARY HAEMORRHAGIC TELANGIECTASIA

S Al-Deen, G Bachmann-Harildstad

Rikshospitalet, Oslo, Norway

Background. Epistaxis is the most common symptom in patients with Hereditary Haemorrhagic Telangiectasia (HHT). Different institutions are using different treatment modalities and different grading systems. The treatment options depend on the grade of epistaxis. It is important to have a common grading system to compare and evaluate the effectiveness of different treatment options. Furthermore, it is important to correlate quality of life with an epistaxis grading system as an option. The aim of this work was to propose a new grading system for epistaxis in HHT. *Method.* The literatures were searched for grading systems of epistaxis in HHT. A questionnaire on five criterias for a new grading system was sent to 22 international medical professionals, who have published results on epistaxis in HHT. *Results.* Four different grading systems are in use for the grading of epistaxis in HHT nowadays. The response rate of the questionnaire was 43%. All the medical professionals, who have answered the questionnaire, agreed that the aimed grading system should be easy to understand for the patients. 90% of them wanted the system to focus on a definite time period. 70% answered that blood transfusion should be included in the grading system as an important factor. There was no clear tendency whether the system should be a single multi-item scale or a scale consisting of more than one scale, and similarly there was no clear tendency towards an absolute scale or a relative one. *Conclusion.* The aimed system should be easy to understand for the patients, focus on a definite time period of observation, and blood transfusion should be included as a parameter in the grading system. For statistical reasons, an epistaxis grading scale with at least one absolute end point would be preferable.
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C46
ANTI ESTROGEN THERAPY FOR HEREDITARY HEMORRHAGIC TELANGIECTASIA – A DOUBLE BLIND PLACEBO CONTROL CLINICAL TRIAL

E Yaniv, M Price, M Haddad

Rabin Medical Center, Israel

Background. Hereditary hemorrhagic telangiectasia (HHT) is associated with recurrent epistaxis in 90% of cases. Good response to hormone treatment has been documented, although its use remains controversial. The aim of this study was to examine the efficacy of an antiestrogenic agent, tamoxifen, in the treatment of HHT-associated epistaxis. *Methods.* Twenty-five patients (11 men, 14 women; mean age 51 years) with a diagnosis of epistaxis due to HHT were randomly assigned to receive treatment with oral tamoxifen 20 mg/d or placebo for 6 months. Follow-up consisted of physical examination and once-monthly blood tests. *Findings.* The groups were

similar in age and sex distribution. Of the 21 participants who completed the trial, alleviation of the epistaxis was noted in 9 of 10 tamoxifen-treated patients and 3 of 11 placebo-treated patients (including 2 with only temporary improvement). The difference between the groups at the trial end-point was significant for both frequency (p=0.01) and severity (p=0.049) of the disease. Hemoglobin concentration rose in 4 tamoxifen-treated patients and decreased in 5 controls. *Interpretation.* Tamoxifen appears to be an effective agent for the treatment of epistaxis due to HHT.

C15
CLOSURE OF THE NASAL CAVITY ACCORDING TO YOUNG FOR THE TREATMENT OF RECURRENT EPISTAXIS IN HHT

U Geisthoff,[1] A Mainka[2]

[1]Department of Otolaryngology, Hospitals of the City of Cologne, Cologne, Germany; [2]Department of Otolaryngology, Hospital Dresden Friedrichstadt, Dresden, Germany

Background. Epistaxis is the most frequent manifestation in HHT and can severely affect quality of life. The modified Young's procedure is a radical treatment option which is seldom used. *Patients and methods.* Retrospective evaluation of cases which underwent a modified Young's procedure between 2004 and 2008 by chart review and a standardized telephone interview including the Glasgow Benefit Inventory (GBI). *Results.* 8 patients were operated (7 m, 1 f, age: 43-77 a). Mean postoperative obeservational period was 26 months (9 – 48 months). One patient died 1 year before the interview and the information was obtained by his widow and his son, who at the same moment was his family physician. One patient was operated only on one side. Small dehiscences made revisions necessary in 6 cases. Complete closure of the nasal cavity resulted in absolute cessation of the bleeding in all cases and improvement of transfusion requirement in 6 patients. All patients said that they would decide again to be operated by the same method. However, the operation was reversed in one patient after 7 months because of a small dehiscence producing a noise not tolerated by his partner. Total quality of life measured by GBI improved in all patients with a mean total score of 44.1, general score of 61.5 and bodily health score of 16.7. *Conclusion.* Modified Young's procedure is a valuable treatment option for selected patients. It can improve quality of life and is the only method resulting in a certain absolute cessation of epistaxis.

PC1
EXTENDED EXPERIENCE WITH YOUNG'S PROCEDURE FOR THE MANAGEMENT OF EPISTAXIS AND HEREDITARY HEMORRHAGIC TELANGIECTASIA

LP Johnson,[1] F Miller,[2] TM Davidson[3]

[1]Division of Otolaryngology-Head and Neck Surgery, Department of Surgery, University of Utah Health Sciences Center, Salt Lake City, Utah; [2]Department of Radiology, University of Utah Health Sciences Center, Salt Lake City, Utah, University of California at San Diego, San Diego, CA; [3]Division of Otolaryngology-Head and Neck Surgery, University of California at San Diego, San Diego, CA, USA

Early results of Young's procedure for management of epistaxis in six patients with HHT were presented as a poster at the 7th HHT Scientific Conference. This report is an extended follow up from 24 to 41 months for these patients and the experience with spontaneous re-opening of the initial closure and resultant epistaxis. Follow up was by clinic visit and telephone contact. Re-closure was performed on four of the six patients, with complete resolution of the epistaxis. Re-closure consisted of primary re-closure and in one patient, the use of local flaps. All of these patients continued to maintain normal hemoglobin levels and have required no transfusions. One patient required a single IV iron infusion and surgery. *Conclusion.* All patients, including those that developed small re-opening of the initial closure, maintained normal hemoglobin and hematocrits and they no longer required transfusion for management of anemia. Young's procedure remains the only surgical treatment (when the closure remains intact) that eliminates epistaxis in the HHT patient. In this select group of patients, the loss of the nasal airway has not been a significant complaint when the epistaxis has been eliminated.

C14
TREATMENT OF EPISTAXIS WITH AN ANGLED 980 NM DIODE LASER IN PATIENTS WITH HHT

G Bachmann-Harildstad, S Al-Deen

Rikshospitalet, Oslo, Norway

The surgical treatment of epistaxis in patients with morbus Osler consists of Nd:YAG laser, pulsed dyed laser, bipolar electrocautery, argon plasma coagulation and septodermoplasty. Treatment with angled diode laser is presented with focus on treatment complications. During the period 11-2007 until 1-2009, 21 patients from a cohort of 132 patients with known morbus Osler were included for the treatment using angled diode laser with a wavelength of 980 nm and a diameter of 1.2 mm. The tip of the diode was without sharp edges and the laser beam was delivered in an 80 degree angle. In combination with a 2.7 mm 30 degree angled endoscope, regions posterior to the vestibulum nasi or nasal valve were accessible. The patients were treated on a day case basis. The gender ratio was 57.1/42.9 f/m. 20 patients were treated under local anaesthesia, 3 of them with intravenous sedation; one patient was treated under general anaesthesia due to panic attacks. The range of the operating time was between 30 and 60 minutes. The treatment was tolerated by all patients. Four patients (23 %) complained of transient nasal crusting which resolved after 3 weeks. One patient (5.8 %) complained of increased nasal obstruction, which resolved after 4 weeks. In one case (5.8 %), a nasal septum perforation occurred. The preliminary results indicate that angled diode laser is a promising option for the local treatment of telangiectasia in the posterior nasal cavity. The simultaneous treatment on corresponding areas on the nasal septum should be avoided when using angled diode laser.

C32
QUALITY OF LIFE IN INDIVIDUALS AFFECTED OF HEREDITATY HEMORRHAGIC TELEANGIECTASIA

AØ Geirdal, S Al-Deen, G Bachmann-Harildstad, K Heimdal

Oslo University College, Department of Medical Genetics and Department of ENT, Oslo University Hospital, Rikshospitalet, Norway

Purpose. To examine quality of life in individuals affected of hereditary hemorrhagic telangiectasia. Patients and methods: 39 women and 27 men all affected with HHT and with a mutation in ENG or ALK1, were included. Quality of life was measured with three well-established questionnaires, Short Form 36 (SF36), Cantrils Ladder and Slotosch questionnaire. Comparisons were made between these patients and age and gender adjusted norm data from the Norwegian population. *Results.* Compared to the norm, the level of mental and physical quality of life was significantly lower in the HHT patients. The more time was used on *nose-care* the poorer experience of physical quality of life. No significant differences were observed between the women and men on any measures of quality of life. *Conclusion.* The results substantiate that the individuals that are affected of HHT must deal with emotional impact due to nose bleeding and that the nose bleeding also seems to hinder in activities that include health.

SESSION XI: ENDOGLIN, ALK1 AND SMAD4 IN TGF-β AND BMP PATHWAYS

B2
BMP9 RESPONSES MEDIATED VIA ALK1 RELY ON DIFFERENT INPUTS FROM TYPE II RECEPTORS IN HUMAN PULMONARY ARTERY ENDOTHELIAL CELLS

PD Upton, RJ Davies, RC Trembath, NW Morrell

Department of Medicine, University of Cambridge School of Clinical Medicine, Addenbrooke's and Papworth Hospitals, Cambridge, UK. King's College London, Department of Medical and Molecular Genetics, Guy's Hospital, London, UK

ALK1 mutations cause hereditary haemorrhagic telangiectasia (HHT), whereas bone morphogenetic type II receptor (BMPR-II) mutations underlie familial pulmonary arterial hypertension (FPAH). Recently, ALK1, utlilsing ActR-II or BMPR-II, was identified as a BMP9/10 receptor in endothelial cells. However, BMPR-II mediates signals to a wider range of BMP ligands than ALK1. We asked whether these differing pharmacologies of ALK1 and BMPR-II explain the differing pathologies of HHT and FPAH. Human pulmonary artery endothelial cells (HPAECs) were stimulated with BMPs and lysed for protein for Smad Western blotting or for RNA for qPCR. In subsequent experiments, HPAECs were transfected with specific siRNAs (siALK1, siALK5, siEndoglin, siActR-II, siBMPR-II, siSmad2, siSmad3 or siSmad4) followed by stimulation with BMP9 (1ng/mL). BMP9 selectively induced phosphorylation of Smad1/5, Smad2 and Smad 3 and transcription of Id1, Id2, IL-8 and E-selectin in HPAECs. siALK1, but not siALK5 or siEndoglin, abrogated the Smad phosphorylation and gene transcription responses to BMP9. Co-transfection of both siBMPR-II and siActR-II were required to significantly attenuate Smad 1/5 and Smad 3 phosphorylation and Id1 and Id2 transcriptional responses to BMP9. In contrast, siActR-II significantly abrogated the Smad2 response, although cotransfection of siBMPR-II and siActR-II abolished this response. Conversely, siBMPR-II potently attenuated the induction of IL-8 and E-selectin by BMP9. siSmad4 abrogated the gene responses to BMP9, whereas siSmad2 only attenuated IL-8 induction. BMPR-II controls a subset of transcriptional responses (IL-8 and E-selectin) mediated by BMP9 through ALK1. Therefore, the differing consequences of ALK1 and BMPR-II mutations may explain the differing pathologies of HHT and FPAH.

B5
THE ALK1 LIGAND, BMP9, IS A PLASMATIC VASCULAR QUIESCENCE FACTOR

L David, M Bidart, C Mallet, N Ricard, M Keramidas, N Lamandé,[1] S Dupuis-Girod,[2] H Plauchu,[2] J-J Feige, S Bailly

INSERM U878 iRTSV / LAPV, CEA, Grenoble, France, [1]INSERM U833, Collège de France, Paris, France,

[2]*Hôpital Hôtel-Dieu, Lyon, France*

ALK1 is an endothelial-specific type 1 receptor of the TGFβ receptor family whose mutations are responsible of HHT2. Two years ago, we reported that BMP9 is a specific ligand for ALK1 that potently inhibits microvascular endothelial cell migration and growth. We now confirm that BMP9 is a potent inhibitor of angiogenesis in two *in vivo* angiogenic assays. Indeed, we observed that BMP9 strongly inhibited neo-angiogenesis in the subcutaneous mouse sponge assay. Interestingly, in this assay, we found that BMP9 could induce the destabilization of pre-formed angiogenic vessels. Further, we found that BMP9 inhibits blood circulation in the chicken chorioallantoic membrane (CAM) assay without affecting vessel architecture and that this effect was reversible. We have found that BMP9 is present in blood at a concentration of around 2 ng/mL as determined by a cellular assay (BRE-luc) and confirmed by a home-made ELISA. We could further demonstrate that plasmatic BMP9 is responsible for Smad1/5/8 phosphorylation in endothelial cells of physiological quiescent vessels. Further, we found that circulating BMP9 plasmatic levels in HHT patients were not different with those of a healthy population. Taken together, our results demonstrate that BMP9 is a potent anti-angiogenic factor that is likely to play a physiological role in the control of adult blood vessel quiescence. This would suggest that HHT patients who have less functional ALK1 and, a similar BMP9 plasmatic level, have vessels that are in an activated angiogenic state. Therefore we can propose from our data that anti-angiogenic treatments should be beneficial to HHT patients.

B4
FUNCTIONAL ANALYSIS OF THE BMP9 RESPONSE OF ALK1 MUTANTS FROM HHT2 PATIENTS

N Ricard, G Lesca,[1] C Mallet, S Giraud,[1] A Calender,[1] J-J Feige, S Bailly

[1]*Service de Génétique Moléculaire et Clinique, Hôpital Edouard Herriot, Lyon, France*

HHT is an autosomal dominant genetic vascular disease originated by mutations in receptors of the TGFβ signalling pathway: endoglin (ENG) in HHT1 and ALK1 (ACVRL1) in HHT2. Although haplo-insufficiency is the model currently accepted for HHT1, the mechanism for HHT2 is controversial. The recent discovery of BMP9 as the specific ligand for ALK1 now allows us to study the functional significance of ALK1 mutations. We generated 15 disease-related ALK1 missense mutants distributed throughout the protein (extracellular, GS box and kinase domains) by site-directed mutagenesis. We investigated their expression, localization and signalling activities in response to BMP9. We show that all the ALK1 mutant proteins are expressed. Interestingly, all these mutants are defective in both basal and BMP9 signalling activities as measured through Smad1/5 phosphorylation or a luciferase reporter assay driven by the BMP responsive element (BRE), except the one in the GS box (D179A) that was found in a family with primary pulmonary hypertension. None had a dominant negative effect on wild-type ALK1. These data supports the fact that HHT2 results from functional haplo-insufficiency reducing BMP9 signalling. Although the finding of an additional unreported ALK1 substitution in a patient with an already known mutation in ENG or ALK1 is rare, setting whether it is a silent polymorphism or leads to a non-functional ALK1 protein is important for genetic counselling. We used the same functional assays to determine the significance of 4 of these substitutions. This demonstrates that the cellular assay that we developed using the BMP9-induced BRE response can be used as a diagnostic tool in HHT.

B6
A NEW ROLE FOR TGFβ1 IN VASCULAR SYSTEM: TGFβ1 INDUCES PODOSOME FORMATION IN AORTIC ENDOTHELIAL CELLS IN AN ALK1/SMAD1/5 DEPENDENT MANNER

P Rottiers, C Billottet, F Saltel, V Tridon, E Reuzeau, E Génot

IECB/INSERM U889, France

Studies from knockout mice and from humans with naturally occurring mutations in TGFβ1 signaling pathways have revealed its critical role in vessel homeostasis. In ECs, two TβRI associate with TβRII, ALK5 and ALK1. TGFβ1 contributes to both the activation and resolution phases of angiogenesis but the respective roles of ALK1 (Smad1/5) and ALK5 (Smad2/3) in these steps remains unresolved. Of note, BMP9 signaling through ALK1 was recently reported to promote vessel quiescence. We have discovered that TGFβ1 induces podosome formation in cultured aortic EC, and detected similar structures in the endothelium of arterial vessels. Podosomes are actin-rich adhesion microdomains containing MMPs, bestowing them with ECM degradation capacities. Since podosome formation is ALK1-dependent, we are investigating ALK1 downstream signaling and exploring the role played by these structures in the vessel. Both TGFβ1 and BMP9 trigger ALK1/Smad1/5 pathways but BMP9 antagonizes TGFβ1 effect on podosome formation. Since TGFβ1-induced ALK1 stimulation does not trigger podosomes when unable to phosphorylate Smad1/5, the process appears dependent on ALK1/Smad1/5 signaling triggered by TGFβ but not by BMP9. Because podosomes are found in cell types capable of travelling across anatomical boundaries, we investigated the invasive potential of EC bearing podosomes. ALK1 promotes cellular invasiveness upon TGFβ stimulation but cell quiescence in response to BMP9. TGFβ1 and BMP9 are two ALK1 ligands displaying antagonistic effects on EC behaviour. Our observations establish a novel role for TGFβ1/ALK1 signaling in vascular biology by promoting cell invasiveness and suggest that endothelial podosomes represent cellular devices devoted to vessel remodelling.

B34
CK2β, AS A NOVEL ACTIVATOR/MEDIATOR OF ALK-1 SIGNALING

JC Haney, J Sogani, GC Blobe

Duke University, Durham, NC, USA

ALK-1 is a transforming growth factor β (TGF-β) superfamily receptor that is preferentially expressed on endothelial cells and is essential for angiogenesis as demonstrated by the embryonic lethal phentoype when targeted for deletion in mice and its mutation in the human disease, hereditary hemorrhagic telangiectasia. Although ALK-1 and the endothelial specific TGF-β superfamily coreceptor, endoglin, interact with similar TGF-β superfamily ligands and form a complex together, the mechanism by which signaling through these receptors is regulated in endothelial cells remains to be defined. Here we report the identification of CK2β The regulatory subunit of protein kinase CK2, as a novel activator of ALK-1 signaling. The cytoplasmic domain of ALK-1 specifically binds to CK2β *in vitro* and *in vivo*. NAAIRS mutagenesis studies define aa181-199 of CK2β and aa207-212 of ALK-1 as the interaction domains, respectively. CK2β increased both TGF-β1 and BMP-9-stimulated Smad1/5 phosphorylation and ALK-1-mediated reporter activation. In a reciprocal manner, siRNA-mediated silencing of endogenous CK2β inhibited TGF-β1 and BMP-9-stimulated Smad1/5 phosphorylation and ALK-1-mediated reporter activation. Functionally, CK2β enhanced the ability of activated or ligand (TGF-β1 or BMP-9) stimulated ALK-1 to inhibit endothelial cell migration. These studies support CK2β as an important regulator of ALK-1 signaling and ALK-1-mediated functions in endothelial cells.

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B35
ALK5 PHOSPHORYLATION OF THE ENDOGLIN CYTOPLASMIC DOMAIN REGULATES SMAD1/5/8 SIGNALING AND ENDOTHELIAL CELL MIGRATION

BN Ray, NY Lee, T How, GC Blobe

Duke University, Durham, NC, USA

Endoglin, an endothelial cell specific transforming growth factor-β (TGF-β) superfamily co-receptor, has an essential role in angiogenesis, with endoglin null mice having an embryonic lethal phenotype due to defects in angiogenesis and mutations in endoglin resulting in the vascular disease hereditary hemorrhagic telangiectasia type I. While endoglin is thought to regulate TGF-β superfamily signaling in endothelial cells through regulating the balance between two TGF-β responsive pathways, the ALK5/Smad2/3 pathway and the ALK1/Smad1/5/8 pathway, the mechanisms by which endoglin regulates angiogenesis has not been fully defined. Here we investigate the role of the cytoplasmic domain of endoglin and its phosphorylation by TGF-β superfamily receptors in regulating endoglin function in endothelial cells. We demonstrate that the cytoplasmic domain of endoglin is basally phosphorylated by ALK5, primarily on serines 646 and 649, in endothelial cells. This basal ALK5-mediated phosphorylation primes and is necessary for subsequent phosphorylation of endoglin by ALK1, as inhibition of ALK5 or genetic deletion of ALK5 abrogates ALK1-mediated endoglin phosphorylation. Functionally, the loss of phosphorylation at serine 646 resulted in a loss of endoglin mediated inhibition of TGF-β stimulated Smad1/5/8 signaling, while loss of phosphorylation at serine 646 or serine 649 resulted in a loss of endoglin mediated inhibition of BMP-9 stimulated Smad1/5/8 signaling. In addition, loss of phosphorylation at serine 646 resulted in a loss of endoglin mediated inhibition of endothelial cell migration. Taken together these results support a model of sequential phosphorylation of endoglin by ALK5 then ALK1 as an important mechanism for regulating TGF-β superfamily signaling and migration in endothelial cells.

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B20
ENDOGLINS DIFFERENTIALLY MODULATE TGFβ1 SIGNALLING

S Velasco, M Pericacho, C Bernabéu, JM López-Novoa, A Rodríguez-Barbero

Instituto "Reina Sofía" de Investigación Nefrológica, Departamento de Fisiología y Farmacología, Universidad de Salamanca, Spain

Transforming growth factor β 1 (TGFβ1) regulates cellular processes by binding to type I and type II TGFβ receptors. In addition to these signalling receptors, endoglin, acts an auxiliary receptor for TGFβ. There are two different alternatively spliced isoforms of endoglin, L-endoglin (L, long) and S-endoglin (S, short) however, little is known about the effects of S-endoglin isoform on TGFβ signalling. Here, we have analyzed the TGFβ1 signaling pathways and the effects of L- and S-endoglin in endoglin-deficient L6E9 cells. We found that TGFβ activates two distinct TβRI-Smad signaling pathways: ALK1-Smad1-Id1 and ALK5-Smad2-PAI1, in these cells. ALK1, ALK5 and T,RII were detected at the level of mRNA and protein by PCR and Western blot. TGFβ1 induced Smad1, Smad2 and Smad3 phosphorylation and nuclear translocation determined by Western blot and immunocytofluorescence. TGFβ1 induced Id1 and PAI-1 expression. Interestingly,the expression of endoglina in these cells modulates the TGFβ signalling pathways. L-endoglin enhanced the ALK1-Id1 pathway, while S-endoglin promoted the ALK5-PAI1 route. Our data demonstrate that endoglins regulate the signalling pathway of TGFβ1 in L_6E_9 cells.

B21
NETWORK ANALYSIS SUGGESTS SEVERAL NOVEL PROTEINS SHARED BY ALK1, TβRII AND ENDOGLIN: IMPLICATIONS FOR HHT

M Letarte, G Xu, M Barrios-Rodiles, D Voulgaraki, E Cheng, Z Jawed, R Nadon, JL Wrana

Molecular Structure and Function Program, The Hospital for Sick Children, Heart and Stroke Richard Lewar Center of Excellence, and Department of Immunology, University of Toronto, Toronto, Canada; Centre for Systems Biology,Samuel Lunenfeld Research Institute, Mount Sinai Hospital, Toronto, Department of Human Genetics, McGill University, Montreal, Canada

Previous studies reported that endoglin and ALK1 interact with TβRII to mediate TGF-β1/β3 effects via the Smad1,5 pathway. To identify novel signaling networks implicating these receptors and potentially altered in HHT, we measured proteins interacting with endoglin, ALK1 and TßRII. We used the luminescent-based mammalian interactome mapping (LUMIER) automated high-throughput technology to screen 640 Flag-tagged cDNA preys by co-transfection with endoglin, ALK1 or TβRII luciferase (RL)-tagged baits. The RL bait bound to the Flag-tagged prey is detected enzymatically in the immunoprecipitates as light emission. The data were analyzed by 3 methods to generate a stringent list of significant preys for subsequent validation: LUMIER intensity ratio (LIR) (Science 2005, 307:1621), Robust Z score (RZ) (J Royal Statistical Society. Series B (Methodological) 1995, 57:289) and 10% Trimmed Polish (TP10) (Nat Biotechnol 2006, 24:167). The 3 methods were relatively well correlated (r=0.8). A first list was made from any proteins in the top 100 scores using each of these methods; only those with RZ scores > 3 and LIR values > 6 were then considered strong interactors. These criteria identified 26 proteins binding to both ALK1 and TßRII. Of these proteins, 6 also interacted strongly (LIR>6) with endoglin while 7 showed a weaker, perhaps indirect association (LIR>3) with endoglin. In addition, 6 proteins interacted strongly with TβRII and endoglin. These data reveal several TGF-β networks involving endoglin and/or ALK1 that are potentially affected in HHT. The confirmation of some of these interactions and their functional relevance will be discussed.

Xu is a recipient of a Heart and Stroke Foundation of Canada Fellowship; this research is supported by The Canadian Institutes of Health Research).

B29
TGF-β SIGNALING IN ENDOTHELIAL CELLS PLAYS A TEMPORAL AND SPATIAL ROLE DURING CEREBRAL VASCULAR DEVELOPMENT

HL Nguyen, YJ Lee, E Lee, SO Park, SP Oh

Department of Physiology and Functional Genomics, University of Florida, Gainesville, FL, USA

The interaction between ALK1 and ALK5 in vascular endothelial cells (ECs) has been a controversial subject. Recently, our lab suggested that ALK1 signaling in ECs is independent of ALK5 and TGFBR2 signaling *in vivo*. We showed that conditional deletion of *Alk1* by an EC-specific cre line (L1cre) resulted in vascular abnormalities, whereas *Alk5* and *Tgfbr2* deletion by L1cre did not affect vascular development. Interestingly, recent data of *Itgav-null*, *Itgb8-null*, and *Tgfb1/Tgfb3* double knockout mice showed that these mutant embryos exhibited strikingly similar phenotypes of cerebral vessel dilation and hemorrhage within the ganglionic eminence starting at E11.5. Other than the brain area, the vascular beds were largely unaffected. These findings indicate a spatial and temporal role of TGF-β signaling in brain vessel development. Because cre is not expressed until E13.5 in the L1cre line, we might have missed this cerebral phenotype in the L1cre(+)$Alk5^{fl/fl}$ and L1cre(+)$Tgfbr1^{fl/fl}$ mice. To test this, we used a novel EC-specific cre knockin line ($Alk1^{Cre}$), in which cre was inserted into the *Alk1* locus and is expressed in ECs beginning at E9.5. $Alk1^{Cre}$;$Alk5^{fl/fl}$ and $Alk1^{Cre}$;$Tgfbr2^{fl/fl}$ exhibited the same specific cerebral vessel dilation and hemorrhage at E11.5. The phenotype became more severe by E13.5. $Alk1^{Cre}$;$Alk5^{fl/fl}$ were found dead by E15.5. The stage of embryonic lethality in $Alk1^{Cre}$;$Tgfbr2^{fl/fl}$ has yet to be determined. These results suggest that TGF-β signaling in ECs plays a pivotal role in blood vessel invasion into the neuroectoderm and further support that ALK1 signaling is independent of ALK5 or TGFBR2 signaling.

SESSION XII: SCREENING FOR PAVMs

C48
CONSIDERATIONS FOR PAEDIATRIC SCREENING AND TREATMENT PROGRAMMES IN FAMILIES WITH HEREDITARY HAEMORRHAGIC TELANGIECTASIA (HHT)

CL Shovlin,[1,4] A Bush,[2] D Edwards,[3,5] JE Jackson,[5] N Coote[6]

[1]NHLI Cardiovascular Sciences and [2,3]Pediatrics, Imperial College London [2]Royal Brompton Campus; [3]Hammersmith Campus); [4]Respiratory Medicine, [5]Imaging and [6]Pediatrics, Hammersmith Hospital , Imperial College Healthcare Trust, London, UK

Introduction. Symptomatic children from HHT families deserve full evaluation and treatment of causative AVMs. For asymptomatic healthy children, there are few data regarding screening risk-benefit considerations. Our HHT centre has in the past deferred screening in asymptomatic children until after puberty, so we evaluated data in favour of changing practice. *Methods.* We performed a preliminary clinical risk benefit analysis incorporating factors which would be in favour of screening (degree of danger posed by silent AVMs; AVM treatability; evidence of reduced long-term AVM complications) versus factors mitigating against screening. The latter include screening and treatment-associated risks such as general anaesthesia; increased susceptibility of children to radiation-induced morbidity, and ethical considerations of screening an asymptomatic child, who is too young to give consent and will likely not understand the implications of testing. *Results.* While for pulmonary AVMs the lack of complications in asymptomatic children prior to the pubertal PAVM growth/maturation period and adult onset of neurological complications makes it difficult to justify pre-pubertal screening and treatment, considerations for cerebral AVMs may differ. Cerebral AVMs develop perinatally, may occasionally bleed in childhood; screening can be performed by cerebral MRI without ionising radiation, and there are higher risk cerebral AVMs for which treatment is advocated. *Conclusions.* In view of our initial analyses, we have commenced discussions on introducing paediatric cerebral MRI screening. In keeping with UK practice, this will be dictated by evidence of treatment efficacy in improving the natural history of cerebral AVMs, existing paediatric healthcare practices, and families' perception of risk.

C9
SCREENING FOR PULMONARY ARTERIOVENOUS MALFORMATIONS USING TRANSTHORACIC CONTRAST ECHOCARDIOGRAPHY

MWF van Gent,[1] MC Post,[1] JGLM Luermans,[1] RJ Snijder,[2] CJJ Westermann,[2] HW Thijs Plokker,[1] TT Overtoom,[3] JJ Mager[2]

Department of [1]Cardiology, [2]Pulmonology and [3]Radiology; St Antonius Hospital, Nieuwegein, The Netherlands

Background. Pulmonary arteriovenous malformations (PAVMs) are associated with neurological complications in patients with hereditary hemorrhagic telangiectasias (HHT) and therefore screening is warranted. We studied, prospectively, the diagnostic value of transthoracic contrast echocardiography (TTCE) as a screening technique for PAVM using chest HRCT as the gold standard for treatable PAVMs. *Methods*. We included 399 persons who were referred for HHT screening and underwent both a chest HRCT and TTCE. We excluded 24 persons in whom a TTCE could not be performed because of failure or refusal of placement of an intravenous line, 2 persons in whom TTCE image quality was too poor and 4 persons who did not have a chest HRCT (refused or contra-indicated). *Results.* TTCE was positive in 155 (39%), indistinguishable from a patent formamen ovale in 4 persons (1.0%), and negative in 240 persons (60.2%), respectively. Chest HRCT was positive in 80 (20%), indeterminate in 5 (1.3%) and negative in 314 (78.7%) persons, respectively. Five patients with a negative TTCE were diagnosed with PAVMs on CT; in all these cases PAVMs were too small for transcatheter embolotherapy. Sensitivity and specificity of TTCE were 94.0% (95%CI 85.8-97.9) and 76.0% (95%CI 71.0-80.8); the negative and positive predictive value 98.0% (95%CI 95.1-99.3) and 50.3% (95%CI 42.0-58.7), respectively. *Conclusion.* TTCE has an excellent negative predictive value and might be used as an initial screening procedure for PAVM. The high falsely positive rate of TTCE might represent microscopic PAVMs below the detection limit of chest HRCT and possibly normal variation.

C26
CONTRAST ECHOCARDIOGRAPHY OR CT SCAN FOR THE DETECTION OF PULMONARY ARTERIOVENOUS MALFORMATIONS (PAVMS) IN PATIENTS WITH HEREDITARY HAEMORRHAGIC TELANGIECTASIA (HHT)?

S Blivet, Th Chinet, JH Blondel, I Bourgault-Villada, C Fagnou, G Lesur, A Ozanne, JP Pelage, B Raffestin, F Soubrier, J Roume, P Lacombe

HHT Center of Paris, AP-HP, Hospitals Ambroise Paré, Bicêtre & Pitié-Salpêtrière, France

PAVMs are associated with a high incidence of severe complications, especially neurological complications. It is therefore important to screen patients with HHT for PAVMs since embolisation of PAVMs may prevent complications. It has been suggested that transthoracic contrast echocardiography (TTCE) is the most sensitive technique to detect PAVMs. We decided to measure the sensitivity and the specificity of TTCE with reference to chest high resolution computed tomography (HRCT). We enrolled all consecutive adult patients referred to our Center for evaluation of HHT between 2003 and 2008. The diagnosis of HHT was based on the Curaçao criteria and/or the presence of a mutation in the ALK1 gene or the ENG gene. TTCE and chest HRCT were performed in all patients as part of our routine screening protocol. We report the results for 160 patients (mean age: 47.8 yrs, range: 16-83 yrs; 44% male). Chest HRCT revealed PAVMs in 86 patients (of which 31 had at least one

PAVM with a feeding artery diameter >3mm). TTCE was positive in 91 patients. Importantly, TTCE was negative in 21 patients with PAVMs on the chest HRCT, including 2 patients with PAVM with a feeding artery diameter >3 mm. Overall, the sensitivity of TTCE was 75.6% and the specificity was 64.9%. When considering only PAVMs with a feeding artery diameter >3mm, the sensitivity of TTCE was 93.5% and the specificity was 51.9%. In conclusion, these data indicate that chest HRCT is clearly superior to TTCE to detect PAVMS in patients with HHT.

C28
COMPLICATIONS TO CONTRAST ECHOCARDIOGRAPHY (CE) FOR SCREENING OF PULMONARY ARTERIOVENOUS MALFORMATIONS (PAVMS): A PROSPECTIVE SURVEY

P Gazzaniga,[1] E Buscarini,[2] G Manfredi,[2] L Reduzzi,[3] C Danesino,[4] C Olivieri,[4] F Pagella,[5] M Grosso,[6] G Pongiglione,[7] E Boccardi,[8] on behalf of HHT-NET

[1]Cardiology Dept, [2]Gastroenterology Dept, [3]Radiology Dept, Maggiore Hospital, Crema; [4]Genetic Institute, University of Pavia; [5]ENT Institute, University of Pavia; [6]Radiology Dept, Ospedale S. Croce, Cuneo; [7]Paediatric Cardiology Dept, Ospedale Gaslini, Genova; [8]Interventional Neuroradiology Unit, Niguarda Hospital, Milan; Italy

Aims. This study is aimed to evaluate safety profile of CE for screening of PAVMs. *Methods.* A prospective study was conducted in 328 consecutive subjects (males 146, mean age 40, range 4-77) at risk for HHT who underwent our multidisciplinary screening protocol for HHT, including CE for detection of PAVMs. CE positivity: for PAVMs, if any bubble appeared in the left atrium after more than 3 cardiac cycles after initial opacification of the right chambers; for patent foramen ovale (PFO), with an earlier bubble appearance. *Shunt grading*. according to the contrast opacification of the left-sided chambers, from 0 to 3. All CE procedures were recorded for review. Patients were observed during and for two hours after CE for detection of complications -defined as mild, severe, fatal- resulting from paradoxical air embolism. Complications were correlated (χ^2 with Yates correction) with affection status, CE grading, PAVMs (presence and features) as defined by multirow CT. *Results.*

Table.

	n (%)
Affected	275 (83)
CE grade 1	106 (32)
CE grade 2	57 (17)
CE grade 3	36 (10)
PFO	27 (8)

Mild complications occurred in 9 patients (2.7%): migraine in 4, associated with nausea and vomiting in 1 case, blurred vision in 3, numbness in 2; paresthesias, associated or not to migraine, occurred in 6. Complications occurred within 2-25 minutes after saline injection, and showed rapid and spontaneous recovery in all cases. All complications occurred in affected subjects with PAVMs, in 5 with grade 3 shunt, and in 4 with grade 2. Correlation was found between the affection status and CE grading and complications (p 0.01 and <0.0001, respectively). Correlations between PAVM features and complications will be presented.
Conclusions. Our findings indicate CE is a safe diagnostic tool for suspected PAVMs.

C18
UTILITY OF TRANSCRANIAL DOPPLER CONTRAST STUDY IN PULMONARY ARTERIOVENOUS MALFORMATION ASSESSMENT IN HEREDITARY HEMORRHAGIC TELANGIECTASIA

D Manawadu, D Vethanayagam, M Saqqur, C Derksen, J Choy, K Khan

Department of Medicine and Edmonton HHT Center, University of Alberta, Edmonton, Alberta, Canada

Introduction. Transcranial Doppler contrast study (TCDc) is a simple noninvasive procedure used routinely in stroke centers to identify cardiac right to left shunts. Pulmonary arteriovenous malformations (PAVMs) are common in, and can act as right to left shunts in Hereditary Hemorrhagic Telangiectasia (HHT). Screening of PAVMs is most sensitive with chest radiograph plus transthoracic contrast echocardiography (TTCE). Accredited HHT centres have investigated several screening methods to detect PAVMs but not TCDc. We aim to evaluate the sensitivity of TCDc in relation to TTCE or Transesophageal echocardiogram (TEE) in shunt detection and safety in patients with HHT. *Methods.* Patients with HHT underwent insonation of both middle cerebral arteries using a TCD head frame during routine screening TTCE (4 patients) or at times remote from this using similar agitated saline protocols. All TCDc recordings were assessed by three readers, blinded to echocardiogram and clinical findings, for microembolic signals suggesting right to left shunt. *Results.* Twelve patients (10 probable, 2 possible HHT), 5 female, mean age 42 years (range 19 to 72) were assessed. Echocardiography detected presence of right to left shunts in 10 patients and TCDc in 9. The sensitivity of TCDc against echocardiography in shunt detection is 90%, specificity 100%, positive predictive value 100%. There were no adverse events. *Conclusion.* We report the first case series of TCDc in patients with HHT. In this pilot study, TCDc appears to be a sensitive and well tolerated screening tool and offers a simple and possibly more accessible monitoring tool to this group of patients.

C36
DETECTION OF REPERFUSED PULMONARY ARTERIOVENOUS MALFORMATIONS WITH CONTRAST-ENHANCED MAGNETIC RESONANCE ANGIOGRAPHY IN PATIENTS WITH HEREDITARY HEMORRHAGIC TELANGIECTASIA (OSLER-RENDU-WEBER DISEASE)

GK Schneider, A Opitz, UW Geisthoff, M Katoh, A Buecker, A Massmann

Saarland University Hospital Homburg/Saar, Germany; Clinics of City Cologne/Holweide, Germany

Purpose. To evaluate contrast-enhanced magnetic resonance angiography (CE-MRA) for detection of reperfused pulmonary arteriovenous malformations (r-PAVM) after catheter embolization in patients with hereditary hemorrhagic telangiectasia (HHT). *Materials and Methods.* 230 patients (mean age: 46.9; male 96; female 134) with proven HHT according to Curacao criteria, or first-degree relatives, underwent MRI/MRA screening for PAVM. Detection of r-PAVMs was based on CE-MRA (Gadolinium-BOPTA 0.1 mmol/kg bodyweight) and confirmed by catheter angiography (CA). *Results.* 40 patients with 104 PAVMs underwent embolization with initial complete occlusion. Follow-up CE-MRA at 3 and 12 months revealed reperfusion of 5/104 embolized PAVMs in 4/40 patients and 6 r-PAVMs in 3 patients who underwent embolization elsewhere. All patients with r-PAVMs underwent re-embolization, which detected no additional r-PAVMs. Due to overlying embolization materials CE-MRA was especially helpful for the re-embolization of complex PAVMs to identify reperfused vessels. Reperfusion of 5 PAVMs in 4 patients treated at our centre was caused by corrosion (2 r-PAVMs in 1 patient) of tungsten filaments which are no longer used at our institution; insufficiently packing of the embolization coils (1 PAVM in 1 patient); and opening of collateral feeding vessels (2 PAVMs in 2 patients) which were not present on screening CE-MRA and 3 months after embolization. Of the 3 patients initially embolized at other centres reperfusion of 6 PAVMs were caused by insufficient packing of the embolization material. *Conclusion.* Compact packing of platinum coils is a prerequisite for sufficient and durable occlusion of PAVMs. In spite of initial successful embolization, reperfusion may occur at later time. CE-MRA is a useful tool for necessary follow-up.

C43
POST 2007-2008 GUIDELINES: SHOULD ANTIBIOTIC PROPHYLAXIS BE GIVEN PRIOR TO DENTAL PROCEDURES FOR PATIENTS WITH PULMONARY ARTERIOVENOUS MALFORMATIONS AND HEREDITARY HAEMORRHAGIC TELANGIECTASIA?

CL Shovlin, KB Bamford, D Wray

Imperial College London, and University of Glasgow, UK

Introduction. Recently published British and American guidance state antibiotic prophylaxis is no longer required for most patients with heart disease at risk of infective endocarditis. What should happen to patients with pulmonary arteriovenous malformations (PAVMs) who were previously recommended antibiotic prophylaxis? *Methods.* We reviewed whether the British NICE committee considered PAVM risks; why recommendations were changed; and explored risk differences between patients with PAVMs and structural heart disease. *Results.* 1) The NICE committee did not consider people with PAVMs at risk of brain abscess when reviewing the evidence regarding antibiotic prophylaxis. 2) For patients with heart disease, withdrawal of antibiotic prophylaxis was recommended because i) there is no evidence that prophylactic antibiotics prevent dental bacteraemias; ii) The intensity of bacteraemias during tooth brushing and flossing may exceed those from dental procedures; iii) antibiotic prophylaxis is cost ineffective with potential medical risks when treating large numbers of people each individually at a low risk of endocarditis. 3) The risk of brain abscess for an HHT/PAVM patient differs due to both magnitude of risk, and likely mechanism. The overall risk of brain abscess per PAVM patient is several orders of magnitude higher than heart patients at risk of endocarditis. *Conclusions.* We conclude that antibiotic prophylaxis should still be given to PAVM/HHT patients prior to dental and surgical procedures.

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WORKSHOP: OUTCOMES WITH NEW DEVICES IN THE MANAGEMENT OF PAVMs

C35
OCCLUSION OF PULMONARY ARTERIOVENOUS MALFORMATIONS WITH AMPLATZER VASCULAR PLUG II – PRELIMINARY RESULTS

R Andersen, E Dorenberg, P Giæver, K Heimdal, G Hafsahl

Departments of Interventional Radiology, Pulmonary Medicine and Medical Genetics; Oslo University Hospital, Rikshospitalet, Oslo, Norway

Background/Purpose. Angiographically confirmed recanalization of primary successful occluded pulmonary arteriovenous malformations (AVMs) are reported to be as high as 17% of treated patients. With optimized coil embolization techniques this number has probably fallen below 10%. The Amplatzer Vascular Plug II (AGA Medical Corp. ,Plymouth, MN, US) is approved for arterial and venous embolizations in the peripheral vasculature. We evaluated outcome and possible serious side effects after deploying this new device in the feeding artery of pulmonary AVMs. *Material and Methods.* 10 patients (age range: 18-78 years), were treated with 15 Amplatzer Vascular Plug II (3-12 mm) for AVMs with feeding arteries diameter 2.5-8 mm. Clinical and radiological follow up at mean 5.5 months (range 3-8). *Results.* All feeding vessels treated with the Amplatzer Vascular Plug II occluded within 5 minutes after deployment. No hemopthysis or other chest symptoms was observed or reported. All occluded feeders remained occluded at follow up as verified by CT (7pts) or conventional pulmonary angiography (8 pts). Neither migration of the plug nor erosions produced by the device was seen. *Conclusions.* The Amplatzer Vascular Plug II effectively occlude feeding vessels in pulmonary AVMs. No recanalization of AVM and no device related complications was detected during follow up.

C37
EMBOLOTHERAPY OF PULMONARY ARTERIOVENOUS MALFORMATIONS WITH AMPLATZERPLUGS: LONG TERM RESULTS

EM de Gussem,[1*] J Sala,[2*] M van Leersum,[2] CJJ Westermann,[1] TT Overtoom,[2] JJ Mager[1]

Department of [1]Pulmonology and [2]Radiology, St Antonius Hospital, Nieuwegein, The Netherlands. [*]both authors contributed equally.

Objective. To study the effectiveness of Amplatzerplugs for emoblization of pulmonary arteriovenous malformations (PAVMs). *Methods.* retrospective review study of 65 patients with PAVMs embolized with Amplatzerplugs between August 2004 and June 2008 in the St Antonius Hospital Nieuwegein. Most were followed by repeat CT-chest or pulmonary angiography. *Results.* In 65 patients (41 women, 24 men) PAVMs have been embolized by using vascular plugs. Twenty-two patients have been previously embolized by coils. In total 190 plugs and 36 coils have been used in 85 procedures. Complications happened during 5 procedures: 3 minor hemoptysis, 1 dissection of the artery causing thrombosis of the artery, 1 luxation of the plug to the femoral artery. Follow up was performed by CT chest (19/85) or pulmonary angiography (20/85). Time to follow-up varying between 7 days and 47.7 months (mean 14.2 months, SD 10.3 months) Recanalisation of coils was detected in 6/39 and recanalisation of vascular plugs in 2/39. *Conclusions.* The use of vascular plugs to embolize PAVMs is save since no major complication occurred and the incidence of recanalisation is low. Radiation exposure time appears shorter when using Amplatzer plugs than coils.

C54
MEDIUM TERM RESULTS OF USE OF AMPLATZER VASCULAR PLUGS IN TREATING PULMONARY ARTERIOVENOUS MALFORMATIONS

GJ Robinson, DF Ettles, PM Scott, R Lakshminarian, AH Morice

Hull Royal Infirmary, Hull, East Yorkshire, UK

Purpose. PAVMs treated by embolotherapy may recur as a result of recannalisation or the development of new feeding arteries. The Amplatzer Vascular Plugs (AVP), both types 1 and 2, are recoverable, screw detachable nitinol embolic devices that offer lower risks of paradoxical embolisation than using regular pushable coils. This study presents our medium term results of their use in PAVMs. *Materials and Methods.* 15 patients with PAVMs (age range 19-67 years, M:F=3:12), 9 of whom were asymptomatic and detected on screening, and 6 of whom were symptomatic, were treated with AVPs between December 2004 to January 2009. Our initial experience was with type 1 devices, but since the release of the type 2 device this has been preferred as it produces more rapid occlusion. *Results.* A total of 24 PAVMs were deemed suitable for the AVP, and all were successfully occluded. 14 type 1 and 10 type 2 AVPs were deployed. There were no device or procedural complications and no repeat procedure has been necessary. 6 patients have undergone check angiography, 4 have undergone chest CT. All patients remain well and symptom-free with respect to their PAVMs at a mean follow-up of 34months (range 10-49) for type 1 and a mean of 9 months (range 1-16) for type 2. *Conclusions.* Embolotherapy is the preferred treatment modality for occlusion of PAVMs, and the AVP has added a new option to our range of embolic devices. We present medium term outcome of using these devices.

C1
DOES USE OF COILS IN ADDITION TO AMPLATZER VASCULAR PLUGS PREVENT RECANALIZATION?

S Trerotola, R Pyeritz

Hospital of the University of Pennsylvania, PA, USA

Purpose. When an Amplatzer vascular plug (AVP) is used as the sole device to treat a PAVM, recanalization has been reported. We report our experience with use of at least one coil whenever possible in addition to an AVP

when treating PAVM. *Materials and Methods.* IRB approval was obtained and HIPAA compliance was observed. 32 patients had 42 feeders in 39 PAVM treated with 42 AVP; in all but three PAVM at least one coil was used in addition. 12 PAVM (29%) were complex, 9 (23%) were solitary. Additional PAVM in these patients treated using coils alone (n=50) are not reported here. CT scanning was scheduled at 6 months; scans were evaluated for persistent sac perfusion, sac shrinkage and/or complete resolution of the PAVM. *Results.* Complete occlusion was achieved in 100% of PAVM. The mean number of coils used in addition to an AVP was 1.5 (range, 0-5). Six patients were noncompliant with follow-up and three patients are not yet due for imaging; 24 patients with 33 AVP-treated PAVM had follow-up imaging (mean 8 months, range, 6-13). No PAVM exhibited recanalization on followup-up CT; sac shrinkage or disappearance was seen in 100%. A characteristic CT appearance to the AVP was noted. Longer term surveillance imaging is scheduled and not yet due in any patient. *Conclusions.* AVP, when used in conjunction with coils, offer excellent occlusion of PAVM, with no recanalization seen in this study. The CT appearance of the AVP must not be confused with failure of sac shrinkage.

SESSION XIII: WHAT CAN WE LEARN FROM OTHER RARE DISEASES?

OVERVIEW OF MEMBER STATES POLICIES IN THE FIELD OF RARE DISEASES AND ORPHAN DRUGS

S Aymé

Director of Orphanet, chair of the EC Rare Disease Task Force, chair of the WHO Topic Advisory Group for Rare Diseases

Member states' policies and actions in the field of rare disease are rapidly evolving. Up till now, several countries have taken action to support the development of orphan medicinal products (OMP) and adapt their health care system to meet the needs of the RD patient community. They share common features but diverge in some areas. With regard to centres of expertise, there are three categories of countries in Europe: those which have a policy regarding RD and have established centres of expertise within this framework (Denmark, France, Italy, Norway and Sweden); those which have established centres of expertise, though not specifically for RD (Belgium, Croatia, Czech Republic, Finland, Greece, Ireland, Portugal, Great-Britain) and those which have no centres with this denomination, although they have centres with all characteristics of a centre of expertise (almost all of the other countries). With regard to provision of information to patients and professionals, several MS have established web-based information services (Sweden and France) and telephone help lines (Bulgaria, Denmark, France, Italy, Netherlands, Norway, Spain, Sweden, UK) although their resources vary considerably. Orphanet was developed by France initially but several European countries are now supporting it financially as well (Germany, Israel, Italy, Spain, Switzerland). Funding for research on rare diseases is provided through common calls for proposals in Belgium, France, Germany, Israel, Italy, Netherlands, Spain, Turkey. Some of these countries have national calls as well. Among MS, major disparities in access to treatment are observed. Although all OMP receive market authorisation at the EU level, their accessibility at MS level depends both on marketing decisions by the Company and on the willingness of health authorities in each MS to quickly establish OMP prices and reimbursement rules. A few MS have taken initiatives to improve access to treatment (France, Germany, Hungary, Ireland, Italy, Netherlands, Poland). Initiatives to empower patient organisations are also an important element of a positive policy in some MS (Denmark, France, Netherlands, Italy, Spain, Sweden), but most of the initiatives came from the patient organisations themselves without official support from governmental bodies. France is the only country in the world to have adopted a national plan with a specific budget to start solving the many challenges raised by the rarity of thousands of rare diseases. Rare diseases (RD) were included as one of the five major priorities in the 9 August 2004 law rela-

ting to public health policy. The national plan was elaborated through working groups comprised of health professionals, patient representatives and policy makers. It was published on 20 November 2004 as a four year plan with a budget of 100 millions Euros. The national plan outcome is currently under external evaluation. A report should be published in early 2009. The two main successes of this plan are Orphanet, the portal of rare diseases, and the establishment of 131 centres of reference. Two countries have recently adopted a set of coordinated measures which can be considered as a national plan, with an associated budget (Bulgaria) or a not yet known budget (Portugal). Some other countries have initiated the process of defining a national plan (Austria, Belgium, Germany, Hungary, Romania, Spain, Turkey). Outcomes of all these initiatives have to be made known for the other countries to be able to benefit from the experience gained.

THE SPANISH RESEARCH CENTER FOR RARE DISEASES (CIBERER)

F Palau

Institute of Biomedicine, CSIC, and CIBER de Enfermedades Raras (CIBERER), Valencia, Spain

Rare diseases are characterized by low frequency (less than 5 patients per 10,000 inhabitants in the European Union). Most of these disorders have a chronic course, are associated with moderate or severe physical or mental disability, and therapeutic resources are limited. It has been estimated that 80 percent of disorders are genetic. As a whole rare diseases have to be considered as a public health challenge. Patients' needs include integrative health and clinical assistance, genetic counselling, social support, specific training for medical and health professionals, and promotion of specific research programmes. The integrative approach also includes generation of a national and international network of centre of expertise that provide an integrative setting for diagnosis, management, therapeutics, including clinical trials, and research. The Biomedical Network Research Centre for Rare Diseases (CIBER de Enfermedades Raras or CIBERER) was set up as one of the measures in the Ingenio 2010 initiative form the Spanish Government, to increase critical mass and research excellence in Rare Diseases. This is one of the nine CIBER consortiums with their own legal personality and own management partly financed by the Carlos III Health Institute (ISCIII) as part of its plan to set up stable Cooperative Research structures. The CIBERER is an innovative structure for networking research on rare diseases. It is currently made up by 61 research groups from 30 health or academic institutions across Spain. It stands on the basis of the development and research potential of the research groups that form the consortium. The consortium provides strategic coordination, human and material resources, apart from a cooperation setting in which the synergies produced by the great potential of multidisciplinary and complementary knowledge can be taken advantage of. The groups are integrated in scientific areas where this cooperation is coordinated and fostered. These areas include mitochondrial diseases, inherited metabolic diseases, neurogenetics, endocrinological diseases, birth defects and developmental disorders, clinical genetics and genetic epidemiology, and genetic instability and predisposition to cancer. The CIBERER is thus a centre designed for the development and implementation of cooperative research in the field of rare diseases, furthering basic biomedical research, clinical research and epidemiological research, giving particular emphasis to transferring research from the laboratory to the patient's bedside and providing a scientific answer to the questions stemming from the doctor-patient interaction.

MOLECULAR GENETICS OF VASCULAR MALFORMATIONS

M Vikkula

Human Molecular Genetics, de Duve Institute, Université catholique de Louvain, Brussels, Belgium

Vascular malformations are *localized* errors of vascular development. They are often identified on the skin as "birthmarks" of various sizes and shapes. They usually slowly grow with the growth of the child. They may also be encountered in other organs, such as the liver, intestine and the brain. The lesions are consisted of tortuous vascular channels of various types, with continuous endothelium surrounded by various numbers of support cells. Most of these lesions occur sporadically, yet sometimes as part of a syndrome or as an inherited disorder. Genetic studies of such families have led to the identification of a number of genes that can cause vascular malformations. Our first discovery was the identification of the TIE2/TEK gene encoding an endothelial receptor tyrosine kinase to be responsible for hereditary mucocutaneous venous malformations (VMCM). As a continuation to this work, we unraveled that a loss-of-function mutation in the VEGFR3 gene, encoding the vascular endothelial growth factor 3 receptor, is responsible for congenital hereditary lymphedema. We also linked mutations in the KRIT1 gene to cutaneous capillary-venous malformations associated with cerebral cavernous malformations. More recent work has lead to the identification of mutations in glomulin to be responsible for hereditary glomuvenous malformations ("glomangiomas"), SOX18 mutations to cause lymphedema-hypotrichosis-telangiectasia syndrome and RASA1 mutations to cause a newly recognized disorder, which associates atypical hereditary capillary malformations with fast-flow anomalies (CM-AVM). In 1994, when we mapped the 9p21 locus for VMCM, we hypothesized that the variation in size, number and localization of these multifocal lesions may follow Knudson's double-hit hypothesis for retinoblastoma. Proof for this has started to pile up supporting the idea of paradominant inheritance, the need for a combination of an inherited change with a somatic second-hit in the same gene, i.e. the inherited mutations have only recessive effects at tissular level. Moreover, we have identified local, somatic genetic defects that cause one of the more common sporadic forms of these malformations. This highlights the importance of assessing for tissue-based genetic chan-

ges, especially acquired genetic changes, as possible pathophysiological causes, which have been largely overlooked in developmental disorders. Large-scale somatic screens are likely essential in uncovering the nature and prevalence of such changes, and their downstream effects. *In vivo* models are also important to dissect the molecular pathways involved. Such models will enable direct evaluation of the developmental function and significance of the genes in *vasculogenesis* and *angiogenesis*. In addition, they will serve for screening of novel therapeutic modalities.

miikka.vikkula@uclouvain.be;
http://www.deDuveInstitute.be/vikkula

POSTERS

BASIC SCIENCE

B18
THE PROGNOSTIC VALUE OF SOLUBLE ENDOGLIN IN ACUTE MYOCARDIAL INFARCTION

A Rodríguez-Barbero, M Pericacho, I Cruz, J Martín-Moreiras, P Pavón, C Martín-Luengo, JM López-Novoa

Instituto "Reina Sofía" de Investigación Nefrológica. Departamento de Fisiología y Farmacología. Hospital Universitario de Salamanca. Universidad de Salamanca, Spain

Abundant efforts have focused on unravelling the mechanisms that underlie post-infarction neovascularization. Therefore, the identification of markers capable to reflect the formation of blood vessels should be desirable. Endoglin is a proliferation-associated and hypoxia-inducible protein expressed in endothelial cells. However, the role of endoglin in myocardial infarction has not been explored. Thus, the aim of this study was to investigate the levels of soluble circulating endoglin and their prognostic significance in patients with acute myocardial infarction (AMI). Serum endoglin was determined by ELISA in 183 AMI patients upon admission to hospital and 48 hours later. The control group comprised 72 healthy subjects who were sex and age matched to the patients. Endoglin levels in AMI patients on admission were significantly lower than in healthy controls (4.25±0.99 ng/mL vs. 4.59±0.87 ng/mL; p=0.013), and decreased further in the first 48 hours (3.65±0.76 ng/ml, p<0.001). Upon follow-up (median 319 days), patients who died had a significantly greater decrease in serum endoglin level over the first 48 hours than those who survived (1.03±0.91 vs. 0.54±0.55 ng/ml; p=0.025). Endoglin decrease was an independent predictor of short term (30 days) (hazard ratio 2.33; 95% CI= 1.27-4.23; p=0.006) cardiovascular mortality, and also predicts overall cardiovascular mortality during the follow-up (median 319 days) in AMI patients (hazard ratio 2.13; 95% CI= 1.20-3.78; p=0.01). In conclusion, early changes in serum endoglin may predict mortality after acute myocardial infarction

B26
PULMONARY ENDOTHELIAL SYNTHESIS AND PROCESSING OF COAGULATION FACTOR VIII, THE PROCOAGULANT BIOMARKER ELEVATED IN PATIENTS WITH HHT AND PULMONARY AVMS

CL Shovlin,[1,2] G Angus,[2] GN Okoli,[1] FS Govani,[1] IG Mollet,[3] FA Mauri[1,2]

[1]Imperial College London; [2]Hammersmith Hospital, Imperial College Healthcare NHS Trust, London, UK; [3]University of Lisbon, Portugal

Introduction. Patients with hereditary haemorrhagic telangiectasia (HHT) are at significant risk of venous thromboses, and of thromboembolic strokes through pulmonary AVMs. We have shown that HHT patients have high plasma levels of coagulation factor (F)VIII, a strong biomarker for recurrent venous thromboemboli, and pulmonary hypertension, and hypothesised that the pulmonary endothelium might be a source of plasma FVIII after demonstrating an age-independent association between FVIII levels and pulmonary AVMs.[1] *Methods.* Endothelial sources of FVIII were defined using immunohistochemistry, confocal microscopy, flow cytometry, and ELISA. FVIII transcripts predicted from database mining were identified by rt-PCR and sequencing in resting and stimulated endothelial cells (EC). *Results.* FVIII mAb-reactive material was demonstrated in CD31+ EC lining large vessels and pulmonary capillaries in normal human lung tissue, and normal primary pulmonary artery and pulmonary microvascular EC. The EC secreted low levels of FVIII to conditioned media, and demonstrated cell surface expression of FVIII mAb-reacting protein compared to an isotype control. Four endothelial splice isoforms, including two novel variants, were identified. A reciprocal relationship between the presence of two short isoforms and full length FVIII transcript suggested a potential splice switching mechanism. Importance of the alternate splice isoforms was suggested by strong evolutionary conservation of flanking sequences. *Conclusions.* The pulmonary endothelium is a site of FVIII synthesis, secretion and cell surface expression, involving complex alternate transcription initiation from the FVIII gene. Further analysis of perturbation of these pathways in HHT is warranted.

Funded by British HHT patients

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PB1
ENDOGLIN IS A MORE SPECIFIC MARKER THAN VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF) IN CERVICAL PARAGANGLIOMAS

N Eleno,[1] A Düwel,[1] A Muñoz,[2] J Paz-Bouza,[3] JM López-Novoa,[1] F Lozano,[4]

[1]Instituto "Reina Sofía" de Investigación Nefrológica & Departamento de Fisiología y Farmacología, Universidad de Salamanca; [2]Servicio de Otorrinolaringología y [3]Servicio de Anatomía Patológica, Hospital Clínico Universitario; [4]Departamento de Cirugía, Facultad de Medicina, Universidad de Salamanca & Servicio de Cirugía Vascular, Hospital Clínico Universitario, Salamanca, Spain

Background. Endoglin, an accessory non signalling receptor for transforming-growth-factor-β1 (TGF-β1), is expressed on endothelium and is implicated in the control

of angiogenesis. In the last years, several investigations put forward the importance of endoglin for tumour growth and progression. Endoglin appears strongly expressed in the neo-vasculature of several solid tumours, and its expression is weaker in non-malignant adult tissue vessels than in tumour vessels. *Objective.* To study the expression of endoglin in cervical paraganglioma compared with the expression of vascular endothelial growth factor (VEGF), the cytokine commonly used as marker for neo-angiogenesis in this kind of tumours. Design of the study and method- Tumours were surgically obtained from five patients and compared with non-tumoral samples of lung tissue obtained from five patients subjected to pulmonary resection; lung is a highly vascularized tissue that exhibits maximal endoglin expression. Detection with specific antibodies was used to determine the expression of the proteins VEGF and endoglin, by using immunoblotting and immunohistochemistry. The expressions of hypoxia-inducible factor (HIF) and vascular cell adhesion molecule-1 (VCAM-1) were used to determine the degree of hypoxia and tumour capillarization, respectively. *Results.* As expected, endoglin is located at the plasma membrane of endotehelial cells, whereas VEGF is a soluble factor. The increase found in VCAM-1 expression suggest a higher capillarization in paragangliomas than in lung. The relative expression of endoglin is significantly higher in paragangliomas respect to lung ($p<0.02$), whereas that of VEGF is similar. *Conclusion.* We described for the first time a high expression of endoglin in CPG that is significantly superior to the expression of VEGF. Besides, endoglin is the angiogenic factor that best correlates with tumour vascularization. These data put forward the role of endoglin in diagnostic, prognostic, and therapeutic approach to CPG.

PB2
KLF6 IS INVOLVED IN THE TRANSCRIPTIONAL UPREGULATION OF ALK1 AFTER VASCULAR INJURY

EM Garrido-Martín,[1] C Vary,[2] M Tarocchi,[3] U Lee,[3] SL Friedman,[3] LM Botella,[1] C Bernabéu[1]

[1]Centro de Investigaciones Biológicas. CSIC, and Center for Biomedical Research on Rare Diseases (CIBERER), Instituto de Salud Carlos III, Madrid, Spain; [2]Center for Molecular Medicine, Maine Medical Center Research Institute, Scarborough, Maine; [3]Division of Liver Diseases, Mount Sinai School of Medicine, New York, NY, USA

Activin like kinase receptor type 1 (ALK1) is a type I TGFβ receptor predominantly expressed in endothelial cells and activates angiogenesis after stimuli like vascular injury. Because little is known about its transcriptional regulation, we performed an *in silico* analysis over a fragment of 1235 bp of genomic DNA containing the theoretical transcription start site and part of the transcribed not translated first exon. This fragment does not contain TAATA or CAAT boxes, but encodes multiple G/C rich regions with consensus motifs for Sp1. We have demonstrated that basal transcriptional activity of ALK1 promoter is null in absence of Sp1, and increasing amounts of Sp1 remarkably transactivate it. KLF6 is a transcription factor related with vascular repair in endothelium, and transactivates other genes of the TGFβ signalling pathway. We find that overexpression of KLF6 is able to transactivate ALK1 promoter by synergistic cooperation with Sp1 in HEK293T cells. Using a wound healing *in vitro* model in HUVECs (*human umbilical vein endothelial cells*) we have detected that the levels of ALK1 mRNA and cell surface protein are upregulated after 2 hours of injury. By chromatin immunoprecipitation experiments we have demonstrated the binding of KLF6 and Sp1 on the promoter, showing stronger binding after wound healing. Moreover, total RNA of liver tissue from $KLF6^{+/-}$ mice showed decreased levels of ALK1 mRNA compared with their $KLF6^{+/+}$ siblings. These data provide evidence that injury-induced KLF6 and preexisting Sp1 may cooperate potentiating ALK1 expression in vascular repair.

PB3
ANALYSIS OF DIFFERENTIAL GENE EXPRESSION IN MACROPHAGES FROM HHT PATIENTS

ML Ojeda, C Bernabeu, LM Botella

Centro de Investigaciones Biológicas, CSIC (Madrid); Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), Spain

HHT is a vascular dysplasia originated by mutations in Endoglin and Alk-1 genes that are predominantly expressed in endothelial cells, which constitute the main cellular target of the disease. However, Endoglin and ALK1 are also expressed in the mieloid lineage. In particular, Endoglin is upregulated during the process of differentiation to macrophages. Although the role of this upregulation remains unknown, it is conceivable that Endoglin and ALK1 may play a role in the immune system, where both genes are expressed. Therefore, as a consequence of lower expression of Endoglin/ALK1, the HHT patients may have affected their immune response. In fact, certain reports in the literature show that some HHT patients suffer from recurrent infections that are infrequent in the rest of the population. To deepen into the problem of how Endoglin/ALK1 haploinsufficiency may affect the immune system in HHT patients, a complete genome microarray study was made comparing expression of macrophages from HHT and non-HHT volunteers. RNA samples from *in vitro* differentiated macrophages were used as probes. In total, independent RNAs from 3 controls, 3 HHT1 and 2 HHT2 patients were used for the final microarray comparisons in a GeneChip® Human Genome U133 plus 2.0 from Affymetrix. For the purpose of the analysis HHT1 and HHT2 were considered as an HHT pool, versus non-HHT samples. The results of the microarrays analysis have rendered genes differentially expressed; most of them downregulated in HHT patients compared to controls. Some of the differentially expressed genes are biologically significant for the immunological process and are currently under investigation by molecular and functional assays. The genes differentially expressed in macrophages of HHT patients are compatible with an altered immune response and with an abnormal vascular remodelling during inflammatory processes.

PB4
EFFECTS OF ESTROGEN (RALOXIFENE) ON ENDOGLIN AND ALK1 EXPRESSION IN ENDOTHELIAL CELLS

V Albiñana,[1,2] ME Bernabeu-Herrero,[1] R Zarrabeitia,[2,3] C Bernabeu,[1,2] LM Botella[1,2]

[1]Centro de Investigaciones Biológicas, Spanish Research Council (CSIC), Madrid, Spain; [2]Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), Instituto de Salud Carlos III (ISCIII), Madrid, Spain; [3]Spanish HHT Unit, Hospital de Sierrallana. Torrelavega, Santander, Spain

The clinical manifestations of the hereditary haemorrhagic telangiectasia (HHT) are epistaxis, mucocutaneous and gastrointestinal telangiectases, and arteriovenous malformations. There are two main HHT types, HHT1 and HHT2, which are caused by mutations in *Endoglin* (*ENG*) and *ALK1* (*ACVLR1*) genes, respectively. Both genes code for proteins involved in the TGF,-signalling pathway. It is generally accepted that Endoglin or ALK1 haploinsufficiency is the origin for the pathogeny of the disease. Some patients show severe epistaxis which notably interfere with their quality of life. So far, there are very few drugs available for a pharmacological therapy in HHT. Tranexamic acid (Fernandez-L *et al*., 2007) has shown efficacy to decrease epistaxes, however, its side effects prevent a generalized used. In this context, the screening for drugs able to increase the transcriptional activity of the promoters of ENG and ACVLR1, is essential to propose therapies for HHT. The efficacy of estrogens, in particular raloxifene, was assessed in postmenopausal women diagnosed of osteoporosis. The study is being currently conducted with HHT women in the Spanish Hospital of reference for the disease, Sierrallana. In parallel, we have carried out a study to unravel the molecular mechanisms involved in the therapeutic effects of Raloxifene. According to our results, Raloxifene increases the expression of Endoglin and ALK1 at the endothelial cell surface, and the origin of the effect is at the transcriptional level. These results suggest that by upregulating Endoglin and ALK1, the treatment with this estrogen may decrease nosebleeds, consequently improving the quality of life in HHT patients.

Acknowledgement. This paper is dedicated to the HHT Association of Spanish patients, and in general to all families affected by HHT. This work was supported by grants from Ministerio de Educación y Ciencia (SAF05-01090 and SAF08-01218 to LMB, and SAF2007-61827 to CB), Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), Instituto de Salud Carlos III (ISCIII-CIBER CB/06/07/0038), Fundacion Ramón Areces of Spain, and Instituto Fundación Marqués de Valdecilla (IFIMAV).

PB5
ALLELIC DROP-OUT DUE TO NUCLEOTIDE VARIATION IN TRANS ON ACVRL1 AND ENDOGLIN GENES HINDERS THE IDENTIFICATION OF MUTATIONS IN TWO FAMILIES WITH HEREDITARY HEMORRHAGIC TELANGIECTASIA

F Coulet,[1] J Roume,[2] P Lacombe,[2] T Chinet,[2] B Raffestin,[2] B Girerd,[3] M Humbert,[3] F Soubrier[1]

[1]Laboratoire d'Oncogénétique et d'Angiogénétique Moléculaire, Groupe hospitalier Pitié-Salpêtrière, Paris; [2]HHT Center Paris, CHU Ambroise Paré, Boulogne; [3]UPRES EA2705, Service de Pneumologie et Réanimation Respiratoire, Hôpital Antoine-Béclère, Clamart, France

The diagnosis of Hereditary Hemorrhagic Telangiectasia (HHT) is established on clinical criteria, and further confirmed by the identification of causative mutations in either the ENG or the ACVRL1 genes coding for endoglin and activin receptor-like kinase-1, respectively. We reported two cases of allelic drop out occurring because of a primer binding site polymorphism in *trans* i.e on the non mutated allele. In the two families, PCR and direct sequencing allowed identification of two mutations in index cases (the mothers), a mutation in ACVRL1 (c.1281A>T, p.Asp427Ala) and one mutation in ENG gene (c.991G>A, p.Gly331Ser). In the first family, the ACVRL1 mutation was found in the grandmother and her grandchild but not in the mother who died of pulmonary hypertension. In the second family, the mutation was not found in several relatives presenting with HHT phenotype. After further investigations, we found that the negative subjects had herited from their fathers a variant (c.991+58 in the intron 7 of ACVRL1 for the first family and c.1377+45T>C in the intron 9 of ENG for the second family) located in the reverse primers initially used. We conclude that presence of polymorphisms in the primers even in trans may lead to allelic drop-out and generate unforeseen errors in genotype determination. Our results also emphasize the need for careful quality control in all molecular genetic studies, particularly concerning the choice of primers which can take benefit of the exhaustive SNP database.

PB7
GENOTYPE-PHENOTYPE CORRELATION IN HEREDITARY HEMORRHAGIC TELANGIECTASIA IN PATIENTS WITH ACVRL1 MUTATIONS: IS THE c.1112dupG MUTATION A MILDER MUTATION?

S Dupuis-Girod,[1] S Giraud,[2] E Decullier,[3] B Gilbert-Dussardier,[4] MF Carette,[5] G Plessis,[6] S Riviere,[7] P Magro,[8] G Lesca,[2] P Edery,[9] A Calender,[2] H Plauchu,[1] on behalf of the HHT Network.

[1]Hospices Civils de Lyon, Hôpital de l'Hôtel Dieu, Service de Génétique et centre de référence pour la maladie de Rendu-Osler, Lyon, France; [2]Hospices Civils de Lyon, Laboratoire de Génétique moléculaire, Lyon, France; [3]Hospices Civils de Lyon, Pôle IMER, France; [4]Hôpital Jean Bernard, Service de Génétique, Poitiers; [5]Hôpital Tenon, Service d'Imagerie et de Radiologie

Interventionnelle, Paris, France; [6]Hôpital Côte de Nacre, Service de cytogénétique, Caen, France; [7]Hôpital Saint Eloi, Service de Médecine Interne, Montpellier, France; [8]Hôpital Bretonneau, Service de génétique, Tours, France; [9]Hospices Civils de Lyon, Service de Cytogénétique, Lyon, France

Introduction. Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant disorder characterized by recurrent epistaxis, cutaneous telangiectasia, and visceral arteriovenous malformations (AVMs) affecting the lungs (PAVM), gastrointestinal tract (DAVM), liver (HAVM), and brain (CAVM). It results from mutations in two major genes: ENG (HHT1) or ACVRL1 (HHT2).
Our objective was to determine the influence of the c.1112dupG mutation on clinical phenotype in HHT2 patients. *Methods*. We retrospectively compared the frequency of the clinical features of HHT between a subgroup of patients with mutation c.1112dupG (group A) and those with the other ACVRL1 mutations (group B), using a clinical HHT database (CIROCO), built by the HHT reference centre in France and used by the French-Italian Network. *Results*. 351 HHT2 patients were included in 6 HHT centres in France. Eighty-three patients were in group A and 268 patients were in group B. Epistaxis was present in both groups and occurred at a younger age in group B patients (Median=16 vs 21 years old, $p<0.001$). Pulmonary involvement appeared to be significantly more frequent in group B patients (8 vs 18 %, p=0.03). The frequency of hepatic, digestive and neurological AVM were not significantly different in either group but hepatic AVM were more severe in group B. No liver transplants were performed in group A (0 *vs* 5%, $p=0.04$). *Conclusion.* This study highlighted major differences between the clinical expression of the ACVRL1 mutation c.1112dupG, which appeared to be milder, and other ACVRL1 mutation phenotypes.

PB8
APPLICATION OF MULTIPLEX LIGATION-DEPENDENT PROBE AMPLIFICATION METHOD IN HEREDITARY HEMORRHAGIC TELEANGIECTASIA ITALIAN PATIENTS

C Canzonieri,[1,3] L Boeri,[1] A Colombo,[2] E Matti,[2] F Chu,[2] M Perego,[3] A Minelli,[1] C Olivieri[1] and on behalf of the HHT-NET (C Danesino, E Buscarini, G Manfredi, P Gazzaniga, L Reduzzi, F Pagella, M Grosso, G Pongiglione, E Boccardi)

[1]Medical Genetics - University of Pavia, Pavia, Italy; [2]ENT Unit - IRCCS Policlinico San Matteo, Pavia, Italy; [3]GI Endoscopy Unit - IRCCS Policlinico San Matteo, Pavia, Italy

A total of 1032 DNA samples from HHT families (including patients and their unaffected relatives) were collected by our research group. A disease causing mutation has already been found in 115/172 index cases in whom the screening has been completed. The screening methods include DHPLC, direct sequencing and endonuclease restriction digestion. Among the 57 patients, in whom we haven't identified any mutations, we found 30 sporadic and 27 familial cases, 4 of them non-Italian (they include cases from Ireland, Hungary, Germany and Croatia). We revaluated the clinical picture for all the index cases, confirming the diagnosis according to the Curaçao criteria for all of them and selected for further investigations the larger families. We chose the Multiplex Ligation-dependent Probe Amplification (MLPA) method, using a commercially available kit, MRC-Holland SALSA MLPA kit P093-B1 HHT/PPH1 in order to detect large deletions or insertions. This kit will provide information about *ENG, ACVRL1* and BMPR2 genes. Preliminary results from the Italian families we collected are reported.

PB9
ENG IS A MODIFIER OF ARTERIO-VENOUS MALFORMATION IN HEREDITARY HAEMORRHAGIC TELANGIECTASIA TYPE I AND TYPE II

TGW Letteboer,[1,2] M Benzinou,[1] KA Harradine,[1] F Clermont,[1] R Roy,[1] B Aouizerat,[3,4] HK Ploos van Amstel,[2] CJJ Westermann,[5] RJ Akhurst[1,4]

[1]Helen Diller Family Comprehensive Cancer Center, UCSF, CA, USA; [2]Department of Medical Genetics, University Medical Center Utrecht, Netherlands; [3]Department of Physiological Nursing, UCSF, CA, USA; [4]Institute for Human Genetics, UCSF, CA, USA; [5]Department of Cardiology, St. Antonius Hospital, Nieuwegein, Netherlands

HHT shows considerable phenotypic variability both between and within the HHT subtypes, HHT1 and HHT2, and even within families with the same pathogenic mutation, suggesting the existence of environmental and/or genetic factors that modify penetrance and expression of the clinical manifestations. We undertook a screen for genetic modifiers of PAVMs (pulmonary AVMs). We screened SNPs within candidate genes encoding TGFβ and BMP signaling components, including the causative genes for HHT1 and HHT2, respectively *ENG* and *ACVRL1*. A 768 gene-centric Illumina SNP screen, for variants within and flanking *TGFBM2* (1q41) and *TGFBM3* (2p25), and within 74 known TGFβ or BMP pathway or response genes, was performed on 486 HHT mutation carriers, of whom 204 had clinically documented PAVMs, and 250 non-mutation carrying family members. Data was analysed by Gamete Competition using the program MENDEL. A single *ENG* SNP with a minor allele frequency of 49% was shown to be significantly associated with the presence of PAVM ($p=0.00016$) in HHT1. This indicates that the genotype of the wild type *ENG* allele can influence the severity of pulmonary manifestations in HHT1 patients. Furthermore, the data also suggest an association between this *ENG* allele and presence of PAVM in HHT2. Further studies are underway to fine map the PAVM-predisposing *ENG* allele, and to determine linkage to altered *ENG* gene expression in human lung and lymphoblastoid tissues.

PB10
DATEBASE FOR HHT CLINICAL AND LABORATORY DATA MANAGEMENT USING PROGENY

J Robles, P Bayrak-Toydemir, C Miller, E Lyon, R Mao, J McDonald

University of Utah; ARUP Laboratories, USA

Objective. 1) To create databases for clinical and laboratory data management of HHT cases at the University of Utah Center of Excellence and ARUP Laboratories. 2) To make the clinical database readily available to other HHT Centers or groups. *Results.* We identified PROGENY as ideally suited for our database needs. It is a SQL database software with integrated management of pedigree and individual data. It has LAN (local area network) and WAN (wide area network) capabilities. Unlimited, customized fields can be created and data entry forms can be custom designed using these fields. It allows for customized queries on the fly, multiple image report formats, importing of XML and multiple flat file formats. We created on outline of data fields for the clinical database based on input from a multi-disciplinary faculty group at our own Center, as well as other North American HHT Center Directors. Database scripting has been generated. We are currently piloting and refining the data fields for the clinical database. The laboratory database is in full use. *Conclusion*. Databases created using PROGENY software are ideally suited for use by HHT Centers for the purpose of data management for clinical and research purposes. We will present an overview of this database.

PB11
RE-EXAMINATION OF THE TWO-HIT HYPOTHESIS FOR HHT PATHOGENESIS

C Gallione,[1] Y Qin,[1] P-L Chu,[1] A Akers,[1] W Young,[2] D Marchuk[1]

[1]Duke University Medical Center, Durham, NC, USA; [2]University of California, San Francisco, CA, USA

The two-hit mutational model of disease pathogenesis posits that a malformation, tumor, or lesion develops only when both copies of a critical gene are mutated in a progenitor cell. This model was originally proposed to explain phenotypes that exhibit solitary lesions in sporadic cases but multiple lesions in inherited cases. In inherited diseases, the germline mutation confers the first hit, and a bi-allelic second, somatic mutation in a progenitor cell seeds the formation of the lesion. Although sporadic AVMs versus HHT-associated AVMs mirror a similar epidemiological pattern, molecular evidence to support the two-hit model for HHT has been lacking. This negative history of the two-hit model for HHT resembles that of cerebral cavernous malformations (CCM). We recently re-evaluated the two- hit hypothesis for CCM (Human Molecular Genetics, 2009 Akers et al.). Using a staged, cloning and re-sequencing strategy in lesion tissue, we identified bi-allelic somatic mutations in CCM tissue from all three different inherited forms of CCM. Importantly, these mutations were present in only a small fraction of endothelial cells in the malformation tissue, and were invisible with routine bulk sequencing of the DNA from the malformation. In light of this discovery, we are now re-evaluating the two-hit model for HHT, beginning with HHT1. We have obtained tissue from cerebral AVMs from 4 different HHT1 patients. Using our novel strategy, we are re-sequencing *Endoglin* to identify cryptic second site somatic mutations in the AVM tissue. This work is currently in progress and we will report on our findings.

PB12
TREATMENT STRATEGIES AND MOLECULAR MECHANISMS UNDERLYING ENDOGLIN RELATED VASCULAR DEFECTS

RMJP Nauw,[1] S van den Brink,[2] CJ Westermann,[3] H-J Mager,[3] F Disch,[3] R Snijder,[3] F Lebrin,[4] CL Mummery[1]

[1]Dept. of Anatomy and Embryology, Leiden University Medical Center, Leiden, The Netherlands; [2]Hubrecht Laboratory, Netherlands Institute for Developmental Biology, Utrecht, Netherlands; [3]St Antoinius Hospital, Nieuwegein, Netherlands; [4]INSERM U833. Laboratory of Embryonic and Pathological Angiogenesis, Collège de France, Paris, France

Background. Mutations in Endoglin cause HHT1. Absence of Endoglin severely disrupts vascular smooth muscle cell (VSMC)/endothelial cell (EC) association, resulting in weak vessel walls, severe nosebleeds and mucotaneous telangiectases. Recently, our clinical collaborators discovered that Thalidomide reduced nosebleeds dramatically in some HHT patients. We are investigating the underlying mechanisms using mutant mouse embryonic stem cells (mESC) and deriving induced pluripotent stem (iPS) cells as models in humans. *Design and methods.* A collagen based assay allows induction of vasculogenesis and angiogenesis mESC in response to FGF and VEGF. Adult mouse and human skin fibroblasts can now be reprogrammed into iPS cells that resemble ESCs. hiPS cells from HHT1 pateints are being developed as models to identify molecular mechanisms of VSMC/EC association and elucidate Thalidomide action. *Results.* Thalidomide was shown to induce EC/VSMC association in differentiated vascular derivatives of $Eng^{+/-}$ mESC. Since $Eng^{-/-}$ embryos die in utero we derived iPS cells from (Eng mutant) mouse embryos with view to deriving lines lacking the gene entirely ($Eng^{-/-}$). We now have $Eng^{+/-}$ miPS cell lines with $Eng^{-/-}$ pending. In addition, we have derived fibroblasts from waste tissue from control individuals and HHT1 and HHT2 patients. Cell lines are growing and are presently being characterized for their ability to form ECs and VSMCs in culture. Analysis of the effects of Thalidomide will follow with view to determining whether miPS and their human counterparts show similar responses.

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PB13
ROLE OF TGF-β TYPE II RECEPTOR IN CARDIOVASCULAR DEVELOPMENT

A Robson, R Anderson, D Henderson, H Arthur

Institute of Human Genetics, Newcastle University, UK

The TGFβ type II receptor (TGFBR2) is widely expressed and plays multiple roles in development and in adult life. We were interested to investigate its role in vascular endothelial cells as disruption of the functional interaction between TGFBR2, endoglin and ALK1 hetero-oligomers may play a role in HHT. We also had an interest in its role (independent of HHT) in cardiac development. As Tgfbr2 expression in mouse is essential for survival beyond embryonic day 10.5 (E10.5), we used Cre/LoxP genetics to specifically delete this receptor in 3 different cardiovascular tissues during development: (i) in atrioventricular myocardium using GATA6-Cre, (ii) in ventricular myocardium using MLC2v-Cre and (iii) in vascular endothelium/endocardium using the tamoxifen-inducible VE-Cadherin-Cre-ERT2. Inactivating Tgfbr2 in AV myocardial cells from E8.5 leads to a mildly abnormal valve phenotype that does not affect viability. Loss of Tgfbr2 in the ventricular myocytes from approximately E8 leads to a diverse array of heart defects in 40% (4/10) embryos including membranous ventricular septal defects (VSD), hypoplastic left ventricle and common arterial trunk. Finally, inducible inactivation of Tgfbr2 in the vascular endothelium from E11.5 leads to embryonic death between E15 and E18 in all mutants examined to date. Mutant embryos exhibited extensive cerebral haemorrhage (13/13) and most of them (11/13) had a membranous VSD that was sometimes associated with an overriding aorta (3/13) and a double outlet right ventricle (1/13). The high mortality (100%) of these vascular-specific Tgfbr2 knockout embryos highlights the continued critical role of TGFβ signalling in vascular endothelial cells, during embryonic development.

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PB14
SEVERE PULMONARY HYPERTENSION IN YOUNG CHILDREN REVEALING PARENTAL ACVRL1 MUTATIONS

F Coulet,[1] K Nguyen,[2] A Fraisse,[3] V Drouin-Garraud,[4] B Girerd,[5] M Humbert,[5] F Soubrier[1]

[1]Laboratoire d'Oncogénétique et d'Angiogénétique Moléculaire, Groupe hospitalier Pitié-Salpêtrière, Paris; [2]Département de Génétique Médicale, Hôpital de la Timone, Marseille; [3]Service de Cardiologie Pédiatrique, Département de Cardiologie, Hôpital de la Timone, Marseille; [4]Unité de Génétique Clinique, CHU, Rouen; [5]UPRES EA2705, Service de Pneumologie et Réanimation Respiratoire, Hôpital Antoine-Béclère, Clamart, France

Pulmonary hypertension (PH) is a progressive disease characterised by obstructive lesions of small pulmonary arteries. Patients with heritable PH mainly bear mutations in the bone morphogenetic protein receptor type II (BMPR2) gene, but also in rare cases in the activin receptor-like kinase-1 (ACVRL1) gene. In this latter case, PH is associated with hereditary haemorragic telangiectasia (HHT). The present data reported 2 families with severe PH in young children and attenuated phenotype of HHT in other family members. In the first family, four children developed PH (two homozygous twins died of PH at 7 and 14 months). BMPR2 mutation search was negative (point mutations and large rearrangement) but an ACVRL1 mutation (c.1450C>T, p.Arg484Trp) was identified. The mutation was subsequently found in the mother's DNA. Clinical investigations of the mother revealed only epistaxis. In the second family, a single child died of PH at 12 months. Similarly, BMPR2 mutation search was negative but an ACVRL1 mutation (c.602A>G, p.Gln201Arg) was identified. This mutation was subsequently found in the father's DNA. The father suffers rare epistaxis associated with nasal vascular ectasia. Echocardiography and angio-chest CT showed a small pulmonary arteriovenous malformations. These 2 families are characterized by the low penetrance of the HHT phenotype in the transmitter parent and a severe PH in children revealing the HHT disease in the family. The severity of lung disease observed in these cases suggests additional genetic or environmental factors at play in PH development, which remain to be identified.

PB15
ENDOGLIN AND TRANSFORMING GROWTH FACTOR-β SUPERFAMILY MEMBER SIGNALING IN PRIMARY LIVER CELLS

SK Meurer, L Tihaa, R Weiskirchen

Institute for Clinical Chemistry and Pathobiochemistry, RWTH University Hospital Aachen, Germany

In up to 30 percent of HHT-1 patients, the Endoglin haploinsufficiency results in liver pathology that leads finally to cirrhosis.[1] Endoglin is highly expressed in hepatic stellate cells (HSC) representing one of the key profibrogenic liver cell in addition to portal myofibroblasts (pMF).[2] Endoglin expression is increased during activation and transdifferentiation of HSC into myofibrobast like cells (MFB). This expression profile paralleled those of the transforming growth factor-β1 (TGF-β1) which paticipates in the forced expression of endoglin. In addition, endoglin is relocalized to the cell surface in activated HSC and MFB. Endoglin binds TGF-β1 in MFB and as a prerequisite interacts physically with and is phosphorylated by TβRII. However, siRNA-mediated reduction of endoglin expression did not cause a gross change in Smad activation and extracellular matrix (ECM) expression, hallmarks of the fibrotic response. Nevertheless, ectopic overexpression of endoglin in HSC cell lines leads to a reduction in Collagen I expression. Since endoglin is only sparsely expressed in pMF, this receptor is obviously not generally needed to modulate pro-fibrogenic functions. Even more, endoglin enhances BMP-7 signaling,[3] a ligand discussed as TGF-β1 antagonists in HSC.[4] In line, endoglin is phosphorylated by activin type II receptors. The exact role of endoglin in TGF-β superfamily signaling in HSC is currently under debate and will be addressed in more detail in the future.

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PB16
ENDOGLIN DIFFERENTIALLY REGULATES BMP2- AND BMP9-INDUCED SMAD1 PHOSPHORYLATION IN MOUSE ENDOTHELIAL CELLS

G Xu,[1,2] M Letarte[1,2]

[1]Molecular Structure and Function Program, The Hospital for Sick Children; [2]Heart and Stroke Richard Lewar Center of Excellence and Department of Immunology, University of Toronto, Toronto, Ontario, Canada

The TGF-β superfamily plays an important role in endothelial cell function. Dysregulation of receptors of this superfamily leads to vascular disorders such as hereditary hemorrhagic telangiectasia (HHT) and familial pulmonary arterial hypertension (PAH). Mutations in ENG are associated with HHT1 while mutations in ALK1 lead to HHT2 and to a lesser degree PAH. Endoglin can modulate TGF-β1/β3 and various BMP responses by association with the appropriate ligand receptor. ALK1 mediates the BMP9 responses while ALK3 and ALK6 mediate the BMP2 effects, both signaling via the Smad1/5 pathway. We investigated the role of endoglin in regulating the BMP2 and BMP9-induced Smad1 phosphorylation in $Eng^{+/+}$ and $Eng^{-/-}$ mouse embryonic endothelial cell lines. BMP-9 was more potent than BMP2 in $Eng^{+/+}$ cells in terms of the concentration needed to obtain maximal stimulation. Endoglin potentiated this response as the BMP9 effect was much reduced in $Eng^{-/-}$ cells. On the contrary, the BMP2 response was greater in $Eng^{-/-}$ than $Eng^{+/+}$ cells suggesting that endoglin inhibited the BMP2-induced Smad1 phosphorylation. These data suggest that endoglin may favor the ALK1 over the ALK3 or ALK6 pathways of Smad1 phosphorylation. We are currently investigating the expression and stability of these receptors and the regulation of downstream effectors in the $Eng^{+/+}$ and $Eng^{-/-}$ endothelial cells. (Xu is recipient of a Fellowship from The Heart and Stroke Foundation of Canada; this research is supported by The Canadian Institutes of Health Research)

PB17
L- AND S-ENDOGLIN DIFFERENTIALLY MODULATE BIOLOGICAL PROPERTIES IN L6E9 MYOBLASTS

S Velasco, M Pericacho, C Bernabéu, JM López-Novoa, A Rodríguez-Barbero

Instituto "Reina Sofía" de Investigación Nefrológica, Departamento de Fisiología y Farmacología, Universidad de Salamanca, and Red de Investigación en Enfermedades Renales (RedinRen) Salamanca, Spain

Transforming growth factor β 1 (TGFβ1) regulates cellular processes by binding to type I and type II TGFβ receptors. In addition to these signalling receptors, endoglin, acts an auxiliary receptor for TGFβ. There are two different alternatively spliced isoforms of endoglin, L-endoglin (L, long) and S-endoglin (S, short) little is known about the effects of S-endoglin isoform on TGFβ signalling. The aim of this study was to investigate the effect of S-endoglin expression on biological properties of myoblast. L_6E_9 myoblasts were transfected with L- and S-endoglin or with the empty vector (Mock). Endoglin transfection was assessed by western blot, PCR, and immunofluorescence. We analyzed the effects of L-and S-endoglin on extracellular matrix synthesis by western blot, cell proliferation by MTT, cell cycle by FACS and expression of cyclin D1 by western blot. Thus, while L-endoglin decreased collagen I and CTGF expression and increased proliferation, S-endoglin strongly increased collagen I and CTGF expression, and reduced cell proliferation. Moreover S-endoglin enhanced TGFβ-induced COX-2 expression and PGE_2 production while L-endoglin reduced these responses. Our data demonstrate a different and sometimes opposed effect of L and S isoforms of endoglin on the regulation of biological properties in L_6E_9 myoblasts.

PB18
ENDOGLIN REGULATION OF DERMAL FIBROBLASTS PROLIFERATION IS DEPENDENT ON AKT ACTIVATION

M Pericacho, S Velasco, M Prieto, JM López-Novoa, A Rodríguez-Barbero

Instituto "Reina Sofía" de Investigación Nefrológica, Departamento de Fisiología y Farmacología, Universidad de Salamanca, and Red de Investigación en Enfermedades Renales (RedinRen) Salamanca, Spain.

The accurate regulation of dermal fibroblasts function plays a crucial role in several physiological processes such as wound healing. Furthermore, many pathological processes could arise from a deregulation in fibroblasts function. Endoglin, a TGFβ type III receptor, is widely considered an endothelial marker but several other cell types also express endoglin. Moreover, it has been shown that endoglin mediates several cellular responses in different cell types. However, endoglin expression and function in dermal fibroblasts has not been investigated. In this report, we demonstrate that primary cultured murine dermal fibroblasts express endoglin. This expression is lower in fibroblasts from endoglin haploinsufficient mice than in control cells. The endoglin deficiency is associated to an increase in cell proliferation, migration and extracellular matrix production. Besides, ALK1 and ALK5 TGFβ signaling pathways are present, functional and independent of endoglin expression in dermal fibroblasts. Furthermore, the proliferation differences found between endoglin haploinsufficient and control cells seem to be independent of TGFβ. Interestingly, endoglin haploinsufficiency induces Akt activation and PI3K inhibition abolishes the proliferation differences between endoglin haploinsufficient and control cells, suggesting that Akt activation mediates cell proliferation associated to endoglin haploinsufficiency.

PB19
NOVEL PATHOGENETIC MECHANISMS GENERATED FROM STUDYING THE ROLE OF ENDOTHELIAL ENDOGLIN IN VASCULAR DEVELOPMENT

HL Nguyen, YJ Lee, N Fleiss, C Bradford, J Tabora, HM Arthur,[1] SP Oh

Department of Physiology and Functional Genomics, University of Florida, Gainesville, FL, USA; [1]Institute of Human Genetics, Newcastle University, UK

Based on the fact that the three known HHT genes (ENG, ALK1, and SMAD4) are members of the TGF-β signaling pathway, it has been postulated that these function in a linear TGF-β Smad-dependent manner. Furthermore, *in vitro* studies suggest that ENG is required for ALK1 signaling in endothelial cells (ECs). Our lab recently described a conditional knockout model in which *Alk1* was deleted specifically in ECs using the L1cre line. In this line, cre expression is limited to ECs of certain organs, including the brain, lungs, GI tract and eye, starting at E13.5. The L1cre(+);$Alk1^{f/f2f}$ mice developed AVMs within the brain, lungs, and intestines. To determine potential roles of ENG in the ECs for vascular development and for ALK1 signaling *in vivo*, *Eng* was conditionally deleted in ECs using the L1cre line. Surprisingly, L1cre(+);$Eng^{f/f}$ mice were viable and phenotypically indistinguishable from control littermates. Molecular, biochemical, and histological analyses confirmed a normal cre activity, deletion of the Eng gene, and reduced (or absent) expression of ENG in the mutant lungs. Conversely, when *Eng* was deleted using a cre knockin line ($Alk1^{cre}$), in which cre is expressed in ECs and endocardial cells beginning at E9.5, $Alk1^{cre}$;$Eng^{f/f}$ mice were embryonic lethal at ~E11.5 with phenotypes similar to global *Eng*-null embryos. These data suggest that vascular ECs may not be the primary cells type where ENG deficiency incites HHT pathogenesis. They also suggest there may be disparities between the pathogenetic mechanisms underlying HHT1 and HHT2.

PB20
HEREDITARY HEMORRHAGIC TELANGIECTASIA: MECHANISM FOR TWO DISTINCT ENG DELETIONS IN ONE PEDIGREE

F Gedge,[1] M McDonald,[1] W Wooderchak,[1] P Krautscheid,[1] CJ Bukjiok,[1] P Bayrak-Toydemir[1,2]

[1]ARUP Institute for Clinical and Experimental Pathology, [2]Department of Pathology, University of Utah, USA

Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant disorder characterized by aberrant vascular development. Mutations of either endoglin (ENG) or activin A receptor type II-like 1 (*ACVRL1*) gene cause over 85 percent of HHT patients. Approximately 10 percent of these patients have large deletions or duplications. We observed a deletion of exons 4-7 of *ENG* in an HHT patient. During the family-specific mutation analyses we found the same mutation in several other affected members of the family. However, we also found that some affected members of this family were carriers of an exon 3 deletion, not exon 4-7 deletion. These deletions were detected using multiplex ligation-dependent probe amplification (MLPA, MRC-Holland). The presence and nature of these deletions were confirmed by mRNA sequencing and by a custom designed oligo-CGH array. In order to determine the mechanism underlying these two distinct deletions segregating in this family, we wanted to determine if these individuals inherited the same chromosome. Using short tandem repeat markers, we identified that the individual with the exon 3 deletion inherited the same chromosome from his mother who has exon 4-7 deletion. We have since determined the breakpoint locations for each deletion type. We speculate large repeats in *ENG* introns 2 and 3, which have 85% sequence identity, could serve as break points for these deletions. Our results suggest a unique mechanism for HHT etiopathogenesis where one *ENG* deletion can give rise to another leading to the same HHT phenotype.

CLINICS

C6
ISO 9001:2000 QUALITY CERTIFICATION OF THE HHT UNIT IN HOSPITAL SIERRALLANA, SPAIN

R Zarrabeitia, T Dosal, J Hernández, M Angulo, M Rodríguez, C Fariñas, D Acón

Hospital Sierrallana. Torrelavega, Spain

The Spanish HHT Unit in Hospital Sierrallana started working in 2002 with a multidisciplinary team from Sierrallana and Valdecilla Hospitals collaborating with the Spanish Patient´s Association and the Centro de Investigaciones Biológicas in Madrid.

The 1302/2006 Spanish law establishes the criteria to be designated as national reference center including quality standards. As rare diseases have not been included yet in this process, the HHT unit decided to analize its processes and adecuate them to the ISO 9001:2000 standards in order to advance in the continuous improvement and equity in the access to health services for the HHT population. During all 2007 a process file that covers three kind of services (in patients, consultancy and genetic test) was designed. A "Clinical Way" that standarizes activities achieving very short stays with good coordination and security, was established. Under supervision of the management team, interactions with service providers were defined evaluating times for response, quality of reports, security measures regarding material checkings and communication. A specific database was created , all consent forms and services portfolio were reviewed, updated and published in the web site. The nursery team created a specific plan for care of HHT patients included in the intranet. A tool to register incidences, internal audits and specific surveys served to consider patient satisfaction while parameters about days of admission, quality ant time to get reports, papers and conferences served to measure security and research compromise. The external audit was performed by Det Norske Veritas in December 2007.

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C10
GRADING OF PULMONARY RIGHT-TO-LEFT SHUNT WITH TRANSTHORACIC CONTRAST ECHOCARDIOGRAPHY PREDICTS THE INDICATION FOR EMBOLOTHERAPY

MWF van Gent,[1] MC Post,[1] RJ Snijder,[2] MJ Swaans,[1] HWM Plokker,[1] CJJ Westermann,[2] TT Overtoom,[3] JJ Mager[2]

Department of [1]Cardiology, [2]Pulmonology and [3]Radiology; St Antonius Hospital, Nieuwegein, The Netherlands

Rationale. Because of its association with neurological complications, screening for pulmonary arteriovenous malformations (PAVMs) is routinely performed in patients with hereditary hemorrhagic telangiectasia (HHT). Transthoracic contrast echocardiography (TTCE) can effectively detect pulmonary right-to-left shunting (RLS). *Objectives.* To prospectively determine the predictive value of TTCE grading to detect PAVMs on chest HRCT and the indication for embolotherapy. *Methods.* All consecutive persons screened for HHT, who underwent both a chest HRCT and showed a pulmonary shunt on TTCE, were included. We excluded all patients without a pulmonary shunt on TTCE (n=239), a poor image quality (n=5), and indistinguishably between a pulmonary and cardiac RLS (n=4). Embolotherapy was performed of all PAVMs judged large enough for treatment. *Results.* In total 151 persons could be included (mean age 43.1±15.4 yr; 64% female). Chest HRCT was positive in 74 (49%), negative in 74 (49%) and indeterminate in 3 (2%) patients, respectively. The positive predictive value of shunt grade for the presence of PAVMs on chest HRCT was 12% for grade 1 (n=50), 36% for grade 2 (n=33) and 86% for grade 3 (n=65), respectively. Of the patients with PAVMs on chest HRCT and a TTCE grade 1 (n=6), 2 (n=12), and 3 (n=56); none, 2 (17%), and 35 (63%) patients underwent embolotherapy. Kappa interobserver variable 0.83. *Conclusion*: An increased echocardiographic shunt grade correlates with increased probability of PAVMs on chest HRCT. Only patients with a TTCE grade 2 and 3 displayed PAVMs on chest HRCT large enough for embolotherapy.

C27
SIZE OF PULMONARY RIGHT-TO-LEFT SHUNT PREDICTS MIGRAINE WITH AURA

MWF van Gent,[1] MC Post,[1] HWM Plokker,[1] CJJ Westermann,[2] JJ Mager,[2] WJ Schonewille,[3] V Thijs,[4] RJ Snijder[2]

Department of [1]Cardiology, [2]Pulmonology, and [3]Neurology, St Antonius Hospital, Nieuwegein, The Netherlands, and [4]Department of Neurology, University Hospital Gasthuisberg, Leuven, Belgium

Background. An increased prevalence of migraine with aura (MA) has been described in the presence of pulmonary arteriovenous malformation. The size of this pulmonary right-to-left shunt (RLS) and the relation to MA has never been investigated. *Methods*. A sufficient transthoracic echocardiography with contrast (TTCE) was performed in 377 consecutive persons who were referred for screening for hereditary hemorrhagic teleangiectasia (HHT). TTCE was positive for a pulmonary RLS if microbubbles appeared in left atrium after four cardiac cycles. Opacification of the left ventricle was graded as either minimal, moderate, or large. All patients received a structured headache questionnaire prior to TTCE. *Results*. The questionnaire was filled in by 350 persons (age 44±15y, 60% female). The prevalence of MA was 16% in patients with a pulmonary RLS, and 6% in those without a pulmonary shunt (p=0.004). A pulmonary RLS was present in 21 patients with MA (62%) and in 100 non-migraine controls (35%) (OR 3.0: 95%CI 1.4–6.2, p=0.003). Only a moderate or large shunt was found more often in MA patients (56%) compared to non-migraine controls (22%) (p<0.001). The presence of a large pulmonary shunt increased the odds of having migraine with

aura 7.0 times (95%CI 3.1–15.8, $p<0.001$), also after adjustment for gender and a history of a cerebral ischaemic event (OR 6.4: 95%CI 2.6–15.7, $p<0.001$). *Conclusion.* A pulmonary RLS was found more often in patients with MA compared to non-migraine controls. A larger shunt size is associated with MA in patients screened for HHT.

C40
CONTRAST ENHANCED MR ANGIOGRAPHY FOR DETECTION OF PULMONARY ARTERIOVENOUS MALFORMATIONS IN PATIENTS WITH HEREDITARY HEMORRHAGIC TELANGIECTASIA (HHT)

A Massmann, P Fries, UW Geisthoff, M Koehler, M Uder, A Buecker, GK Schneider

University Hospital Homburg/Saar, Germany; University Hospital Münster, Germany; University Hospital Erlangen, Germany; Clinics of City Cologne, Germany

Purpose. To evaluate contrast-enhanced MR angiography (CE-MRA) as a screening procedure for detection of pulmonary AV-malformations (PAVM) in patients with hereditary hemorrhagic telangiectasia (HTT). *Methods and Materials.* 249 patients (mean age 46.5; male 103; female 146) with confirmed HHT according to Curacao criteria underwent screening pulmonary CE-MRA (Gadolinium-BOPTA 0.1 mmol/kg bodyweight) for the presence of PAVMs. PAVM presence was scored as 0 (=none present), 1 (=definitely present) or 2 (=uncertain) and was evaluated by patient gender, age and size of PAVM. Patients scored as 1 or 2 with at least one PAVM of ≥5 mm were referred for conventional pulmonary angiography (PA) for possible embolization. *Results.* 74/249 (29.7%) patients were scored as 1 (definite) and 3/249 (1.2%) as 2 (uncertain) for PAVM presence on CE-MRA. Overall, CE-MRA detected 238 PAVMs in 74 patients (116 in 35 men; 122 in 39 women; 79 in 27 women ≤50 years). Two or three PAVMs were detected in 24 patients and four or more in 15 patients. Most PAVMs detected on CE-MRA were small (<5 mm: n=49; 5-10 mm: n=63). 55 of 74 patients with 192 evaluable PAVMs detected on CE-MRA underwent global or selective PA. Significantly ($p<0.001$) fewer pAVMs (139/192 [72.4%]) were demonstrated on PA of which 130 were embolized. *Conclusion.* CE-MRA is a suitable screening procedure for patients with HHT, permitting accurate detection and staging of PAVMs and appropriate differentiation of lesions requiring embolization.

C56
PULMONARY ARTERIOVENOUS MALFORMATIONS: COMPARISON OF REPERFUSION RATE FOLLOWING EMBOLIZATION WITH IDC AND AMPLATZER DEVICES

K Fulop, ME Faughnan, L Letourneau-Guillon, G Gahide, P Chabrot, MF Giroux, G Soulez, VL Oliva, E Therasse

Department of Medicine and Li Ka Shing Knowledge Institute, St. Michael's Hospital, University of Toronto, Toronto, Canada; Departement de Radiologie, CHUM, Universite de Montreal, Montreal, Quebec, Canada

Purpose. To compare long-term efficacy of Interlocking Detachable Coils (IDCs) versus Amplatzer vascular plugs (AVPs) in treatment of pulmonary arteriovenous malformations (PAVMs). *Materials and Methods.* Between 2004 and 2009, 32 consecutive patients had 70 PAVMs treated by embolotherapy. Forty-two PAVMs were treated by IDCs in 22 patients and 29 PAVMs were treated with AVPs in 21 patients. Immediate success was defined as complete absence of flow through the PAVM after embolization without need for other embolization material. Long term success was defined either as a complete resolution of the PAVM nidus and the reduction in size of the draining vein on follow-up scans or an absence of flow through the PAVM on a subsequent pulmonary angiogram. *Results.* All attempts at PAVM closure were successful initially. Imaging follow-up after embolization (17 months; 1-40 months) was available in 35 PAVMs treated with IDCs and in 26 PAVMs treated with AVPs. Ten (29%) of 35 PAVMs treated with IDCs and 2(8%) of 26 PAVMs treated with AVPs demonstrated recanalization. Recanalization was the only cause of PAVM reperfusion with either IDCs or AVPs. Mean feeding artery diameter was 3,5 mm and 5,1 mm respectively for PAVMs treated with IDC and AVPs ($p=0.0003$). The OR of developing reperfusion, adjusted for feeding artery size, is 7.2 (95%CI: 1-52) for IDC compared to AVP, ($p=0.05$). *Conclusion.* Embolization of PAVMs with AVPs was associated with a significantly lower recanalization rate than with IDC.

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C57
AVMS: NO CONSISTENT EFFECT ON PULMONARY ARTERY PRESSURE

CL Shovlin, HC Tighe, RJ Davies, JSR Gibbs, JE Jackson

Imperial College London and and Hammersmith Hospital, Imperial College Healthcare NHS Trust, UK

Introduction. We tested the null hypothesis that PAVM embolization does not increase pulmonary artery pressure (PAP) in patients without baseline severe pulmonary hypertension. *Methods.* Pulmonary angiography was performed in unpremedicated, conscious patients who had not been fluid-restricted. Systolic, diastolic and mean PAP were recorded routinely prior to contrast injection via a multi-sidehole catheter. Measurements were repeated immediately after embolization in individuals with higher PAP. Statistical validation of effectiveness of embolization was determined by pre and post embolization SaO2 (erect). With ethical approval, pre and post embolization, and pre and age-adjusted post embolization measurements, were analysed by two tailed paired t-test, and significance assessed at false discovery rate (FDR)=0.05 level. *Results.* In 143 patients, PAP was significantly correlated with age. For 35 patients with serial measurements prior to consecutive embolization sessions, there was no significant change in PAP although SaO2 increased in all except one of the patients ($p<0.0001$). For nine pairs of same-session pre and post

embolization PAP measurements, embolization again resulted in a consistent improvement in SaO_2 (p=0.0039), but no increase in PAP mean (p=0.93). In half of all patients, post embolization PAP were lower than prior to embolization. The maximum rise in PAP mean was 8mmHg. Test balloon occlusion was performed in one of these individuals, and did not predict the subsequent rise in PAP following definitive embolization of the pulmonary AVMs. *Conclusions.* In this series, PAP was generally not increased by PAVM embolization. Occasional rises were not predicted by test balloon occlusion.

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PC2
CLINICAL MANIFESTATIONS OF RENDU OSLER WEBER DISEASE IN CHILDREN

C Fagnou, Th Chinet, M Sznajder, S Blivet, JH Blondel, I Bourgault-Villada, G Lesur, A Ozanne, JP Pelage, B Raffestin, F Soubrier, J Roume, P Lacombe

HHT Center of Paris, AP-HP, Hospitals Ambroise Paré, Bicêtre & Pitié-Salpêtrière, France

We report the characteristics of HHT in 31children (0-16 yrs) referred to our center between 2003 and 2008. The diagnosis of HHT was based on the Curaçao criteria (n=22) and/or on the presence of a mutation on the ALK1 gene (n=15) or on the ENG gene (n=15). Seven children were the index cases of their family. The mean age at the time of diagnosis was 9.5 yrs; 58% were male. Four children were totally asymptomatic. Epistaxis were present in 21 (67.7%) patients with a mean age of onset of 4.8 yrs. The clinical examination revealed telangiectases in 14 (45.1%) children aged from 4 to 16 yrs. Fifteen (48%) children had visceral vascular malformations, which were clinically symptomatic in 8. The number of affected organs was 1 in 11 patients, 2 in 3 and 3 in 1. Six patients had cerebral of spinal arteriovenous malformations, leading to life-threatening manifestations in 3 cases. Eleven (35.4%) children had pulmonary arteriovenous malformations. Their age ranged from 4 to 16 yrs (mean: 10.1 yrs). Seven of them were symptomatic. Embolization of the pulmonary arteriovenous malformations was recommended in 6 children. Five (16.1%) patients had hepatic vascular malformations. Their age ranged from 0 to 16 yrs (mean: 7.5 yrs). In one child, the hepatic disease led to cardiac insufficiency. In conclusión, these data show that clinical manifestations of HHT are frequent and sometimes severe in children even at a young age, which supports screening children for HHT in families affected by this disease.

PC3
HEPATIC MICROBUBBLE ULTRASONOGRAPHY CONTRAST IN HEMORRHAGIC HEREDITARY TELANGIECTASIA: A PROMISING TOOL?

D Marion,[1] PJ Valette,[2] E Guillot,[2] E Decullier,[3] MT Cuinet,[1] C Goudon,[4] J Dumortier,[5] F Chapuis,[3] C Trepo,[6] A Calender,[7] H Plauchu,[4] JC Saurin,[8] S Dupuis-Girod[4]

[1]Hospices Civils de Lyon, Hôpital de l'Hôtel Dieu, Service de Radiologie, Lyon; [2]Hospices Civils de Lyon, CH Lyon Sud, Service de radiologie, Pierre-Bénite; [3]Hospices Civils de Lyon, pôle IMER, Lyon, Université de Lyon; [4]Hospices Civils de Lyon, Hôpital de l'Hôtel Dieu, Service de Génétique et centre de référence pour la maladie de Rendu-Osler, Lyon; [5]Hospices Civils de Lyon, Hôpital E. Herriot, Service d'Hépato-gastroentérologie, Lyon; [6]Hospices Civils de Lyon, Hôpital de l'Hôtel Dieu, Service d'Hépato-gastroentérologie, Lyon; [7]Hospices Civils de Lyon, Laboratoire de Génétique moléculaire, Lyon, France; [8]Hospices Civils de Lyon, CH Lyon Sud, Service d'Hépato-gastroentérologie, Pierre-Bénite; [9]Hospices Civils de Lyon, Hôpital E. Herriot, Laboratoire de Génétique moléculaire, Lyon; [10]Hospices Civils de Lyon, Hôpital E. Herriot, Service d'ORL, Lyon; [11]Hospices Civils de Lyon, Hôpital de la Croix Rousse, Service d'ORL, Lyon; [12]Hospices Civils de Lyon, Hôpital de l'Hôtel Dieu, Service de Radiologie, Lyon; [13]Hospices Civils de Lyon, Hôpital E. Herriot, Service d'anatomo-pathologie, Lyon; [14]Hospices Civils de Lyon, Hôpital E. Herriot, Service de transplantation hépatique, Lyon, France

Introduction. Liver vascular malformations are present in 50-78% of HHT patients and Doppler ultrasound is currently recommended for liver VM screening. Computed tomography, however, is often used because of its reproducibility. SonoVue is a "second generation ultrasound contrast agent" that makes continuous real time examination possible during the different phases of contrast enhancement using a low mechanical index. It has led to better depiction of both the micro- and macro-vasculature of the liver parenchyma. *Objective.* To evaluate the effectiveness of contrast-enhanced ultrasound (CEUS) in the diagnosis of hepatic liver lesions in HHT *versus* conventional ultrasound (US). *Methods.* Contrast-specific ultrasonography was used to assess 16 patients with a definite HHT diagnosis (patients with significant, not previously treated pulmonary arteriovenous malformations were excluded). CEUS used a low-MI technique with a 1.2 to 2.4 ml i.v bolus of SonoVue (Bracco, Italy). The contrast-enhanced dynamic ultrasound investigation was carried out with contrast harmonic imaging in true detection mode during the arterial, portal venous and late phases. CHI Q software was used for data analysis. *Preliminary results.* 9 patients out of 16 had hepatic involvement using US criteria. Of them, hepatic transit time using CEUS (TTAVSH) was significantly decreased (p<0.001) and appeared to be a very sensitive criterion for liver involvement in HHT. Furthermore, CEUS identified 1 case of hepatic involvement that had been missed by conventional US and confirmed by CT. Other parameters are detailed in the study. *Conclusion.* Contrast-enhanced

real-time ultrasonography is a promising approach in the non-invasive characterization of HHT liver lesions and can be useful as a first-line imaging technique that is as sensitive as CT. Further studies are needed in HHT.

PC4
IMMUNOHISTOCHEMICAL ANALYSIS OF A MERKELOMA OBSERVED IN A PATIENT AFFECTED BY HEREDITARY HEMORRHAGIC TELEANGIECTASIA

L Boeri,[1] E Rossi,[2] P Morbini,[3] A Colombo,[4] E Matti,[4] F Chu,[4] C Olivieri,[1] V Villanacci,[2] A Minelli,[1] C Canzonieri[1] and on behalf of the HHT-NET (C Danesino, E Buscarini, G Manfredi, P Gazzaniga, L Reduzzi, F Pagella, M Grosso, G Pongiglione, E Boccardi)

[1]Medical Genetics, University of Pavia, Pavia, Italy; [2]Patology Department, University of Brescia, Spedali Civili of Brescia, Brescia, Italy; [3]Pathological Anatomy Department, University of Pavia, IRCCS Policlinico S. Matteo, Pavia, Italy; [4]ENT Unit, IRCCS Policlinico S. Matteo, Pavia, Italy

Merkeloma is a primary neuroendocrine carcinoma of Merkel cells. Merkel cell is a nondendritic, nonkeratinocytic epithelial clear cell normally found in the epidermis and dermis of mammals and humans. It is believed to be of neuroendocrine origin and functions as a specific slowly adapting sensory touch receptor. Merkeloma is a rare neoplasm, with fewer than 1000 reported cases to date. The tumor is most common in the 60- to 80-year-old age group. The merkeloma was observed in a HHT patient carrying a mutation in *ENG* gene (c. 1478delG). To the best of our knowledge, this is the first case of Merkeloma found in a HHT patient. We analysed the tumor with immunohistochemical methods using primary antibodies against CD105 (Endoglin), TGF-β, Smad4, CD31 and CD34. Tumor cells were positive for Smad4, weakly positive for TGF-β and negative for CD105. Vasal endothelial cells were highly positive for CD105, CD31 and CD34. We haven't observed any remarkable immunohistochemical difference between cancer and normal cells in the patient neither between the merkeloma observed in our patient and two control merkelomas. It is most likely that the presence of a merkeloma in a HHT patient is an occasional association.

PC5
TRAVELLING KNOWLEDGE

B Bjerkely, K Iversen

Oslo University Hospital, Rikshospitalet, Norway

One of the responsibilities of the specialist health services in Norway is to provide knowledge and guidance to hospitals and the primary health service. Expert knowledge on Hereditary Hemorrhagic Telangiectasia (HHT) and its treatment is situated at Oslo University Hospital, Rikshospitalet. In Norway the provisional known cases of HHT is 184; about 45 of these patients live in Rana, a small area in the northern region of Norway. These patients often experience problems when in contact with their local hospital and physicians due to paucity of knowledge of the disease. It is also inconvenient and expensive to travel to Oslo to obtain necessary treatment and follow-up. The Centre for Rare Disorders is an interdisciplinary centre of competence, specialising in the dissemination of information, counselling and expertise building, for both professionals, patients and their families. In order to transfer knowledge and competence to hospitals and health care services, one method is to travel to where the patients live. A multidisciplinary HHT-team of experts at Oslo University Hospital, Rikshospitalet has compiled a holistic programme of treatment and follow-up. Two meetings were arranged in collaboration with the local hospital, one for the doctors at the hospital and general practitioners, and one for the patients and their next of kin.

PC6
IMPACT OF HEREDITARY HEMORRHAGIC TELANGIECTASIA ON HEALTH RELATED QUALITY OF LIFE

R Zarrabeitia, C Fariñas, J Bueno, B Señaris, A Pérez del Molino, C Morales

Hospital Sierrallana, Torrelavega, Spain

Aim. To evaluate impact of HHT on health related quality of life in a cohort of Spanish HHT population. *Method.* Euroquol 5D (EQ-5D) is an easy tool that evaluates five dimensions: motility, personnel care, usual activities, pain and emotional role. It includes an analogical visual scale. 53 questionnaries of HHT patients were included. Stadistical analysis was performed with SPSS. *Results.* 30 males and 23 females completed the questionnaire (age range 16-69). HHT patients tend to show more problems relating all the dimensions (mainly pain/discomfort and emotional role). There are no diferences regarding sex except in HHT women that show higher values of emotional problems than men (p<0,005). Severity of epistaxis and findings in the ENT examination corelate with higuer rates of problems dealing mainly with discomfort and emotions with no statistical significance, however self perception of quol considering epistaxis (mild, moderate and severe compromise) corelates with motility problems (p<0,005). If transfusion has been required, rate of motility and usual activities compromise is higher (p<0,005). HHT 1 or 2 have not significative diferences while patients over 65 have got poorer puntuation on personnel care and emotional role (p<0,005). The value of the analogical visual scale in HHT patients is 71,38±18,35 and similar to that obtained for general population, however HHT patients with personnel care problems give a significative lower puntuation. *Conclusions*. HHT patients present a high percentage of disability regarding the EQ-5D dimensions. This questionnaire must be validated for HHT population but seems to be useful for this evaluation.

PC7
DETERMINATION OF AN AGE-RELATED THRESHOLD OF NASAL AND NASO-PHARYNGEAL TELANGIECTASIA NUMBER FOR DIAGNOSIS OF HEREDITARY HEMORRHAGIC TELANGIECTASIA IN 163 RELATIVES BELONGING TO 80 GENOTYPED FAMILIES

JH Blondel,[1] I Bourgault Villada,[1] B Raffestin,[1] J Roume,[1] S Blivet,[1] T Chinet,[1] F Coulet,[3] C Fagnou,[1] P Lasjaunias,[2] G Lesur,[1] A Ozanne,[2] JP Pelage,[1] F Soubrier,[3] P Lacombe[1]

HHT center of Paris, AP-HP, France; [1]CHU Ambroise Paré; [2]Neuroradiology CHU Kremlin Bicêtre; [3]Oncoangiogenesis laboratory, CHU Pitié Salpétrière, Paris, France

Background. Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant disease characterized by Curaçao criteria which include epistaxis related to the presence of nasal and naso-pharyngeal telangiectasia. *Objective.* To determine according to age the lower threshold of nasopharyngeal telangiectasia number which allows to predict HHT. *Materials and method.* The same otorhinolaryngologist not aware of the diagnosis examined 163 family members of 80 genotyped HHT patients by nasal and naso-pharyngeal endoscopy between January I, 2004 and December 31, 2008. The number of telangiectasia was counted in the nasal fossa and cavum. Comparisons were performed between subjects with mutation (n= 95) or disease according to Curaçao criteria (n=7) and related family members without the mutation of the proband (n=61). *Results.* The number of telangiectasia increases with age in HHT group in contrast to the non HHT members who have no telangiectasia in nasal and naso-pharyngeal sites. Mean number ± SD are summarized in the following table:

Table

Age [yr]	*0-20*	*20-40*	*40-60*	*>60*
HHT (subjects number)	6.3 ± 8 (n=32)	15 ± 12 (n=28)	33.3 ± 32.9 (n=27)	32.8 ± 17.9 (n=15)
Non HHT (subjects number)	0.6 ± 1.5 (n=19)	0.7 ± 2.2 (n=26)	0.25 ± 0.62 (n=13)	0 ± 0 (n=3)

Conclusion. In non HHT subjects, there is no telangiectasia in nasal and naso-pharyngeal sites. Their presence is then highly specific of the disease.

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PC8
ABDOMINAL INVOLVEMENT IN HEREDITARY HEMORRHAGIC TELANGIECTASIA

JP Pelage, S Blivet, JH Blondel, I Bourgault, Th Chinet, G Lesur, A Ozanne, B Raffestin, J Roume, F Soubrier, P Lacombe

Consultation pluridisciplinaire Rendu-Osler, APHP, Boulogne, France

Purpose. To review current indications of computed tomography, magnetic resonance imaging and ultrasound to evaluate abdominal involvement in HHT.
To illustrate the different imaging findings in HHT. *Materials and methods.* Pictorial review based on our pluridisciplinary consultation for HHT patients. All consecutively seen patients with HHT were evaluated using Doppler ultrasound, multidetector computed tomography (MDCT) and occasionally magnetic resonance imaging (MRI) to assess liver, pancreatic, splenic and gastrointestinal involvement in HHT. *Results.* During a 4-year period a total of 230 patients with HHT were evaluated at our center. The imaging findings obtained using Doppler ultrasound, contrast-enhanced MDCT or MRI will be presented. Special attention will be paid to liver involvement: telangiectases, confluent vascular masses, perfusion abnormalities, intrahepatic shunts, focal nodular hyperplasia will be illustrated. Pancreatic involvement with telangiectases and arteriovenous fistulas will be presented. Gastrointestinal tract or splenic involvement will also be demonstrated. *Conclusion.* Liver involvement is frequently diagnosed in HHT patients particularly with the use of cross-sectional imaging with contrast administration. With the use of MDCT, other abnormalities such as pancreatic telangiectases may also be diagnosed.

PC11
HEMODYNAMIC EFFECTS OF PULMONARY ARTERIOVENOUS MALFORMATION EMBOLIZATION IN PATIENTS WITH HEREDITARY HEMORRHAGIC TELANGIECTASIA

JR Gossage, DH Riggans, K Julka

Medical College of Georgia, Augusta, GA, USA

Rationale. Transcatheter embolization (TCE) is the treatment of choice for patients with PAVM. Our aim was to prospectively study the hemodynamic effects of TCE in patients with PAVM. *Methods.* Patients who were scheduled for TCE of moderate to large PAVM were studied. Mean pulmonary artery pressure (PAP), wedge pressure, and thermodilution cardiac output (CO) were measured immediately prior to angiography (baseline) and after TCE. Results. 12 patients with definite HHT, a mean age of 50.2 years, and a mean shunt fraction (SF) of 18.9% were studied. 3 patients had hepatic AVM. A mean of 3.5 PAVM were embolized per patient. The mean estimated cross-sectional area (eCSA) of embolized feeding arteries was 66.2±51 mm^2. TCE decreased CO by 0.85 liters/min (-11%, p=0.0001), increased oxygen saturation by 2.4% (p=0.003), and insignificantly increased PAP by 0.8 mm Hg (p=0.45). The change in CO (-23 to +6%) correlated best with baseline levels of SF (-0.4) and estimated shunt

flow (-0.46). The change in PAP (-4.7 to +8.3 mm Hg) correlated best with estimated shunt flow (0.67) and eCSA (0.67). The change in saturation correlated best with baseline saturation (-0.80) and SF (0.51) but not with shunt flow (0.26). *Conclusions.* TCE of moderate to large PAVM resulted in an 11% decrease in CO, a 2.4% increase in oxygen saturation, and no significant change in PAP. The degree of these changes was more related to SF, shunt flow, and eCSA than to baseline hemodynamics.

PC12
METASTATIC STAPHYLOCOCCAL INFECTION IN PATIENTS WITH HEREDITARY TELANGIECTASIA

D Goodenberger, M Chakinala

Washington University HHT Center, St. Louis, Missouri, USA; Dallas Veterans Affairs Medical Center, Dallas, Texas, USA; and University of Texas Southwestern Medical School, Dallas, Texas, USA

Recently, attention has been drawn to extracerebral infections in hereditary hemorrhagic telangiectasia.[1-3] Staphylococcal infections have been particularly notable. Attention has been called to duration and severity of epistaxis, nature of mutation, and nasal tamponade as risk factors. Intrinsic defects in phagocytic function have also been detected. We reviewed the records of 346 patients with HHT seen at our center between 1999 and 2006. Gender distribution was 36% male, 64% female. Mean age at presentation was 41 (range 10 months to 83 years). From among that group, five were identified with extracerebral staphylococcal infection. 80% were male. Age at diagnosis of infection was 57.8 (range 46-74). All isolates were methicillin sensitive. Heavy nosebleeds were not more frequent than in the overall HHT population. All patients had intrapulmonary right-to-left shunt. All were treated successfully without mortality.

Table

	All HHT	HHT and Staphylococcus
Age	41	58
Gender	36% Male, 64% Female	80% Male, 20% Female
Right-to-left intrapulmonary shunt	75%	100%
PAVM's	57%	80%
Heavy nosebleeds	34%	40%
Nasal packing	Not known	None
Recent previous instrumentation or central intravenous line	Not known	None
Sites of infection	N.A.	Abdominal wall abscess (hematogenous) Septic arthritis (2), Diskitis (2), epidural abscess (1)

In summary, serious staphylococcal infection occurred less frequently in our population than in the major previous report, although at a rate greater than expected for the normal population (1.4 vs. 0.03%). There was no association with nasal packing. All patients had intrapulmonary right-to-left shunt. We suspect that intrapulmonary shunting is a major risk factor for extrapulmonary staphylococcal infections, as it is for cerebral abscess.

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PC13
HEREDITARY HEMORRHAGIC TELANGIECTASIA AND VENOUS THROMBOEMBOLISM

S Rivière,[1] D Pelenc,[1] S Dupuis Girod,[2] B Lorcerie,[3] P Kaminsk,[4] A Lequellec[1] H Plauchu[2] and on behalf of european network of HHT disease

[1]Service de Médecine A, Hopital Saint Eloi, CHU Montpellier France, [2]Service de génétique clinique and national center of Rendu Osler disease, Hotel Dieu, Lyon, France, [3]Service de Médecine Interne, Hopital Le Bocage,CHU Dijon, France, [4]Sevice de Médecine Interne, Hopital Brabois, CHU Nancy, France

Hereditary haemorrhagic telangiectasia (HHT) causes bleeding. Nevertheless, prothrombotic risk habe been outlined with frequent elevation of FVIII: Ag level in HHT affected patients who experienced venous thromboembolism (VTE) in 6,5%. In order to estimate frequency and clinical presentation of VTE in HHT, we reviewed records of 830 HHT patients from 3 centers of HHT european network. Fifty patients (6%) reported VTE but great differences between centers were observed (4,8 to 14,6%). Fourty four patients (61 VTE) were studied, 31F, 13M, median age 62 years (range 27-88). Pulmonary and hepatic arteriovenous malformations were present in 19 (43,2%) and 14 (32%) patients respectively. Family history of TVE was noted in 10 (22,7%). Twelve patients (27,3%) had more than one TVE. Median age at the time of the first TVE was 46 (range19-84). The TVE was proximal for 9 (25,7%), distal for 26 (74,3%) with pulmonary embolism in 11 (30,5%). Clinical risk factors for thrombosis were present in 25 (65,8%).The main was post partum (44%), bedridden 36%, oestrogen therapy 0,08%. Abnormal coagulation was known in 3. If post partum events are excluded, HHT patients reported TVE were 4,45%. Thirty two patients reported treatment tolerance. Increase bleeding occurs 3 times (19%) when heparin were used (n=16), only 1 time when antivitamin K (AVK) (n=16). Our study confirm increased risk of TVE in HHT, especially in post partum. This risk is pro-

bably underestimated with retrospective studies. Prospective studies will be useful to precisely evalue TVE risk in HHT patients and give advices for thrombophilic markers assessments. Moreover, it shows the good tolerance for AVK

PC14
INAPPROPRIATE APPLICATION OF SEPTAL OCCLUDER DEVICE IN PATIENTS WITH PULMONARY ARTERIOVENOUS MALFORMATIONS

D Goodenberger, M Chakinala

Washington University HHT Center, St. Louis, Missouri, USA; Dallas Veterans Affairs Medical Center, Dallas, Texas, USA; and University of Texas Southwestern Medical School, Dallas, Texas, USA

When pulmonary arteriovenous malformations (PAVM's) are present, the most common incorrect diagnosis on saline contrast echocardiography is patent foramen ovale (PFO). The Amplatzer? septal occuder device has been available for use in Europe since 1996, and was FDA-approved for use in the United State in 2001. In 2002 and 2004, we saw two patients with device placement for paradoxical embolic stroke when the correct diagnosis was PAVM. Patient #1 was a 28 year-old woman with definite HHT and juvenile polyposis who presented with a transient ischemic attack (TIA) while on oral contraceptives. Contrast echocardiography showed a large left-to-right shunt with late contrast appearance interpreted as being consistent with PFO. Transeptal puncture was necessary, as the "PFO" could not be crossed with a catheter, and an Amplatzer® septal occluder device was placed. Post-procedure echo remained positive, prompting chest CT, which revealed a right middle lobe PAVM which was successfully embolized. Aspirin and clopidogrel were subsequently discontinued. Patient #2 was a 49 year-old woman with definite HHT. Although PAVM's were known since 1981, they were not embolized at another institution until a right hemisensory TIA in 2001. A second TIA in 2003 resulted in a contrast echocardiogram at a second instition, and an Amplatzer® septal occluder device was placed based solely on it's being positive. Daily aspirin resulted in increased epistaxis. Further evaluation at our center revealed a persistently patent right lower lobe PAVM, due to placement of embolization coils in the aneurysmal sac. The PAVM was successfully occluded, and aspirin was discontinued. In summary, this represents the first known report of this phenomenon. It can be expected that the convergence of this technology and cardiovascular consultants unfamiliar with HHT will result in further errors; professional education will be needed to prevent this.

PC15
HEREDITARY HEMORRHAGIC TELANGIECTASIA (HHT) CLINICAL PATHWAY: IMPROVING QUALITY HEALTH CARE

C Fariñas-Álvarez, R Zarrabeitia-Puente, D Acón-Royo, P Rodríguez-Cundín, ML Fernández-Núñez, O González-Martínez, A Pérez del Molino

Hospital Sierrallana, Cantabria, Spain

Introduction. Clinical pathways are highly useful tools for the systematization and improvement of clinical processes. The objective of this study was to evaluate the impact of a clinical pathway for HHT one year after its introduction. *Methods.* A clinical pathway for hospitalized HHT patients was introduced in our hospital on 1st September, 2007. All patients included were studied. The evaluation criteria were the degree of compliance, clinical care effectiveness (length of stay less than 3 days), clinical security (number of medical complications), number of process incidences, and satisfaction indicators based on a survey. *Results.* Between September 2007 and December 2008, 25 patients were included (9 women and 16 men). The mean age was 46.3 years (range 16 to 68). The clinical pathway coverage was 96%: 87.5% in 2007 and 100% in 2008. Mean Length of stay in the hospital was 2.1 days and effectiveness of clinical pathway was 88%. The percentage of medical complications was 40%: epistaxis (46.6%), pain (20%) and anemia (13.3%) were the most frequent. Incidence rate in the process was 44.4%: major variations were related to diagnosis test appointments (50%). Patient satisfaction with the health care received was high: satisfaction mean degree was 9.4 (range 8 to 10). Information about healthcare process and medical and nursing care showed a satisfaction ratio of more than 90%. *Conclusions.* he clinical pathway has proved to be an effective and efficient tool to reduce the length of hospital stay and improved perceived quality.

PC16
CORRELATION BETWEEN TRANSTHORACIC CONTRAST ECHOCARDIOGRAPHY (TTCE) AND MULTIDETECTOR CT (MCT) FOR THE DETECTION OF PULMONARY ARTERIOVENOUS MALFORMATIONS (PAVMS) IN PATIENTS WITH HEREDITY HEMORRHAGIC TELANGIECTASIA (HHT)

P Ortiz, JM Cuesta, J Bueno, S Díaz-Aja, R Zarrabeitia, JA Parra[1]

Hospital Comarcal Sierrallana, Torrelavega; [1]Hospital Valdecilla, Santander, Spain

HHT is an inherited disorder characterized by the developed of vascular malformations. The most common organs affected are the lungs. MDCT is used for the diagnosis. *Objective*. evaluate the usefulness of echocardiography in the screening of PAVMs in this group of patients. *Methods.* 125 were evaluated. Only 95 patients had at least 3 of the 4 Curacao criterions. TTCE (using as a contrast 10 ml of agitated saline or fluid gelatine, injected into a peripheral vein) and MDCT were performed. According to the amount of contrast seen in the left ven-

tricle the studies were classify into grade 1: minimal left ventricular opacification, grade 2: moderate opacification; grade 3: extensive opacification; and grade 4: extensive opacification with endocardial definition. *Results.* 71 patients (75%) had a positive TTCE. 34 were considered grade 1, 20 grade 2, 10 grade 3 and 7 grade 4. Only 20 patients (21%) had PAVMs according to the MCT findings. None of the group of patients with a negative or grade 1 TTCE had PAVMs on the MCT. We found a significant association between TTCE grades and detection of PAVMs on MCT ($p<0.0001$). Positive predictive values were 0% for grade 1, 25% (5 of 20) for grade 2, 80% (8 of 10) for grade 3 and 100% (7 of 7) for grade 4. *Conclusions*. TTCE grades are useful to select patients for MDCT in the screening of PAVMs. The present findings suggest that in the presence of TTCE grade 1, further MDCT studies may not be necessary.

PC17
SUCCESSFUL EMBOLIZATION OF A LARGE PULMONARY ARTERIOVENOUS MALFORMATION IN A PATIENT WITH HEREDITARY HEMORRHAGIC TELANGIECTASIA AND PULMONARY HYPERTENSION

JR Gossage, K Donahue, DR Riggans

Medical College of Georgia, Augusta, GA, USA

Case. A 66-year-old woman with definite HHT presented with progressive class III dyspnea, bilateral PAVM, multiple liver AVM, and pulmonary hypertension. Conventional pulmonary angiography showed a right PAVM with a feeding artery of 9 mm in diameter and a smaller left PAVM. Concomitant right heart catheterization through a second venous access showed: mPAP 40 mm Hg; PAWP 18 m Hg; CO 10 L/min; PVR 2.2; and a right to left shunt of 9.1%. Repeat hemodynamics during balloon occlusion of the larger PAVM showed: mPAP 41; PAWP 19; CO 8.91; and PVR 2.47. Both PAVM were embolized and 18 months later the patient reported decreased dyspnea and improved exercise tolerance. *Discussion.* We felt that embolization of her PAVM was warranted based on her symptoms and in order to prevent embolic complications; however, we were also concerned that embolization might exacerbate her pulmonary hypertension based on prior case reports. Although PAVM are often believed to be low resistance circuits, in most cases they are actually high resistance circuits relative to the remainder of the pulmonary circuit. In our case, we estimated a resistance of 24.2 through the PAVM and 2.42 through the rest of the pulmonary circuit. Since a PAVM is a parallel component in a pulmonary circuit, embolization of her PAVM would be expected to increase the PVR to 2.42, which is close to the true result of 2.47. We believe that careful hemodynamic evaluation and transient balloon occlusion of PAVM can potentially assist in the management of such complex patients

PC18
ASSESSMENT OF AN AGE-RELATED THRESHOLD OF MUCOCUTANEOUS TELANGIECTASIA NUMBER FOR DIAGNOSIS OF HEREDITARY HEMORRHAGIC TELANGIECTASIA: HHT PARIS CENTER EXPERIENCE IN 165 RELATIVES BELONGING TO 80 GENOTYPED FAMILIES

I Bourgault Villada,[1] J Roume,[1] B Raffestin,[1] JH Blondel,[1] S Blivet,[1] T Chinet,[1] F Coulet,[3] C Fagnou,[1] P Lasjaunias,[2] G Lesur,[1] A Ozanne,[2] JP Pelage,[1] F Soubrier,[3] P Lacombe[1]

HHT center of Paris, AP-HP, France; [1]CHU Ambroise Paré; [2]Neuroradiology CHU Kremlin Bicêtre; [3]Oncoangiogenesis laboratory, CHU Pitié Salpétrière; Paris, France

Background. Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant disease characterized by Curaçao criteria which include the presence of mucosal and cutaneous telangiectasia. *Objective.* To determine according to age the lower threshold of mucocutaneous telangiectasia number which allows to predict HHT. *Materials and methods.* 165 family members of 80 genotyped HHT patients were carefully examined by the same dermatologist not aware of the diagnosis between January I, 2004 and December 31, 2008. The number of telangiectasia was counted in the face, oral cavity, hands, fingers and feet. Comparisons were performed between subjects with mutation (n=97) or disease according to Curaçao criteria (n=8) and related family members without the mutation of the proband (n=60). *Results.* The number of telangiectasia increases with age in both groups. Mean number ± SD are summarized in the following table:

Table

Age (yr)	0-20	20-40	40-60	>60
HHT (subjects number)	9±25.6 (n=29)	56.45±82.5 (n=33)	104.6±74.5 (n=30)	225.3±228.7 (n=13)
Non HHT (subjects number)	2.4±3.1 (n=17)	3.7±7.4 (n=27)	9.25±10.5 (n=13)	29±47.6 (n=3)

Conclusion. In order to determine the mucocutaneous crireria of Curaçao as positive, age of the patient should be carefully considered. A significant number of telangiectasia may be present in older subjects without the disease and therefore the threshold of telangiectasia number should be calculated according to age.

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PC19
DETECTION OF LIVER VASCULAR ABNORMALITIES IN HEREDITARY HEMORRHAGIC TELANGIECTASIA (HHT): VALUE OF EARLY ARTERIAL PHASE, LATE ARTERIAL PHASE AND PORTAL PHASE MULTIDETECTOR CT ACQUISITIONS

J Bueno,[1] JA Parra,[2] C Fariñas-Alvarez,[1] MA Matute,[1] A Pérez del Molino,[1] R Zarrabeitia[1]

[1]Hospital Sierrallana, Torrelavega; [2]Hospital Universitario Marques de Valdecilla, Santander, Spain

Objective. To determine the most convenient postendovenous contrast phase in multidetector CT acquisitions to reduce radiation to the patients. *Methods.* 67 consecutive patients (males 42%, mean age 47 years) underwent a two multidetector CT studies to exclude vascular abnormalities of the liver. All studies were performed with a bolus tracking technique with 3 mm thickness and 1.5 mm reconstruction in three phases: early (20.4±3.6 s), late arterial (39±4.7 s), and portal (66±6.3 s). Records of the three postendovenous contrast phases were evaluated by two independent radiologists in reference to the presence or absence of hepatic shunts, hepatic perfusion abnormalities, telangiectases, and large confluent vascular masses. Sensitivity and 95% confidence interval (CI) for each phase were calculated. *Results.* 35 of 67 (52%) patients had a liver vascular abnormality according to the two readers: telangiectases 25, hepatic perfusion abnormalities 13, large confluent vascular masses 11, and hepatic shunts 7. A total of 18 patients had more than one vascular abnormality. In 34 patients (97%; 95% CI 91–100%), these vascular abnormalities were seen in the early arterial phase, in 29 (83%; 95% CI 70–95%) in the late arterial phase, and in 5 (14%; 95% CI=3% to 25%) in the portal phase. When we compared early and late arterial phases: 8 patients had the vascular abnormalities more visible in late arterial phase (mainly hepatic perfusion abnormalities and large confluent vascular masses), in 10 were equal and in 17 patients were less visible or no visible. All 5 patients with vascular abnormalities seen in portal phase had these alterations seen in arterial phases (4 in early arterial phase and 5 in late arterial phase). The combination of two phases (early and late; early and portal) allowed a 100% diagnostic accuracy, whereas with the use of combined late arterial and portal phase, the diagnosis will be missed in 5 patients. *Conclusion.* Early arterial phase appears as the most adequate for assessing liver abnormalities in HHT. A combination of early and late or early and portal phases allowed diagnosing HHT in all patients.

PC20
CORRELATION BETWEEN CT AND ANGIOGRAPHY MEASUREMENT OF PAVM AFFERENT ARTERY

M Bustamante, J Parra, J Izquierdo, J Bueno, J Jordá, R Zarrabeitia

Hospital Universitario Marqués de Valdecilla, Spain

Objective. To compare the size of the afferent artery in CT and angiography. *Methods.* 10 patients (males 50%, mean age 35,1 years; range 16-54 years) with one or more PAVMs on multidetector CT and angiography. All MDCT scans were performed with 3 mm collimation and 1.5 mm reconstruction thickness and evaluated in a workstation in conventional, MPR, MIP and volume rendering reformations. The presence of a nodule with an afferent artery and efferent vein was considered diagnostic for lung PAVM on CT. Angiographic studies included a bilateral pulmonary angiography in frontal and oblique views followed by selective studies of the PAVMs. The mean time between CT and angiography was 104 days (range 29-152 days).

PC21
CORRELATION OF SEVERITY OF EPISTAXIS WITH MORPHOLOGY AND DISTRIBUTION OF ENDONASAL TELANGIECTASIAS IN HEREDITARY HEMORRHAGIC TELANGIECTASIA PATIENTS

A Colombo,[1] E Matti,[1] G Giourgos,[1] F Chu,[1] C Tinelli,[2] C Olivieri[3] and on behalf of the HHT-NET (C Danesino, E Buscarini, G Manfredi, P Gazzaniga, L Reduzzi, F Pagella, M Grosso, G Pongiglione, E Boccardi)

[1]Operative Unit of Otorhinolaryngology, University of Pavia, IRCCS Policlinico S. Matteo Foundation, Pavia, Italy; [2]Clinical Epidemiology and Biometric Unit, IRCCS Policlinico S. Matteo Foundation, Pavia, Italy; [3]General Biology and Medical Genetics, University of Pavia, Italy

The presence of telangiectasias in nasal mucosa of patients affected by Hereditary Hemorrhagic Telangiectasia (HHT) leads to recurrent epistaxis that affects more than 90% of patients but with unpredictable severity. Endonasal morphology and distribution of telangiectasias can be very variable too. We reviewed nasal endoscopy records of 76 consecutive HHT patients treated for epistaxis between 2003 and 2007 at our institution. Presence or absence of telangiectasias was assessed considering six subsites in nasal fossae: nasal valve, floor of nasal fossae, anterior and posterior nasal septum, superior lateral wall, inferior lateral wall. Morphology of telangiectasias was endoscopically classified as punctate and large: we defined as "punctate lesions" telangiectasias that appeared as punctate and flat lesions; the others, bigger and prominent, were defined as "large". Patients were then divided into three groups: punctate pattern, large pattern, mixed pattern. We evaluated severity of epistaxis using a questionnaire and considering frequency, intensity, duration of nosebleeds and need for blood transfusions. Morphology and distribution of nasal telangiectasias demonstrated a statistically significant correlation with frequency and intensity of epistaxis. Presence of telangiectasias endoscopically appearing as large-prominent correlates with higher frequency of epistaxis. Increase in number of nasal subsites involved correlates with higher intensity of nosebleeds. Our data suggest that, to reduce frequency and intensity of epistaxis in HHT patients, treatments should be directed also on lesions located in posterior part of nasal fossae and especially on telangiectasias endoscopically appearing as large-prominent.

PC22
CLINICAL EVALUATION OF TRANSCATHETER CLOSURE OF HUGE PULMONARY ARTERIOVENOUS MALFORMATIONS WITH HOMEMADE DOUBLE-UMBRELLA OCCLUDERS

H Zhong, K Xu, X Dai, H Shao

Department of Radiology, the First Affiliated Hospital of China Medical University. the Institute of Vascular Interventional Radiology, China

Purpose. To evaluate the effect of transcatheter closure of huge pulmonary arteriovenous malformations (PAVMs) with homemade double-umbrella occluders. *Methods.* 6 consecutive cases with 11 huge PAVMs underwent transcatheter closure with homemade double-umbrella occluder embolization. Family history, clinical manifestations, analysis of arterial blood gases (ABGs) as well as images of CTA and digital subtraction angiography (DSA) pre- and post- the embolizations were retrospectively collected and evaluated by professional specialists. The effect of transcatheter closure were evaluated by the improvement in saturation of O_2 (SaO_2) and Partial pressure of O_2 (PO_2) according to statistical analysis of ABGs and the findings of CTA and DSA. All the patients were followed-up for 21±1 months. *Results.* Primary and secondary technical success rates of this series were 83.3% (5/6) and 100%, respectively. Mean values of SaO_2 and PO_2 before transcatheter closure were 76±5% and 46±3mmHg, respectively. Immediately after the interventional procedure, those value of mean SaO_2 and PO_2 increased to 94±5% ($p<0.01$) and 62±3mmHg ($p<0.05$), respectively. And neither recurrence of clinical manifestations nor recanalization was revealed during the follow-up. *Conclusions.* Transcatheter closure of huge PAVMs with homemade double-umbrella occluder is considered safe and effective.

PC23
KEEPING ON WITH RALOXIFEN FOR EPISTAXIS TREATMENT IN HHT

J Villegas, R Portilla, C Armiñanzas, A Peña, B Señaris, A Bustamante, JL Fernandez Forcelledo, R Ortiz, J Calvo

Unidad HHT, Hospital Sierrallana, Torrelavega, Cantabria, Spain

Aim. We evaluated the efficacy of the selective estrogen-receptor modulator raloxifen for the treatment of epistaxis in a group of postmenopausal women diagnosed of HHT and osteoporosis. *Methods.* During the last three years, nineteen postmenopausal women diagnosed of HHT and osteoporosis received oral treatment with raloxifen (60 mg. daily). Then, we assessed the following parameters: variation of haemoglobin levels, improvement in frequency and quantity of epistaxis (Sadick scale), modification in quality of life (EQ-5D questionnaire) and transfusions requirements. *Results.* Nineteen postmenopausal women (mean age 57´2 years) diagnosed of HHT and osteoporosis were included in the study. Twelve patients were HHT-2 (63%), five were HHT-1 (26%) and two patients (11%) had no molecular diagnosis. Four of them (21%) did not complete the treatment, because of unefficacy or voluntary reasons and eight women (42%) required additional treatment to raloxifen, either topical or surgical. An increase in haemoglobin levels was observed in seven patients out of fourteen (mean increase value of 22%), while four women presented lower haemoglobin levels (mean decrease of 12'75%). Three patients (18%) needed periodical transfusions, although two of them reduced their rate. Thirteen patients (72%) improved in at least one grade in Sadick scale. In those who completed the EQ-5D questionnaire (37%), improvement considering average punctuation on the five dimenssions was observed (1,4 before and 1,2 after treatment). Visual score improved from 75 to 85% in this same group. *Discussion.* In this wider serie of post-peri menopausic HHT women, treated with raloxifen we conclude that raloxifen may be useful in the therapy of epistaxis, regarding improvement in Sadick epistaxis score, transfusion requirement and quality of life.

PC24
DEVELOPING A STUDY OF HEREDITARY HEMORRHAGIC TELANGIECTASIA (HHT) IN CASTILLA LEON (SPAIN)

A Cabezón, E Corral, Á Sánchez, JC Olazábal Ulacía, JM López Novoa, R González-Sarmiento

Leon, Castilla, Spain

Aim. To evaluate the prevalence of HHT first in the population of the province of Salamanca and afterwards in all the region of Castilla-León (Spain) and facilitate the genetic study to the affected families. *Methods.* the search was performed in two phases: first a systematic review of all the patients' dossiers in the University Hospital of Salamanca up to 2007, selecting those with HHT registered code (GRD) as previous illness. In a second phase , those patients diagnosed *de novo* in the hospital fulfilling the Curaçao criteria. In all clinically confirmed cases genetic test was performed, expanding it to relatives if mutation found. *Results.* A total of 20 patients with clinical criteria compatible with HHT were identified. The genetic study showed c.991+25_26 insCCTCCC and p.416 Cys>tyr mutations on ENG in the same patient and p. 82 Thr>Pro mutations on ALK1. Relatives were adviced about genetic test. *Discussion.* HHT is frequently underestimated due to the variability of symptoms and the usual common presentation (epistaxis, telangiectasias). Genetic studes although of great value, can not detect all the mutations involved in the disease until new genes can be identified.

PC25
NURSING PROGRAMME OF CARE FOR HHT PATIENTS ADMITTED IN THE UNIT OF THE HOSPITAL SIERRALLANA

MM Rodriguez Garrido, E Ruiz Santander, PB Gómez-Ullate, E Pérez Martín, R Calderón Arozamena, E Martinez Torre

HHT Unit. Hospital Sierrallana, Torrelavega, Spain

Objective. To unify criteria in the nursing management for HHT patients admitted in the HHT unit and to serve

as guide for the nursery team. *Methods.* Creation of a specific working group with nurses and auxiliaries to elaborate a programme of care for HHT patients admitted in the unit, using the on-line tool "Gacela"and recovering information from the patients´associations and literature. The programme was introduced in daily routine on September 2007. *Results.* Eight issues of main interest were identified in the programme: 1) Problems regarding fear of being in hospital (application of specific welcome protocol and information about techniques and proceedings); 2) Problems regarding ineffective therapeutic management (vein access protocol, blood samples protocol and preparation for techniques); 3) Management of sleeping disorders (quiet atmosphere, comfort and preservation of rest time); 4) Epistaxis prevention (moisturizing and nose cleaning, humid atmosphere, advice about blowing nose); 5) Epistaxis management (pressure on nostrils, evaluation using quantity and frequency scale of Sadick, tamponage if required. Kit for tamponage and epistaxis management accesible); 6) Detection of GI bleeding (vital signs control, stools control, protocol to evaluate medical requirement); 7) Discharge from hospital (specific report with recomendations after discharge; 8) All the registers and protocols have been introduced in the on line tool "Gacela" (hospital intra-net). *Conclusion.* The development of a nursing care programme has helped to manage the illness by making the nursery be more informed, performing a routine protocol, decreasing rates of complications, making the patient be more informed with a better approach and adding extra value to the medical acts. The on-line tool "Gacela" registered all the activity regarding the plan.

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