open access journal

hematology reports

eISSN 2038-8330 | www.hematologyreports.org

non commercial use only

10th International Hereditary Hemorrhagic Telangiectasia Scientific Conference

June 12th - 15th, 2013

Cork, Ireland

Guest Editors
Carmelo Bernabeu, Luisa M. Botella, Adrian Brady, Marie Faughnan, Urban Geisthoff

hematology reports – volume 3, 2013 – supplement 1

HEMATOLOGY REPORTS

ISSN 2038-8322 - eISSN 2038-8330

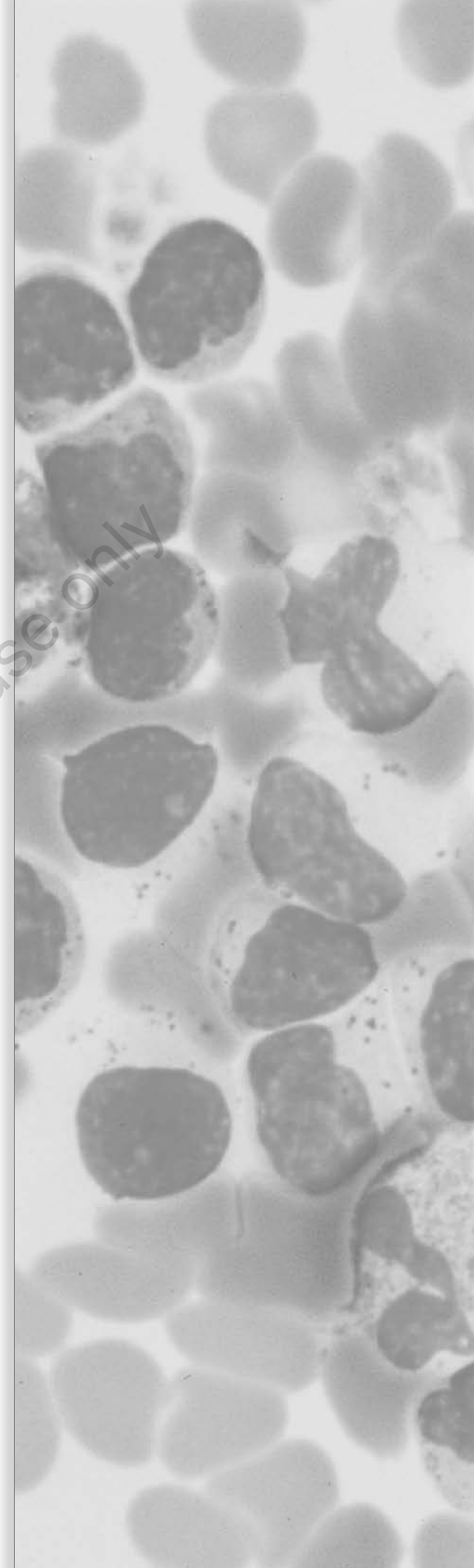
Editor-in-Chief
Giovanni Martinelli, Italy

Deputy Editor
Francesca Palandri, Italy

Editorial Board
Giuliana Alimena, Italy
Luca Arcaini, Italy
David Dingli, USA
Muller Fabbri, USA
Mario Federico, USA
Francesca Gualandi, Italy
Jean-Luc Harousseau, France
Karl-Anton Kreuzer, Germany
Delong Liu, USA
Hans E. Johnsen, Denmark
Taira Maekawa, Japan
Luca Malcovati, Italy
Anne F. McGettrick, Ireland
Ruben Mesa, USA
Markus Raderer, Austria
Manuela Schmidinger, Austria
Evangelos Terpos, Greece
Elisabeth Walsby, UK

Editorial Staff
Emanuela Fusinato, Managing Editor
Cristiana Poggi, Production Editor
Anne Freckleton, Copy Editor
Filippo Lossani, Technical Support

pagepress



non commercial use only

pagepress

HEMATOLOGY REPORTS

is published by PAGEPress Publications, Italy.
The journal is completely free online at www.hematologyreports.org
Publishing costs are offset by a publication fee charged to authors.

For more information
and manuscript submission:
www.hematologyreports.org

Copyright Information
All works published in PAGEPress journals are subject to the terms
of the Creative Commons Attribution License
(http://creativecommons.org/licenses/by-nc/3.0) unless otherwise noted.
Copyright is retained by the authors.
Any non-commercial reuse is permitted if
the original author and source are credited.

Correspondence
Our publishing offices are located
in via Giuseppe Belli 7, 27100 Pavia, Italy.
Our telephone number is +39.0382.1751762
and our fax number is +39.0382.1750481.
E-mail: info@pagepress.org

All PAGEPress journals are Open Access.
PAGEPress articles are freely available online and deposited
in a public archive immediately upon publication.

non commercial use only

10th International Hereditary Hemorrhagic Telangiectasia Scientific Conference

June 12th - 15th, 2013

Cork, Ireland

HEMATOLOGY REPORTS 2013; VOLUME 5, SUPPLEMENT 1

Guest Editors

Carmelo Bernabeu, Luisa M. Botella, Adrian Brady, Marie Faughnan, Urban Geisthoff

non commercial use only

TABLE OF CONTENTS

Conference program ..... f-n

Patient workshop ..... o

Poster program ..... p–s

Abstracts

Invited presentations 1

Oral Communications

Session I. Arteriovenous malformations and animal models. Angiogenesis and vascular development 3

Session II. Hepatic involvement in HHT 5

Session III. Genetics and genotype/phenotype in HHT 10

Session IV. Cellular and molecular involvement in HHT and related pathologies 14

Session V. Central nervous system involvement and treatment in HHT 19

Session VI. Molecular diagnostics, markers and epidemiology for HHT 21

Session VII. Antiangiogenic therapies in HHT and outcomes 24

Session VIII. Anemia, and venothrombous complications in HHT 29

Session IX. Pulmonary involvement: PAVMs and pulmonary hypertension in HHT 32

Session X. Epistaxis and gastrointestinal bleeding in HHT 36

Session XI. Endoglin, ALK1 and Smad4 in TGF-beta and BMP pathways 39

Session XII. Pediatrics and natural history of HHT 42

Posters 47

10th International Hereditary Hemorrhagic Telangiectasia Scientific Conference

June 12th - 15th, 2013

Cork, Ireland

SCIENTIFIC PROGRAM COMMITTEE

Carmelo Bernabeu, PhD, *Co-Chair Scientific Program Committee*
Centro de Investigaciones Biologicas (CSIC) and
Biomedical Network Research Centre on Rare Diseases (CIBERER), Madrid, Spain
Chair, GRMAB, HHT Foundation International, Monkton, USA

Luisa Maria Botella, PhD, *Co-Chair Scientific Program Committee*
Centro de Investigaciones Biologicas CSIC and
Biomedical Network Research Centre on Rare Diseases (CIBERER), Madrid, Spain

Dr. Adrian Brady, FFRRCSI, FRCR, FRCPSC, FRCPI, *Chair, Local Organizing Committee*
Consultant Radiologist
Mercy University Hospital, Cork

Marianne S. Clancy, MPA
Executive Director
HHT Foundation International, Monkton, USA

Derry Cronin
Chairman Grace Nolan Foundation, Cork, Ireland

Marie E. Faughnan, MD, MSc
St. Michaels Hospital, Toronto, Canada
Scientific Director, HHT Foundation International, Monkton, USA

PD Dr. Urban W. Geisthoff, *Chair, Clinical Program Committee*
Department of Otorhinolaryngology, Head and Neck Surgery, Hospitals of the City of Cologne, Cologne, Germany

Mike Nolan
HHT International Director, CEO Grace Nolan Foundation, Cork, Ireland

Dr. Terry O'Connor MD, FCCP, FRCPI
Consultant Respiratory Physician
Mercy University Hospital, Cork, Ireland

Prof. Dr. Jochen A. Werner
Department of Otorhinolaryngology, Head and Neck Surgery, University Hospital of Marburg, Marburg, Germany

non commercial use only

10th International Hereditary Hemorrhagic Telangiectasia Scientific Conference

June 12th - 15th, 2013

Cork, Ireland

PROGRAM

11 June 2013, Tuesday

17:00-20:00 REGISTRATION AND WELCOME RECEPTION

12 June 2013, Wednesday

07:30-08:00 **Registration**
08:00-08:15 **Welcome and opening remarks**
08:15-08:30 **Official inauguration of the conference**

08:30-09:15 **Opening Session (session chairs: Marie Faughnan and Adrian Brady):**
Alan Guttmacher, *Director of the Eunice Kennedy Shriver National Institute of Child Health and Human Development. Bethesda, MD, USA,* **The Future of Scientific Research**

09:15-09:45 **Session I: Arteriovenous malformations and animal models. Angiogenesis and vascular development (session chairs: Helen Arthur and S. Paul Oh)**

Juan C. López-Gutierrez, *Director Vascular Anomalies Center and Head of Pediatric Surgery, La Paz Children's Hospital Division of Quiron Hospital, Madrid, Spain,* **Uncommon Vascular Anomalies**

09:45-10:15 **Coffee break and poster viewing**

10:15-12:00 **Session I: Arteriovenous malformations and animal models. Angiogenesis and vascular development (session chairs: Helen Arthur and S. Paul Oh)**

Pathogenesis of arteriovenous malformations in a mouse model of HHT2
S. Tual-Chalot, M. Mahmoud, K.R. Allinson, S.P. Oh, H.M. Arthur

Endothelial cells are the cellular source for the development of arteriovenous malformations in Alk1 deficiency
E.M. Garrido-Martín, Y. Hwan Kim, S. Choe, T. Cunningham, Z. Jiang, S.P. Oh

Visceral and systemic vascular lesions in patients with non-HHT related pulmonary arteriovenous malformations
M. Maruno, H. Kiyosue, S. Tanoue, J. Kashiwagi, S. Matsumoto, H. Mori

Endoglin and ALK1 play distinct roles in mural cell recruitment and endothelial cell specification during pathological angiogenesis
F. Lebrin, S. Martin, J. Thalgott, D. Bracquart, S. Srun, L. Venance, N. Lamandé, D. Dos-Santos-Luis

Modeling Hereditary Haemorrhagic Telangiectasia (HHT) With Patient Specific Induced Pluripotent Stem Cells (iPSCs)
V. Orlova, C. Freund, K. Gkatzis, Y. Drabsch, L. van den Hil, F. Disch, H.J. Mager, R. Snijder, K. Westermann, P. ten Dijke, C. Mummery

non-commercial use only

12:00-13:00 Lunch break and poster viewing
13:00-14:00 Poster session with authors (Sessions I-IV; P-93 to P-106 & P-113 to P-114)
14:00-16:00 Session II: Hepatic involvement in HHT (concurrent)
(session chairs: Guadalupe García-Tsao and Elizabetta Buscarini)

Manganese-related Central Nervous System injury in HHT patients with hepatic involvement. Relationship with iron deficiency anemia, hepatic vascular malformations and neurological symptoms
M.M. Serra, C. Besada, A. Saenz, C. Stefani, D. Giunta, J.C. Bandi, N. Causada Calo, M.C. Elizondo

Magnetic resonance imaging of the liver in patients with hepatic involvement of HHT
A. Massmann, U. Geisthoff, A. Buecker, G.K. Schneider

Predictors of death in patients with HHT, liver vascular malformations (LVMs) and symptomatic heart failure (HF)
L.H. Young, K.J. Henderson, J.S. Pollak, R.I. White Jr., M.M. Ciarleglio, Y. Deng, G. Garcia-Tsao

Multidetector Contrast-Enhanced Computed Tomography in the Evaluation of Splenic Involvement in Patients with Hereditary Hemorrhagic Telangiectasia: A Prospective Study
M. Bensalah, M. El Hajjam, J. Sellier, S. Binsse, T. Chinet, J. Roume, A. Ozanne, I. Bourgault, G. Lesur, J.H. Blondel, A. Cordier, S. Blivet, C. Fagnou, M. Bonay, C. Karam, A. Nicod-Tran, S. Chagnon, M. Eyries, L. Gouya, P. Lacombe

Any major treatment decision regarding HHT should be discussed with a HHT reference center: C.A.R.D project for HHT patients
S. Alicante, E. Buscarini, G. Manfredi, F. De Grazia, G. Lupinacci, F. Menozzi, G. Brambilla, C. Londoni, S. Crinò, A. Zambelli, P. Gazzaniga, S. Gandolfi, P.A. Forner, C. Danesino, C. Olivieri, C. Canzonieri, F. Ornati, F. Pagella, M. Grosso, G. Pongiglione, E. Boccardi, on behalf of HHT-NET

Improvement of Hereditary Hemorrhagic Telangiectasia Related Ischemic Cholangiopathy Following Treatment with Bevacizumab
P.A. Vlachou, E. Colak, A. Koculym, A. Kirpalani, T. Kyoung Kim, G. M Hirschfield, M.E. Faughnan

Pulmonary capillary blood volume/alveolo-capillary membrane conductance ratio is increased in Hereditary Hemorrhagic Telangiectasia patients with liver arteriovenous malformations
M. Dubois, Y. Retory, C. de Picciotto, J. Sellier, M. El Hajjam, S. Binsse, T. Chinet, J. Roume, A. Ozanne, I. Bourgault, G. Lesur, J.H. Blondel, A. Cordier, S. Blivet, C. Fagnou, C. Karam, A. Nicod-Tran, S. Chagnon, P. Lacombe, M. Eyries, L. Gouya, M. Bonay

Follow-up of HHT patients treated with bevacizumab for severe hepatic vascular malformations and high cardiac output (Metafore clinical trial)
S. Dupuis-Girod, I. Ginon, J.C. Saurin, D. Marion, E. Guillot, E. Decullier, M.F. Carette, B. Gilbert-Dussardier, P.Y. Hatron, P. Lacombe, B. Lorcerie, S. Rivière, R. Corre, S. Giraud, A.E. Fargeton, S. Bailly, G. Paintaud, David Ternant, Pierre-J. Valette, H. Plauchu, F. Faure

14:00-16:00 Session III, part 1: Genetics and Genotype/Phenotype in HHT (concurrent)
(session chairs: Hans Jurgen Mager and Douglas Marchuk)

Mutation analysis of TGF-beta pathway genes in Hereditary Hemorrhagic Telangiectasia patients in Japan: Genotype-phenotype correlations in 119 cases
H. Morisaki, M. Komiyama, O. Yamada, K. Osuga, T. Morisaki, and Japan HHT Consortium.

Mutations on a new gene cause a new vascular malformation disorder similar to Hereditary Hemorrhagic Telangiectasia
W. L. Wooderchak-Donahue, J. McDonald, B. O'Fallon, P.D. Upton, W. Li, B.L. Roman, S. Young, Parker Plant, G. Tamas, C. Langa, N. W. Morrell, L.M. Botella, C. Bernabeu, D.A. Stevenson, J.R. Runo, P. Bayrak-Toydemir

Copy number variation in endoglin locus: mapping of large deletions in Spanish families with hereditary haemorrhagic telangiectasia type 1
A. Fontalba, J.L. Fernández-Luna, R. Zarrabeitia, L. Recio-Poveda, V. Albiñana, M.L. Ojeda-Fernández, C. Bernabeu, C. Alcaraz, L.M. Botella

Non commercial use only

Endoglin mutational mechanisms and genotype-phenotype correlations in hereditary haemorrhagic telangiectasia
F.S. Govani, A. Giess, I.G. Mollet, M.E. Begbie, M.D. Jones, L. Game, C.L. Shovlin

16:00-16:30 Coffee break and poster viewing

16:30-18:00 Session III, part 2: Genetics and Genotype/Phenotype in HHT (concurrent) (session chairs: Cesare Danesino and Anette D. Kjeldsen)

Clinical expression of Hereditary Haemorrhagic Telangiectasia and digestive lesion characteristics in patients with SMAD4 mutation.
M. Bonjean, S. Giraud, E. Decullier, J.C. Saurin, P. Edery, S. Dupuis-Girod

Clinical Analysis of 42 HHT1 and 23 HHT2 Japanese Patients
M. Komiyama, T. Ishiguro, O. Yamada, H. Morisaki

Genotype-Phenotype correlations in Hereditary Haemorrhagic Telangiectasia. Data of the French Rendu-Osler-Weber cohort.
C. Paez, S. Giraud, G. Lesca, E. Decullier, E. Babin, M.F. Carette, R. Corre, P. Duffau, B. Gilbert-Dussardier, P.Y. Hatron, J.R. Harle, P. Kaminsky, P. Lacombe, C. Lavigne, P. Lorcerie, P. Magro, S. Rivière, P. Edery, S. Dupuis-Girod

The Italian Job: our experience in HHT management
C. Olivieri, C. Canzonieri, F. Ornati, F. Pagella, E. Buscarini, L. Lanzarini , G Manfredi , E. Matti, F. Chu, P. Gazzaniga , S. Gandolfi , P.A. Forner , M. Grosso , G. Pongiglione, E. Boccardi, C. Danesino

Does genetic status modify pulmonary arteriovenous malformation phenotypes?
A. Khalil, B. Monod, M. Eyris, J. Cadranel, F. Lebrin, M.F. Carette

16:30-18:30 Session IV: **Cellular and molecular involvement in HHT and related pathologies (concurrent) (session chairs: Luisa M. Botella and Chris Hughes)**

Role of macrophages in HHT pathogenesis
Y. Hwan Kim, S.W. Choe, E.J. Choi, S.P. Oh.

Characterization of a myeloid specific endoglin knock-out mouse: the role of endoglin in the innate immune response
L. Ojeda-Fernández, L. Recio-Poveda, P. Lastres, H.M. Arthur, C. Bernabeu, L.M. Botella.

No link between CXCR4/SDF-1 abnormalities on mononuclear leucocytes and history of severe infection in HHT
A. Guilhem, S. Dupuis-Girod, T. Vincent, P. Portales, D. Cerrutti, P. Guilpain, A. Le Quellec, S. Riviere

The potential role of endoglin in regulating myeloid cells during resolution of inflammation
M. Jerkic, M. Peter, D. Douda, V. Sotov, D. S Ardelean, N. Palaniyar, M. Letarte

The endoglin overexpression compromises the immune response in myeloid cells. Novel insights for Hereditary Hemorrhagic Telangiectasia
F.J. Blanco, M.L. Ojeda-Fernandez, M. Aristorena, L.M. Botella, C. Bernabeu.

Endoglin deficiency leads to increased endothelial cell permeability
M. Jerkic, Z.A. Liang, M. Letarte

Alk1 and Endoglin regulation of endothelial gap junction expression
D. Phan, J.H. Kim, C.C.W. Hughes

Loss of endothelial endoglin weakens the endothelial barrier to cancer cell transmigration and leads to increased metastases
Z. Zhai, R. Redgrave, S. Tual-Chalot, H.M Arthur

non commercial use only

Endoglin expression increases the pro-angiogenic potential of transplanted CDCs following myocardial infarction in mice
R. Redgrave, B. Davison, M. Amirrasouli, B. Keavney, A. Blamire, H.M Arthur

Shedding of soluble endoglin is regulated by oxysterols and is involved in hypertension
A.C. Valbuena-Diez, F.J. Blanco, B. Oujo, C. Langa, M. Gonzalez-Nuñez, E. Llano, A.M. Pendas, M. Díaz, A. Castrillo, J.M. Lopez-Novoa, C. Bernabeu

13 June 2013, Thursday

08:30-10:00 **Session V, part 1: Central Nervous System involvement and treatment in HHT (session chairs: Karel terBrugge and Sophie Dupuis-Girod)**

D. Marchuk, *Department of Molecular Genetics and Microbiology, Duke University Medical Center, Durham, NC, USA.*
Cerebral Cavernous Malformations: The Road from Gene Discovery to Treatment

Malformations of cortical development and brain vessels in patients with hereditary haemorrhagic telangiectasia
J.F. Bergerot, S. Dupuis-Girod, Y. Berthezene, T.H. Cho, F. Tahon, J. Honnorat, H. Plauchu, M. Hermier

Cerebral Abscesses as a first symptom of HHT among Danish HHT patients
A. Drøhse Kjeldsen, P. M.Tørring, H. Nissen, P.E. Andersen

MRI and MRA for the Detection of CAVM in patients with HHT
A. Massmann, U.W. Geisthoff, A. Buecker, G.K. Schneider

10:00-10:30 **Coffee break and poster viewing**

10:30-12:00 **Session V, part 2: Central Nervous System involvement and treatment in HHT (session chairs: Marie Faughnan and Adrian Brady)**

Christian Stapf, *University Professor of Neurology, Diderot Sorbonne University Paris and Adjunct Assistant Professor of Neurology, Columbia University College of Physicians and Surgeons, USA*
Outcomes and Management of Unruptured Brain AVMs

Micro Brain Vascular Malformations associated with Hereditary Hemorrhagic Telangiectasia: Arteriovenous Malformations and Capillary Malformations
T. Nishida, K.G. terBrugge T. Krings, K. Henderson, R.I. White Jr.

Coincidental and acquired neurovascular malformations and shunts associated with HHT disorder
K. terBrugge, T. Nishida, T. Krings

A Comparison of Hemorrhage and Nonhemorrhage in Patients with CCM1 Common Hispanic Mutation
L. Morrison, B. Hart, B. Baca, Y. Khan, J. Nelson, H. Choquet, A. Akers, H. Kim

12:00-13:00 **Lunch break and poster viewing**

13:00-14:00 **Poster session with authors (sessions V-IX; P-107 to P-112 & P-115 to P-122)**

non-commercial use only

14:00-16:00 Session VI: Molecular diagnostics, markers and epidemiology for HHT (concurrent) (session chairs: Pinar Bayrak-Toydemir and Beth Roman)

MiR-205 is a novel biomarker for hereditary hemorrhagic telangiectasia with antiangiogenic function
S. P. Tabruyn, S. Hansen, M.L. Ojeda-Fernández, R. Zarrabeitia, L. Recio-Poveda, N. Bovy, C. Bernabeu, J.A. Martial, L.M. Botella, I. Struman

Clinical utility of a next generation sequencing panel in the diagnosis of Hereditary Hemorrhagic Telangiectasia (HHT) and other syndromes featuring vascular malformations
W.L. Wooderchak-Donahue, B. O'Fallon, T. Lewis, J. McDonald, J. Stocks, P. Plant, D. A. Stevenson, J.F. Grimmer, P. Bayrak-Toydemir.

Multiple deleterious mutations in angiogenesis-related genes generate symptoms indistinguishable from Hereditary Hemorrhagic Telagiectasia (HHT)
B. O'Fallon, W. Wooderchak-Donahue, A. Wilson, J. McDonald, P. Bayrak-Toydemir.

Combined genetic, in-silico and functional tools for interpretation of the pathogenic significance of ACVRL1 missense mutations
S. Giraud, C. Vercherat, C. Auboiroux, S. Bailly, G. Lesca, J.Y. Scoazec, A. Calender

Establishment of an in vitro functional test to screen novel endoglin mutations from HHT1 patients
K. Lamribet, S. Giraud, C. Mallet, J.J. Feige, S. Bailly, E. Tillet

The prevalence of Hereditary Haemorrhagic Telangiectasia in the UK and associations with sex, region of residence and socioeconomic status: a population-based study
J.W. Donaldson, T.M. McKeever, I.P. Hall, R.B. Hubbard, A.W. Fogarty

Urinary angiogenesis biomarkers in Sturge-Weber Syndrome: Update in a longitudinal study
C.D. Bachur, K.E. Lanier, A.S. Curatolo, S.M. Connors, M.A. Moses, A.M. Comi

14:00-16:00 Session VII: Antiangiogenic therapies in HHT and outcomes (concurrent) (session chairs: Carlo Sabbà and Michelle Letarte)

ELLIPSE Study: A phase-1 study evaluating the tolerance of bevacizumab nasal spray to treat epistaxis in Hereditary Haemorrhagic Telangiectasia
A.E. Fargeton, F. Faure, A. Ambrun, E. Decullier, F. Chapuis, F. Disant, G. Samson, C. Rioufol, V. Schwiertz, Y. Donazzolo, G. Paintaud, S. Dupuis-Girod

Bevacizumab in HHT: a retrospective study of 24 patients
S. Riviere, A. Guilhem, A.C. Simon, P. Duffau, M.F. Carette, B. Gilbert-Dussardier, O. Bletry, J.R. Harle, P. Kaminsky, B. Lorcerie, N. Lerolle, C. Lavigne, J.C. Saurin, A. Lequellec, S. Dupuis-Girod

Outcomes of bevacizumab plus laser in the treatment of HHT related epistaxis
A.B. Whitehouse, I. Ortega, J.R. Gossage

Efficacy and safety of thalidomide for treatment of chronic severe GI bleeding in hereditary hemorrhagic telangiectasia
G. Manfredi, E. Buscarini, F. De Grazia, G. Lupinacci, F. Menozzi, G. Brambilla, C. Londoni, S. Alicante, S. Crinò, A. Zambelli, P. Gazzaniga, S. Gandolfi, P.A. Forner, C. Danesino, C. Olivieri, C. Canzonieri, F. Ornati, M. Grosso, G. Pongiglione, E. Boccardi

Beneficial effects of anti-VEGF therapy in the pulmonary vasculature of endoglin and Alk1 heterozygous mice
D.S. Ardelean, M. Jerkic, M. Peter, M. Letarte

Anti-angiogenic therapy in HHT: effects on hepatic vasculature in mouse models
D.S. Ardelean, M. Jerkic, M. Yin, R. S. Kerbe, F. Stuart Foster, M. Letarte

VEGF antibody can prevent and normalize arteriovenous malformations in an animal model for hereditary hemorrhagic telangiectasia
C. Han, S.W. Choe, Y. Hwan Kim, Y.J. Lee, S.P. Oh

non-commercial use only

Topical timolol for treatment of epistaxis in hereditary hemorrhagic telangiectasia associated with bradycardia - A look at CYP2D6
N. Epperla, M.H. Brilliant Humbert, J. Vidaillet

Propranolol as antiangiogenic candidate for the therapy of Hereditary Hemorrhagic Telangiectasia
V. Albiñana, L. Recio-Poveda, R. Zarrabeitia, C. Bernabeu, L.M. Botella

16:00-16:30 Coffee break and poster viewing

16:30-18:00 Session VIII. Anemia and venothrombous complications in HHT
(session chairs: Terry O'Connor and Raj S. Kasthuri)

Developing a tool to assess dietary iron intake in a UK population with HHT
H.E. Finnamore, J. Le Couteur, M. Hickson, K. Whelan, C.L. Shovlin

Left Atrial Appendage Closure for Stroke Prevention in Patients with Hereditary Hemorrhagic Telangiectasia and Atrial Fibrillation
V.M.M. Vorselaars, S. Velthuis, M.J. Swaans, J.J.Mager Repke, J.B. Snijder, J.W.M.L. Rensing, V.A. Boersma, M.C. Post

Low serum iron levels are associated with pulmonary emboli/deep venous thromboses (venous thromboemboli) in hereditary haemorrhagic telangiectasia
J.A. Livesey, R.A. Manning, J.H. Meek, J.E. Jackson, E. Kulinskaya, M.A. Laffan, C.L. Shovlin

Iron deficiency is explained by under-replacement of iron losses in hereditary haemorrhagic telangiectasia
H. Finnamore, J. Le Couteur, M. Hickson, B. Busbridge, K. Whelan, C.L. Shovlin

Iron tablet profiling
C. Gilson, M. Busbridge, C.L. Shovlin

The tolerance of antiplatelet and anticoagulant agents in hereditary haemorrhagic telangiectasia
H.L. Devlin, A.E. Hosman, C.L. Shovlin

Anemia is an important clinical problem in HHT
M. Montifar, R.S. Kasthuri, H. Kim, W.L. Young, M.E. Faughnan and the HHT BVMC Investigator Group

19:00 GRMAB meeting *(on invitation only)*

non commercial use only

14 June 2013, Friday

08:00-08:30 Plenary Session
(session chair: Adrian Brady)
Timothy G. Barrett, *School of Clinical and Experimental Medicine, Birmingham Children's Hospital, Birmingham, England*
Combining rare disease services with research: a European Rare Diseases Register

08:30-10:00 Session IX: Pulmonary involvement: PAVMs and pulmonary hypertension in HHT
(session chairs: Robert White and Gunther Schneider)

Pulmonary shunt grading on transthoracic contrast echocardiography predicts the indication for transcatheter embolotherapy of pulmonary arteriovenous malformations
S. Velthuis, E. Buscarini, MWF. Van Gent, P. Gazzaniga, G. Manfredi, C. Danesino, CJJ. Westermann, RJ. Snijder, J.J. Mager, M.C. Post

Grade of pulmonary right-to-left shunt on contrast echocardiography and cerebral complications; a striking association
S. Velthuis, E. Buscarini, M.W.F. van Gent, P. Gazzaniga, G. Manfredi, C. Danesino, W.J. Schonewille, C.J.J. Westermann, R.J. Snijder, J.J. Mager, M.C. Post

Diagnosis and treatment of thoracic complications of pulmonary arteriovenous malformations: rupture or thrombosis. 22 cases
M. El Hajjam, S. Binsse, J. Sellier, T. Chinet, J. Roume, A. Ozanne, I. Bourgault, G. Lesur, J.H. Blondel, A. Cordier, S. Blivet, C. Fagnou, M. Bonay, C. Karam, A. Nicod-Tran, S. Chagnon, M. Eyries, L. Gouya, P. Lacombe.

Oxygen delivery and consumption is preserved in hypoxaemic patients with pulmonary arteriovenous malformations and hereditary haemorrhagic telangiectasia
V. Santhirapala, L.S.G.E. Howard, K. Murphy, B. Mukherjee, M. Busbridge, H.C. Tighe, J.M.B. Hughes, J.E. Jackson, C.L. Shovlin

The role of transthoracic contrast echocardiography in the clinical diagnosis of hereditary haemorrhagic telangiectasia
S. Velthuis, V.M.M. Vorselaars, M.W.F. Van Gent, C.J.J. Westermann, R.J. Snijder, J.J. Mager, M.C. Post

Peri-procedural complications associated with transcutaneous embolisation for pulmonary arteriovenous malformations: A systematic review and meta-analysis
J.W. Donaldson, I.P. Hall, R.B. Hubbard, A.W. Fogarty, T.M. McKeever

Contrast-enhanced Magnetic Resonance Angiography for Management of PAVMs in Patients with HHT
G.K. Schneider, U.W. Geisthoff, A. Buecker, A. Massmann

Female sex and ENG mutation are associated with an increased risk of PAVM in patients with definite HHT
J.R. Gossage, H. Kim, M.E. Faughnan, W.L. Young and the BVMC Investigators.

10:00-10:30 Coffee break and poster viewing

10:30-12:15 Session X: Epistaxis and gastrointestinal bleeding in HHT
(session chairs: Doug Ross and Urban Geisthoff)

Lifestyle and dietary influences on nosebleed severity in hereditary haemorrhagic telangiectasia
B.M. Silva, A.E. Hosman, H.L. Devlin, C.L. Shovlin

The Minimally Important Difference in the Epistaxis Severity Score among Patients with Hereditary Hemorrhagic Telangiectasia
C.A. Merlo, J.B. Hoag, S. Mitchell, G. Robinson, S. Mathai, P.B. Terry, D.D. Reh

A management algorithm for epistaxis in HHT – a cohort of 363 patients
J. Rimmer, V.J. Lund

Development and validation of an endoscopic staging system for Hereditary Hemorrhagic Telangiectasia (HHT)
D.D. Reh, L.X. Yin, K. Laeeq, C.A. Merlo

Epistaxis severity does not predict likelihood of brain or lung AVM in HHT
K.J. Whitehead, J. McDonald, P.D. Ward, K. Wilson

Long-term results of extensive endoscopic treatment of GI teleangiectases in patients with Hereditary Hemorrhagic Telangiectasia and gastrointestinal bleeding
S. Crinò, E. Buscarini, F. De Grazia, G. Lupinacci, G. Manfredi, S. Alicante, A. Zambelli, P. Gazzaniga, S. Gandolfi, P.A. Forner, C. Danesino, C. Olivieri, C. Canzonieri, F. Ornati, F. Pagella, M. Grosso, G. Pongiglione, E. Boccardi, on behalf of HHT-NET

Non commercial use only

Detection of endonasal telangiectases with Narrow Band Imaging in patients suffering from HHT
B.J. Folz, C.G. Konnerth

12:15- 13:00 Lunch and Poster viewing

13:00-14:00 Poster session with authors (sessions IX-XII; P-123 to P-150)

14:00-16:00 Session XI: Endoglin, ALK1 and Smad4 in TGF-beta and BMP pathways (concurrent)
(session chairs: Carmelo Bernabeu and Sabine Bailly)

Endothelial endoglin is involved in leukocyte adhesion and transmigration. Is this a novel pathogenic mechanism in HHT?
E. Rossi, F. Sanz-Rodriguez, N. Eleno, A. Düwell, F.J. Blanco, C. Langa, L.M. Botella, C. Cabañas, J.M. Lopez-Novoa, C. Bernabeu

BMP9 and BMP10, the two specific ligands for ALK1 are critical for postnatal retinal vascular remodelling
N. Ricard, S. Levet, D. Ciais, M. Subileau, C. Mallet, M. Bidart, J.J. Feige, S. Bailly

Circulating Bmp10 acts through endothelial Alk1 to mediate flow-dependent arterial quiescence
D.W. Laux, S. Young, J.P. Donovan, C.J. Mansfield, P.D. Upton, B.L. Roman

ALK5 and ALK1 play antagonistic roles in TGFβ-induced podosome formation in aortic endothelial cells
F. Curado, P. Rottiers, I. Egana, E. Genot

Targeting endoglin activity improves survival and limits adverse right ventricular remodeling in a murine model of pulmonary hypertension
N.K. Kapur, X. Qiao, V. Paruchuri, E.E. Mackey, G.H. Daly, P. Nepali, M.J. Aronovitz, M. Letarte, R.H. Karas

Atorvastatin prevents endoglin and eNOS decreased expression in TNF-alpha induced inflammation in HUVECs
P. Nachtigal, L. Zemankova, M. Varejckova, J. Pfeiferová, K. Jezkova, I. Nemeckova

14:00-16:00 Session XII: Paediatrics and natural history of HHT (concurrent)
(session chairs: Meir Mei-Zahav and Alan Guttmacher)

Diagnostic yield of rescreening for arteriovenous malformations in children with Hereditary Hemorrhagic Telangiectasia
G.A. Latino, M.E. Faughnan, S. Carpenter, S.A. Al-Saleh, F. Ratjen

Detection of pulmonary arteriovenous malformation by contrast echocardiography in pediatric hereditary hemorrhagic telangiectasia
P. Balagny, C. Karam, J. Sellier, M. El Hajjam, S. Binsse, T. Chinet, J. Roume, A. Ozanne, I. Bourgault, G. Lesur, J.H. Blondel, A. Cordier, S. Blivet, C. Fagnou, M. Bonay, P. Lacombe, O. Dubourg, N. Mansencal.

Children screening for PAVM: 15 years follow-up in The Netherlands
A. Gauthier, A.L. Diederik, C.J.J. Westermann, R.J. Snijder, J.J. Mager

Epidemiological survey on cancer rates in patients with hereditary haemorrhagic telangiectasia and controls
A.E. Hosman, H.L. Devlin, B.M Silva, C.L. Shovlin

Clinical manifestation in large cohort of pediatric patients with HHT1 and HHT2: a cross-sectional study
G.M. Lenato, P. Giordano, P. Suppressa, M. Sangerardi, P. Piccarreta, P. Lastella, F. Dicuonzo, A. Scardapane, M.L. Fiorella, C. Sabbà

non-commercial use only

Epistaxis severity score in pediatric patients with Hereditary Hemorrhagic Telangiectasia
D.A. Stevenson, J. McDonald, P. Bayrak-Toydemir, P.D. Ward, K. Wilson, K. Whitehead

Longitudinal study of natural history of arteriovenous malformations in evolutionary age of hereditary haemorrhagic telangiectasia
P. Suppressa, P. Giordano, G.M. Lenato, M. Sangerardi, P. Lastella, D. Quaranta, L. Chiumarulo, R. Valerio, P. Buonamico, B. Covella, D. De Mattia, C. Sabbà

A hereditary hemorrhagic telangiectasia severity score
G.A Latino, M.E Faughnan, H. Kim, W. Young, The Brain Vascular Malformation Consortium

Age of Presentation in HHT: Brain AVM diagnosis vs. epistaxis
D. Lin, A. Zessler, W. Young, M.E. Faughnan and the Brain Vascular Malformation Consortium (BVMC)

16:00-16:30 Coffee break and poster removal

16:30-18:45 Summary and closing session
(session chairs: Carmelo Bernabeu and Urban Geisthoff)

Dennis L. Sprecher, Senior Director Discovery Medicine and Drug Development, GlaxoSmithKline, King of Prussia, PA, USA, ***Drug Development: A Pharmaceutical Perspective***

Michelle Letarte, Molecular Structure and Function Program, Hospital for Sick Children, Toronto, ON, Canada, ***My life with Endoglin and HHT***

Summaries of Clinical, Basic Science and Genetics areas will be presented by Christopher Hughes, Claire Shovlin and Pinar Bayrak-Toydemir

Evening **Gala dinner**

non commercial use only

15 June 2013, Saturday

Patient workshop

08.30-09.00 Registration

Session 1

09.00 - 09.15 Opening of workshop, explanation of goals and design of workshop
Mr. M. Nolan / Dr. A. Brady

09.15 - 09.45 HHT is an equal opportunity disorder
Dr. B. White

09.45 - 10.15 Genetic aspects of HHT
Dr. L. Botella / Dr. T. O'Connor

10.15 - 10.45 Pulmonary manifestations (incl. PAVM embolization)
Dr. M. Faughnan / Dr. T. O'Connor / Dr. A. Brady

10.45 - 11.00 Q & A

11.00 -11.30 Coffee break

Session 2

11.30 - 12.00 HHT in pregnancy
Dr. C. Shovlin

12.00 - 12.30 Liver, GI tract, cardiac aspects
Dr. S. Dupuis-Girod

12.30 - 12.45 Anaemia& iron deficiency
Dr. C. Shovlin

12.45 - 13.00 Q & A

13.00 - 14.00 Lunch

Session 3

14.00 - 14.30 Cerebral & spinal manifestations
Dr. K. ter Brugge

14.30 - 15.00 Nosebleeds, telangiectases of the mouth & skin manifestations
Dr. U. Geisthoff

15.00 - 15.15 Antibiotic prophylaxis and infection
Dr. L. Botella

15.15 - 15.30 Cork National HHT Centre – what we do, and why.
Dr. A. Brady

15.30 - 15.45 Coffee

Sesssion 4

15.45 - 16.00 Grace Nolan Foundation & HHT International – what's their role for the average patient and family
Mr. M. Nolan / Ms. M. Clancy

16.00 - 17.00 Q & A, Round table discussion
Panel of speakers

non commercial use only

POSTERS

Genetics and Genotype/Phenotype in HHT (Session III; P-93 to P-103)

Genotype-phenotype correlation in a national mutation study of Danish patients with hereditary hemorrhagic telangiectasia
P.M. Tørring, K. Brusgaard, L. Bomme Ousager, P.E. Andersen, A.D. Kjeldsen

Consanguinity in HHT - Screening a Family with HHT in Both Parents
M. Mei-Zahav, H. Blau, E. Bruckheimer

Genetic epidemiology of hereditary hemorrhagic telangiectasia associated with pulmonary arteriovenous malformations in Japan
T. Shioya, M. Satake, A. Kawagoshi, K. Sato, M. Sano, H. Ito

Hereditary hemorrhagic telangiectasia, an Australian cohort: clinical and investigative features
M. Salaria, J. Taylor, M. Bogwitz , A. McLauchlin, I. Winship

Identification of novel variants in Argentinean patients which suffer from hereditary hemorrhagic telangiectasia
A.R. Cajal, C.V. Ramirez, N.C. Bravo, L.D. Costa, M.M. Serra

Hereditary hemorrhagic telangiectasia in North African and Sub-Saharan patients
C. Canzonieri, F. Ornati, E. Matti, F. Chu, G. Manfredi, C. Olivieri, E. Buscarini, F. Pagella, C. Danesino on behalf of HHT-NET

Capillary microscopy in hereditary hemorrhagic telangiectasia: a prospective study of 44 patients
S. Rivière, E. Marnas, A. Khau Van Kien, J.P. Laroche, B. Lorcerie, I. Quere

Search for genetic modifying factors for hepatic vascular malformations in HHT
Giraud S., Dupuis-Girod S., Bardel-Danjean C., Carette M.F., Gilbert-Dussardier B., Riviere S., Saurin JC, Eyries M., Kitzis A., Decullier E., Lesca G., Calender A.

Association of Variants in Inflammatory Genes with Lesion Burden in Familial CCM1
H. Choquet, L. Pawlikowska, J. Nelson, A. Akers, B. Baca, B. Hart, L. Morrison, H. Kim for the Brain Vascular Malformation

Hereditary haemorrhagic telangiectasia in Las Palmas (Canary Islands) Spain
C. Vázquez, A. Santana, L. Recio-Poveda, C. Bernabeu, L.M. Botella

A whole exome search for additional HHT genes
C.J. Gallione, E.T. Cirulli, K. Shianna, J.K. Ploos van Amstel, T.G.W. Letteboer, N. Prigoda-Lee, D. Rushlow, R. Klatt, Michelle Letarte, C.J.J. Westermann, D.A. Marchuk

Cellular and molecular involvement in HHT and related pathologies (Session IV; P-104 to P-106)

Evidence for a compromised immune system in a Spanish cohort with hereditary hemorrhagic telangiectasia
L. Ojeda-Fernández, R. Zarrabeitia, M.M. Serra, L. Recio-Poveda, C. Bernabeu, L.M. Botella

Characterization of circulating endothelial cells in hereditary hemorrhagic telangiectasia
P. Suppressa, G.M. Lenato, P. Lastella, V. Liso, A. Mestice, C. Margiotta, E. Dani, L. Scagliusi, A. Mazzocca, C. Sabbà

Expression of Endoglin isoforms in the myeloid lineage and their role during ageing and macrophage polarization
M. Aristorena, F.J. Blanco, M.L. Ojeda-Fernandez, M. de las Casas-Engel, E. Gallardo-Vara, A. Corbi, L.M. Botella, C. Bernabeu

Central Nervous System involvement and treatment in HHT (Session V; P-107)

Clinico-radiological characteristics of primary and secondary neurological manifestations in a large cohort of hereditary hemorrhagic telangiectasia patients
M. Gallea, P. Favrole, B. Marro, M. Hermier, E. Decuiller, M.F. Carette, J. Dupuis-Girod, S. Alamowitch

non commercial use only

Molecular diagnostics, markers and epidemiology for HHT (Session VI; P-108)

Molecular and genetic heterogeneity in HHT: The results of 12 years of DNA diagnostics in the Netherlands
T.G.W. Letteboer, J.J.Mager, R.J. Snijder, A.J.M. van Erkel, C.J.J. Westermann, J.K. Ploos van Amstel

Antiangiogenic therapies in HHT and outcomes (Session VII; P109 to P-112)

Bevacizumab pharmacokinetics influences cardiac output and epistaxis in hereditary hemorrhagic telangiectasia
N. Azzopardi, S. Dupuis-Girod, D. Ternant, A.E. Fargeton, I. Ginon, F. Faure, E. Decullier, M.F. Carette, B. Gilbert-Dussardier, P.Y. Hatron, P. Lacombe, B. Lorcerie, S. Rivière, R. Corre, S. Bailly, G. Paintaud

Electrical stimulation of single mural cell visualized by fluorescent microscopy as a valuable tool for HHT high output screening drugs
J. Thalgott, D. Dos-Santos-Luis, L. Venance, F. Lebrin

Efficacy of Bazedoxifene in the treatment of hereditary hemorrhagic telangiectasia. Clinical effects and expression analysis
R. Zarrabeitia, L. Ojeda-Fernández, V. Albiñana, C. Bernabeu, L.M. Botella

Local administration of Bevacizumab: a therapeutic option in HHT?
T. Kühnel, C. Rohrmeier

Hepatic involvement in HHT (Session II; P-113 to P-114)

Abdominal involvement in hereditary hemorrhagic telangiectasia (HHT). A pictorial review
M. El Hajjam, J. Sellier, S. Binsse, M. Bensalah, T. Chinet, J. Roume, A. Ozanne, I. Bourgault, G. Lesur, J.H. Blondel, A. Cordier, S. Blivet, C. Fagnou, M. Bonay, C. Karam, A. Nicod-Tran, S. Chagnon, M. Eyries, L. Gouya, P. Lacombe

Diagnostic performance of Doppler ultrasound for the diagnosis of hepatic vascular involvement in HHT patients
M. Kucharczyk, B. Ferreyro, E. Levy Yeyati, N. Napoli, F. Angriman, R. Garcia Monaco, M. Serra

Pulmonary involvement: PAVMs and pulmonary hypertension in HHT (Session IX; P-115 to P-130)

Diagnostic accuracy of the 100% oxygen method in detecting pulmonary right-to-left shunts compared to transthoracic contrast echocardiography
S. Velthuis, V.M.M. Vorselaars, C.J.J. Westermann, R.J. Snijder, J.J. Mager, M.C. Post

Hemoptysis in HHT: a single symptom, various mechanisms. A pictorial review
J. Sellier, M. El Hajjam, S. Binsse, T. Chinet, J. Roume, A. Ozanne, I. Bourgault, G. Lesur, J.H. Blondel, A. Cordier, S. Blivet, C. Fagnou, M. Bonay, C. Karam, A. Nicod-Tran, M. Eyries, L.t Gouya, S. Chagnon, P. Lacombe.

Embolisation of pulmonary arteriovenous malformations (PAVMs) improves quality of life in patients with HHT
S. Blivet, D. Cobarzan, A. Beauchet, J.H. Blondel, M. Bonay, I. Bourgault, C. Fagnou, L. Gouya, G. Lesur, A. Ozanne, J. Roume, P. Lacombe, T. Chinet

PAVM embolization using overlay roadmap guidance
A.L. Diederik, M.J.L. van Strijen, D.A.F. van den Heuvel, M. van Leersum, J.A. Vos

Recanalization after pulmonary arteriovenous malformation (PAVM) embolization
A.L. Diederik, J.J. Mager, D.A.F. van den Heuvel, R.J. Snijder, J.A. Vos

Preliminary results of the PIRANA Trial
A.L. Diederik, J.J. Mager, D.A.F. van den Heuvel, M.J.L. van Strijen, R.J. Snijder, J.A. Vos

Morphological change of the Amplatzer Vascular Plug II in pulmonary arteriovenous malformations – does size and shape matter?
L. Ling, K. Patatas, G.J. Robinson

Treatment effectiveness of pulmonary arteriovenous malformation with Amplatzer Vascular Plug IV in patients with hereditary hemorrhagic telangiectasia
J.M. Rabellino, O. Peralta, E. Levy Yeyati, E. Gentile, M. Ulla, R. Garcia Monaco, M.M. Serra

non commercial use only

Transesophageal echocardiography as part of the screening for pulmonary arteriovenous malformations in HHT
U. Geisthoff, S. Weise, J. Üner, H.W. Angenendt, S. Maune

Direct Hemodynamic Effect of Pulmonary Arteriovenous Malformation Embolisation
V.M.M. Vorselaars, S. Velthuis, J.J. Mager, R.J. Snijder, W.J. Bos, J.A. Vos, M.J.L. van Strijen, M.C. Post

Ischaemic stroke risk increases with the severity of pulmonary arteriovenous malformations
C.L. Shovlin, J.A. Livesey, V. Santhirapala, H.C. Tighe, J.E. Jackson

Pulmonary arteriovenous malformation and embolic complications in adult patients with hereditary hemorrhagic telangiectasia: a cross sectional study
F. Angriman, B. Ferreyro, E. Javier Wainstein, M. Martin Serra

The Amplatzer Vascular Plug II – A safe and effective occluder of pulmonary arteriovenous malformations
L. Ling, K. Patatas, G.J. Robinson

Follow-up of the pulmonary right-to-left shunt with transthoracic contrast echocardiography in hereditary hemorrhagic telangiectasia
V.M.M. Vorselaars, S. Velthuis, J.J. Mager, R.J. Snijder, M.C. Post

Estimated pulmonary artery systolic pressure in a group of 105 HHT patients discloses differences in patients carrying ACVRL1 or ENG mutations
F. Ornati, C. Canzonieri, L. Lanzarini, F. Pagella, E. Matti, F. Chu, G. Manfredi, E. Buscarini, M. Comelli, C. Danesino, C. Olivieri on behalf of HHT-NET

Impact of pulmonary arteriovenous malformations (MAVPs) on pulmonary function in patients with HHT
C. Rotenberg, S. Blivet, D. Cobarzan, A. Beauchet, S. Binsse, M. Bonay, J.H. Blondel, I. Bourgault, A. Cordier, C. Fagnou, L. Gouya, G. Lesur, A. Ozanne, Y. Retory, J. Roume, P. Lacombe, T. Chinet

Epistaxis and gastrointestinal bleeding in HHT (Session X; P-131 to P-141)

First prevalence report of allergy manisfestations in HHT population
M.M. Serra, R. Zarrabeitia, L. Ojeda-Fernández, H.J. Benito, C. Bernabeu, J. Maritano-Furcada, L.M. Botella

Efficacy of Thalidomide in the treatment of severe recurrent epistaxis in hereditary hemorrhagic telangiectasia (HHT): Ongoing results of a prospective study
C.L. Balduini, F. Bellistri, F. Pagella, F. Chu, E. Matti, G. Spinozzi, F. Ornati, C. Canzonieri, C. Olivieri, C. Danesino, M. Benazzo, R. Invernizzi

Heyde's syndrome and hereditary hemorrhagic telangiectasia: report of three cases
P.A. Carrillo, N. Causada Calo, M.C. Elizondo, M.M. Serra

Laser endoscopic surgery for chronic epistaxis in hereditary hemorrhagic telangiectasia
F.A. Urquiola, Y. Lijdens, M.M. Serra

The Centre for Rare Disorders services for the HHT group
G.A. Ruud and K. Iversen

Hereditary hemorrhagic telangiectasia in Uruguay
R. Mezzano, F. Lemos, A. Tiscornia, S. Pisano, B. Boggia

Customized nasal breathing tubes as an alternative to Young's procedure in HHT patients with epistaxis. Preliminary results
B.J. Folz, A.M. Chirtesiu, C.G. Konnerth

non commercial use only

Nasal hygiene education and epistaxis management: nursing intervention for HHT patients
R. Pantalone, E. Leek, J. Lee, M.E. Faughnan

Narrow band imaging (NBI): first impression about its use in the study of nasal telangiectasias in patients affected by hereditary hemorrhagic telangiectasia
F. Chu, F. Pagella, E. Matti, G. Spinozzi, D. Zaccari, C. Olivieri, F. Ornati, E. Buscarini, C. Danesino on behalf of HHT-NET

The relationship of time and ambient air quality to epistaxis severity scores in hereditary hemorrhagic telangiectasia
C.A. Merlo, R. Peng, J.B. Hoag, S. Mitchell, G. Robinson, D.D. Reh, P.B. Terry

Septodermoplasty in hereditary hemorrhagic telangiectasia: a modified technique
J. Rimmer, V.J Lund

Endoglin, ALK1 and Smad4 in TGF-beta and BMP pathways (Session XI; P-142 to P-145)

Endothelial cells derived from HHT1 patient specific induced pluripotent stem cells (iPSCs) show reduced endoglin (ENG) protein levels and altered downstream signaling
K. Gkatzis, V. Orlova, C. Freund, P. ten Dijke, F. Disch, K. Westermann, H.J. Mager, C. Mummery

ALK-1 deficiency is associated to alterations in arterial pressure regulation
M. González-Núñez M., B. Oujo B., F. Pérez-Barriocanal, J.M. López-Novoa

Alteration in endoglin-related angiogenesis in refractory cytopenia with multilineage dysplasia
M. del Rey, M. Pericacho, S. Velasco, E. Lumbreras, J.M. Lopez-Novoa, J.M. Hernandez-Rivas, A. Rodriguez-Barbero

Endoglin haploinsufficiency promotes fibroblast accumulation during wound healing through Akt activation
M. Pericacho, S. Velasco, M. Prieto, E. Llano, J.M. López-Novoa, A. Rodríguez-Barbero

Pediatrics and natural history of hereditary hemorrhagic telangiectasia (Session XII; P-146 to P-148)

Assessing HHT clinical diagnostic criteria in childhood - the Israeli national center experience
M. Mei-Zahav, N. Goldschmidt, S. Metzger, E. Yaniv, H. Blau, E. Brockheimer

HHT Center of Excellence at Johns Hopkins Hospital – organization, screening, and treatment results in children and adults 2009-2013
F. Ul Haq, G. Robinson, C.A. Merlo, Joseph M. Collaco, P. Terry, S.E. Mitchell

Comorbidities in hereditary hemorrhagic telangiectasia patients with epistaxis
B.J. Folz, A.M. Chirtesiu, C.G. Konnerth

Patients' Associations Workshop (P-149 to P-150)

Consequences of hereditary hemorrhagic telangiectasia on working life
U. Geisthoff, A. Al-Habib, L. Hoffmanns, S. Maune

10th Anniversary of the HHT unit in Sierrallana Hospital (Spain)
R. Zarrabeitia, V. Diez, J. Bueno, J.A. Parra, J. Zarauza, A. Fontalba, B. Señaris, M. Bustamante, J. Jordá, C. Menéndez, J.L. Fernández Forcelledo, J. Calvo, R. Megía, J. Rodríguez Iglesias, C. Morales, L. Botella

non-commercial use only

Invited Speakers

THE FUTURE OF SCIENTIFIC RESEARCH

Alan E Guttmacher
Director of the Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, MD, USA

We are arguably entering a new era in scientific research. The availability of novel research tools, such as the human genome sequence and inexpensive genome sequencing have the potential not only to provide new insights into the fundamental biology of many conditions, but, literally, to redefine health and disease. The ability, for the first time, to detail how preconception, prenatal, and early life experiences influence lifelong health, makes understanding the developmental origins of health and disease a real possibility. Improved technologies to measure environmental exposures allow looking at the complicated interweavings of biological and environmental influences on health in ways never before possible. Progress in bioinformatics make both handling huge data arrays and in silico models for human biology practical for the first time. New emphasis on transdisciplinary research and innovative models for supporting it allow research efforts to move from constrained simplistic approaches to much more complex and robust examinations of the complexity that is human health and disease. Changes in the culture of science, such as increasing willingness to share research data and recognition of the power of community based participatory research, mean that research can have more immediate and more lasting impact. In this talk, Dr. Guttmacher will consider what such new influences might mean for the future of scientific research and resultant improvements in health.

UNCOMMON VASCULAR ANOMALIES

Juan C Lopez-Gutierrez
Director of the Vascular Anomalies Center and Head of Pediatric Surgery, La Paz Children´s Hospital, Madrid, Spain

Rare vascular anomalies are conditions characterized by low prevalence, and frequently characterized by a lack of accurate information and adequate therapy. Uncommon vascular anomalies (VA) in primary health care institutions are frequently seen in tertiary referrals, and many times rare VA are simply difficult-to-recognize presentations of common vascular tumors or malformations. In any case, proper diagnosis of patients affected by complex VA is essential. These patients benefit from an interdisciplinary approach involving many medical and surgical specialists. Patients, whose lesions were improperly diagnosed, are more likely to be managed incorrectly when compared with patients whose anomalies are correctly identified. Despite the fact that the classification of VA continues to expand and becomes more precise, as the knowledge of these lesions evolves, up to 5% of patients referred to tertiary centres are unable to be diagnosed; they suffer from VA, not yet been well characterized. In fact, new VAs are described every year. PTEN hamartoma of soft tissue (PHOST), Kaposiform lymphangiomatosis or FAVA (fibroadipous vascular anomaly) are just a few recent examples. Additional problems for an early and accurate diagnosis of VA are the presence of unusual symptoms (i.e. a small minority of individuals with a lymphatic malformation develop severe coagulopathy), uncommon combinations of VAs in a bizarre fashion or rare associations (i.e. malignant tumors, nevi, etc… found in several neurocutaneous disorders). We are also frequently managing VAs, appearing as generalized lymphatic malformations with thoracic duct involvement, chylous reflux and osteolysis, still not well understood. Or the poorly characterized group of hemangioendotheliomas (from uneventful to metastatic behavior). VAs change with time, not only on their aspect, but also on their histopathological findings, making difficult their immediate characterization. Finally, the VA specialist has to be aware of unusual presentations. The vascular tumor is different from the highly vascularized tumor, and a biopsy´s analysis by an expert pathologist is mandatory in those cases, as sarcomas and lymphomas can easily mimick vascular tumors in young patients.

THE ROAD FROM GENE DISCOVERY TO THERAPY FOR CEREBRAL CAVERNOUS MALFORMATIONS: ARE THERE ANY LESSONS FOR HHT?

Douglas A Marchuk
Department of Molecular Genetics and Microbiology, Duke University Medical Center, Durham, NC, USA

Cerebral cavernous malformations (CCMs) are vascular lesions characterized by grossly dilated capillaries, associated with vascular leak and hemorrhage. These lesions can occur in sporadic or inherited (autosomal-dominant) forms, the latter due to inheritance of a single copy, loss-of-function mutation in 1 of 3 genes (CCM 1, 2 or 3). These three genes encode scaffolding proteins for yet uncertain cell signaling complexes, but the CCM proteins themselves are devoid of any signaling capacity. Thus, the identification of the three CCM genes revealed very little about CCM pathobiology. Once we identified the CCM genes, we immediately attempted to generate mouse models of the disease. Unfortunately, we found that mice with a single mutant copy of the murine orthologs (the proper genotype for an autosomal dominant disease) do not phenocopy the human disease, whereas the homozygous mutants are embryonic lethal. In parallel to our mouse studies, we have shown that human CCM lesions harbor a somatic mutation in the remaining wild-type copy of the germline mutated CCM gene. Based on this "two-hit" mutation mechanism for CCM pathogenesis, we then generated robust and faithful mouse models of the CCM disease by crossing our heterozygous mutant mice into genetic backgrounds with elevated somatic mutation rates. These CCM mice allowed us for the first time to visualize and characterize the earliest stages of CCM lesion formation. In parallel to these studies, other investigators demonstrated that mutation of the CCM genes in cells grown in culture leads to the acti-

non commercial use only

vation of Rho kinase, suggesting a common signaling node for all three inherited forms of CCM. Intriguingly, Rho kinase inhibitors are currently available for other clinical indications. We have now shown that these same drugs decrease lesion growth and hemorrhage in our mouse models of CCM. With our clinical colleagues, we are now discussing the best way forward towards clinical trials for CCM patients. While summarizing this nearly 20-year saga of CCM research, I will compare and contrast the trajectory of CCM research with that of HHT, in the hopes of providing some lessons to employ for HHT research.

RARE DISEASES; A PHARMACEUTICAL PERSPECTIVE

Dennis L Sprecher
Senior Director Discovery Medicine and Drug Development, GlaxoSmithKline, King of Prussia, PA, USA

The development pathway for therapeutic agents is long, expensive and risky. From the hypothesis of a relevant biochemical target to defining a molecule or biologic, onto a clinical trial incorporating patients with the relevant phenotype, these efforts require time, infrastructure and commitment. This consumes considerable investment prior to appreciating any notion of the real value of a developed therapeutic. Such concerns are substantially amplified in the setting of rare diseases. However, with the appreciation of over 7000 rare disorders, and >20% of US and European citizens afflicted by these issues, a new wave of thinking has driven efforts towards studying opportunities in these less common maladies. In part spurred by government legislation in the 1980's, but also the economics of value based reimbursement, and payor acceptance, companies have dedicated teams to additional consideration on such rare disease avenues. They have appreciated gateway pathways towards broader disease application, or the re-purposing of already successful agents. GlaxoSmithKline is potentially considering a treatment for HHT. This path, one which repurposes an existing cancer therapeutic, invokes many considerations, including science, a feasible development path, safety, ethics and commercial opportunity. Each of these elements will weigh in on this and future efforts to develop FDA registered products in the rare disease space.

COMBINING RARE DISEASE SERVICES WITH RESEARCH: A EUROPEAN RARE DISEASES REGISTER

Timothy G Barrett
School of Clinical and Experimental Medicine, Birmingham Children's Hospital, Birmingham, England

Rare diseases affect less than 5 in 10,000 of the population. Over 5000 rare diseases have been identified. Although individually rare, together they affect about 7% of the population. They have a high impact of people's lives and collectively form a large part of the work of Health Services. Research into rare diseases can contribute to improved personalised approaches to healthcare, improved therapeutic efficacy and safety, and reduced costs. Rare disease registries are key instruments to increase knowledge on rare diseases and develop clinical research. They are the only way to pool data in order to achieve a sufficient sample size for clinical research. We are fortunate to have National Health Service specialist commissioned services for 3 overlapping rare diseases, Wolfram, Alstrom and Bardet Biedl (WABB) syndromes. These share the characteristics of rarity (less than 1:350,000), vision and hearing loss, and diabetes mellitus. Even with national specialist multidisciplinary clinics, we have struggled to identify enough patients to do research. The aims of the EURO-WABB project (www.euro-wabb.org) are therefore to support efficient diagnosis, treatment, and research for the overlapping WABB syndromes in Europe. We aimed to achieve this by implementing an EU registry for WABB, containing clinical, genetic diagnostic and outcome data. The purpose of the registry is: a) to establish the natural history of the 3 diseases (their characteristics, management and outcomes); b) to assess clinical effectiveness of management and quality of care; c) to provide an inventory of patients for recruitment to intervention studies; d) to establish genotype-phenotype correlations. We have achieved high usage of the registry by linking it to rapid genetic testing; and to up to date, accurate information, FAQS, and education material. So far we have recruited over 200 affected people from 16 countries, with both core datasets, and extended data with detailed phenotyping information. We have created an online open access genetic mutation database for the causative genes, listing all published mutations. We have developed consensus guidelines for health professionals, and information for patents. The Euro-Wabb registry serves as a model for other disorders in promoting European collaboration and patient involvement to support research.

non-commercial use only

Session I
Arteriovenous malformations and animal models. Angiogenesis and vascular development

C-001
PATHOGENESIS OF ARTERIOVENOUS MALFORMATIONS IN A MOUSE MODEL OF HHT2

S Tual-Chalot, M Mahmoud, KR Allinson, SP Oh[1], HM Arthur

Institute of Genetic Medicine, Newcastle University, UK, [1]Department of Physiology, University of Florida, USA

Hereditary Haemorrhagic Telangiectasia (HHT) is a familial multisystemic vascular disorder characterized by arteriovenous malformations (AVMs) and persistent haemorrhage. Most HHT patients carry mutations in either Endoglin or Acvrl1 (also known as ALK1) genes. Despite the identification of these genes, the causes of vascular dysplasia in HHT are not fully understood and recent advances using mouse models have begun to throw light on disease mechanisms. Our goal in this study was to understand the cellular and molecular role played by endothelial Acvrl1 in the formation of AVMs and haemorrhage *in vivo*. Using a mouse with a conditional Acvrl1 mutation, Acvrl1 was depleted efficiently in endothelial cells (ECs) either in the first week of postnatal life or in adult mice. To investigate the effect of Acvrl1 depletion in the developing vasculature, we used the neonatal retinal plexus as an angiogenesis model, and investigated the vascular changes that occurred before the neonates developed a fatal pulmonary oedema. Loss of Acvrl1 led to venous enlargement, hyperbranching of capillaries and AVMs. These phenotypes were associated with loss of arterial Jag1 expression, decreased pSmad1/5/8 activity and increased EC proliferation in vivo. Using an 85 gene custom qPCR array to investigate changes in candidate downstream genes, 13 genes were identified as showing reduced expression. Of these, endoglin was the most dramatically down-regulated, an outcome that was also confirmed at the protein level. The development of retinal AVMs appeared to be angiogenesis dependent and only occurred in the neonatal retina shortly after Acvrl1 knockdown, but not in adult retinas following Acvrl1 knockdown. In contrast, development of haemorrhage in the GI tract occurred only in adult mice, and ultimately led to a fatal anaemia. In summary, Acvrl1 is required in ECs during angiogenesis in vivo to (i) maintain normal endoglin expression (ii)regulate endothelial cell proliferation, (iii) preserve arterial identity and (iv) control vessel branching.

C-002
ENDOTHELIAL CELLS ARE THE CELLULAR SOURCE FOR THE DEVELOPMENT OF ARTERIOVENOUS MALFORMATIONS IN ALK1 DEFICIENCY

EM Garrido-Martín[1], YH Kim[1], S Choe[1], T Cunningham[1], Z Jiang[2], SP Oh[1]

[1]Department of Physiology and Functional Genomics, University of Florida, Gainesville, FL, US, [2]Department of Surgery, University of Florida, Gainesville, FL, USA

Mutations in Activin receptor-Like Kinase-1 (ALK1) give rise to Hereditary Hemorrhagic Telangiectasia type 2 (HHT2), characterized by the development of arteriovenous malformations (AVMs) in mucosa and internal organs. We have previously generated a mouse model of HHT, using tamoxifen-induced Alk1 deletion in adult stages mediated by ROSA26^{CreER}. These mice develop visceral and wound-induced skin AVMs resembling HHT vascular lesions. Since ROSA26 locus drives ubiquitous expression of CreER, this model did not provide information regarding whether the AVM formation is an endothelial cell-autonomous effect or involves other cell types. L1Cre line expresses the Cre recombinase in ECs under the control of Alk1 promoter, and L1Cre; Alk1$^{f/f}$ mice develop AVMs in the brain, lungs, and GI tracts. However, we found that L1Cre also expresses Cre in macrophages. Therefore, the primary cell type responsible for AVM development remains unclear. Although Alk1 was shown to be expressed predominantly in arterial ECs, there are several reports showing Alk1 expression in other cell types including lymphatic ECs. Using Alk1^{lacZ} reporter mice, we confirmed in vivo expression of Alk1 in macrophages. In order to determine the cell type-specific function of ALK1 for the development of AVMs, we directed Alk1 deletion to macrophages, smooth muscle cells or vascular endothelial cells using Lyz2CRE, Myh11-CreER^T, or Scl-CreER^T mice respectively. Lyz2$^{CRE/+}$; Alk1$^{2f/2f}$ mice were viable, and did not exhibit any hemorrhagic signs, visceral AVMs, or wound-induced skin AVMs. Interestingly, however, they showed an increased number of arterial vessels in the area surrounding the wound, indicating that ALK1 in macrophages is involved in arteriogenesis. Specific deletion of Alk1 in smooth muscle cells did not result in AVMs either. However, vascular endothelial-specific deletion of Alk1 in Scl-CreER^T; Alk1$^{2f/2f}$ mice resulted in GI hemorrhages and in wound-induced AVM formation in backskin. Taken together, these genetic evicences demonstrate that the vascular endothelial cells are the primary cell type responsible for the pathogenesis of HHT.

C-003
VISCERAL AND SYSTEMIC VASCULAR LESIONS IN PATIENTS WITH NON-HHT RELATED PULMONARY ARTERIOVENOUS MALFORMATIONS

M Maruno, H Kiyosue, S Tanoue, J Kashiwagi, S Matsumoto, H Mori

Department of Radiology, Oita University Faculty of Medicine, Oita, Japan

Non-commercial use only

Purpose: Pulmonary arteriovenous malformations (PAVMs) are highly associated with hereditary hemorrhagic telangiectasia (HHT) which can involve multiple organs such as the liver, spleen, gastrointestinal tract and brain. However, vascular lesions are detected often even in cases of sporadic PAVMs that do not meet HHT diagnostic criteria in clinical practice. In this study we evaluate visceral and systemic vascular lesions in cases of non-HHT related PAVMs. *Methods:* 18 consecutive cases of PAVMs treated by coil embolization at our institution from April 2005 to February 2013 were reviewed in this study (7 males, 11 females, mean age 49 years). Among these, 3 cases met the HHT diagnostic criteria, 3 were suspected cases, and 12 were sporadic cases that did not meet the criteria. All patients underwent full-body contrast-enhanced CT. MRI of the head was performed in 17 cases. Abdominal angiography was performed in 6 cases, and cerebral angiography was performed in 4 cases. *Results:* Extrapulmonary vascular lesions were detected in 5 of the 6 cases (83%) with and suspected with HHT, which included hepatic telangiectasia (n=5), splenic telangiectasia (n=1), and renal aneurysm (n=1). Extrapulmonary vascular lesions were detected in 6 of the 12 sporadic cases (50%), which included hepatic vascular lesions (arterioportal shunt, portosystemic shunt, telangiectasia, and hemangiomas) (n=4), mesenteric telangiectasia (n=2), cerebral arteriovenous malformation (n=1), and aneurysmal dilatation of splenic or bronchial arteries (n=2). Among these, 2 cases showed multiple extrapulmonary vascular lesions. *Conclusion:* Extrapulmonary vascular lesions were frequently seen in cases of non-HHT related PAVMs. This suggests that another group of vascular disorders potentially related to HHT may be present. Careful evaluation of extrapulmonary vascular lesions should be done even for cases that do not meet HHT diagnostic criteria.

C-004
ENDOGLIN AND ALK1 PLAY DISTINCT ROLES IN MURAL CELL RECRUITMENT AND ENDOTHELIAL CELL SPECIFICATION DURING PATHOLOGICAL ANGIOGENESIS

F Lebrin[1], S Martin[1], J Thalgott[1], D Bracquart[1], S Srun[1], L Venance[1], N Lamandé[1], D Dos-Santos-Luis[1].

[1]*CNRS Unité mixte de recherché 7241/INSERM U1050, Center for Interdisciplinary Research in Biology, Collège de France, Paris, France*

Hereditary Haemorrhagic Telangiectasia (HHT) is a dominant genetic disease characterized by arteriovenous malformations (AVMs), which range from small telangiectases in the nasal septum, oral mucosa and gastrointestinal tract to large AVMs in major organs. Most cases of HHT are caused by mutations in endoglin (ENG) or ALK1 (activin receptor-like kinase 1, ACVRL1), two receptors for Transforming Growth Factor-β (TGF-β) that are expressed in endothelial cells and share functions in signalling. Although their role in TGF-β family signalling has been the subject of considerable investigation, there is still limited understanding of how endoglin or ALK1 haploinsufficiency leads to disease pathology. In particular, the variability in the age of onset of the disease and in clinical manifestations and severity are still not explained. Here, we present in vivo evidence that inflammation is required for blood vessels to develop vascular anomalies in HHT. Sustained airway inflammation in adult Eng+/- or Acvrl1+/- mice (experimental models of HHT) induced an inappropriate and excessive vessel sprouting with the formation of multiple AVMs. Surprisingly, the mechanisms of action leading to the development of these vessel anomalies in Acvrl1+/- mice appeared to be distinct from that of Eng+/- mice. Heterozygous deletion of Acvrl1, but not of Eng revealed an increased numbers of endothelial tip cells compared to controls. Mechanistically, we found that ALK1 signalling regulates VEGFR1 expression in endothelial stalk cells thereby guiding filopodial extension from the specialized endothelial tip cells. We also provide evidences that the excessive angiogenesis response in inflamed Eng+/- mice but not in Acvrl1+/- mice might be partially attributed to mural cell dysfunctions. Our data provide new insights into the pathology of HHT and reveal that endoglin and ALK1 exert distinct roles in pathological angiogenesis, which may be useful as therapeutic strategies for the treatment of vascular malformations.

C-005
MODELING HEREDITARY HAEMORRHAGIC TELANGIECTASIA (HHT) WITH PATIENT SPECIFIC INDUCED PLURIPOTENT STEM CELLS (IPSCS)

V Orlova[1,2], C Freund[1], K Gkatzis[1], Y Drabsch[2], L van den Hil[1], F Disch[3], H-J Mager[3], R Snijder[3], K Westermann[3], P ten Dijke[2], C Mummery[1]

[1]*Department of Anatomy and Embryology,* [2]*Department of Molecular Cell Biology, Leiden University Medical Center, Leiden, The Netherlands,* [3]*St Antonius Hospital, Nieuwegein, The Netherlands*

HHT is a genetic disorder with complex vascular outcomes that is caused by autosomal dominant mutation of genes involved in transforming growth factor (TGF β) mediated signal transduction, specifically Endoglin (ENG, HHT1), Activin receptor like kinase-1 (ALK1, HHT2) and Smad4 (HHT3). The disease results from deregulation of TGF β signaling in endothelial cells (ECs) and involves multiple mechanisms such as: excessive angiogenesis, defective interaction between ECs and pericytes, as well as possible loss of endothelial cell identity. Although, mouse models for HHT are available and widely used to study the disease, they do not faithfully recapitulate the complexity of pathologies observed in HHT patients. This slows down progress on understanding the disease mechanism and drug discovery. Here we aim to develop an in vitro system to model HHT by reprogramming somatic cells from patients to induced pluripotent stem cells (iPSC). iPSCs can be propagated indefinitely in culture and differentiate virtually to all cells of the body. They can represent an unlimited source of vascular bed specific ECs, pericytes and smooth muscle cells (SMCs) carrying the same mutations as patients and

non-commercial use only

could therefore be potentially very useful to study HHT. We derived and characterized multiple HHT1 patient specific iPSC lines, which could be induced to differentiate into both ECs and pericytes/vSMCs as efficiently as control iPSCs. In addition, HHT1 iPSCs-derived ECs expressed comparable levels of major endothelial specific antigens (PECAM1, VE-Cadherin, KDR). In contrast, ENG expression levels were significantly downregulated, and recapitulated our observation with the reduced ENG expression in peripheral blood monocytes.Furthermore, HHT1 iPSC-ECs also exhibited altered downstream signaling responses to TGF β. Interestingly, iPSC-ECs retained their plasticity and capacity to differentiate towards cells with either arterial or venous phenotype, as observed both in vitro and following injection into the early stage zebrafish embryo. Thus, iPSC-ECs can be further used to study vascular bed specific responses observed in HHT patients, as well and mechanism-specific drug discovery. Importantly, we demonstrate that endothelial cells derived from HHT1 iPSCs lines retain ENG levels similar to levels in endothelial cells/monocytes observed in the patients and can be successfully applied to model HHT disease in vitro.

Session II
Hepatic involvement in HHT

C-006
MANGANESE-RELATED CENTRAL NERVOUS SYSTEM INJURY IN HHT PATIENTS WITH HEPATIC INVOLVEMENT. RELATIONSHIP WITH IRON DEFICIENCY ANEMIA, HEPATIC VASCULAR MALFORMATIONS AND NEUROLOGICAL SYMPTOMS

M Serra[1,3,5,8], C Besada[2,8], A Saenz[5], C Stefani[4], D Bauso[4], A Golimstok[4], A Cabana[4], M Garcia Basalo[4], D Giunta[6], JC Bandi[1,7,3], N Causada Calo[5,8], MC Elizondo[6,5]

[1]*Internal Medicine, Hospital Italiano de Buenos Aires. (HIBA),* [2]*Departament of Neurorradiology. HIBA,* [3]*HHT Unit. HIBA.,* [4]*Departament of Neurology. HIBA,* [5]*ARG (Argentine Rendu Study Group),* [6]*Internal Medicine Research Unit, HIBA,* [7]*Section of Hepatology,* [8]*Departament of Gastroenterology HIBA, Argentina*

Introduction: Hemorrhagic Hereditary Telangiectasia (HHT) patients with hepatic involvement may have manganese (Mn) deposits in basal ganglia (BG). Similar findings are seen in cirrhosis and/or portal hypertension. It has been hypothesized that a diminished Mn hepatic clearance could be the cause. Iron deficiency contributes to Mn absorption and deposition in the central nervous system (CNS). These two mechanisms, frequently found in HHT patients, could be responsible for Mn deposition. Clinical implications have not been studied. *Aims:* to determine the prevalence of BG lesions associated with Mn deposits and to describe its relationship with iron deficiency anemia, HHT liver disease and neurological symptoms. *Methods*: Cross sectional study of the Hospital Italiano de Buenos Aires HHT registry. Patients that consented and fulfilled three and four Curaçao criteria were included. Individuals with non-related neurological disorders and without MRI results were excluded. All patients were evaluated clinically and with laboratory and imaging liver studies. Patients with BG T1 MRI hyperintensity are described. *Result*: We included 102 patients, 73 (71.9%) were women (median age: 42.5 years, range 12-83). The prevalence of BG lesions was 28.4% (29/102). In this group, 69% (20) were women, median age was 54 years (23-83) and the prevalence of liver involvement was 93.1% (27/29). The most frequent findings were telangiectasias (28/29, 96.6%)and vascular confluent masses (13/29, 44.8%). Anemia prevalence was 22/29 (75.9%), median hemoglobin 9 (IIc 5.3), median sideremia 30 (51.25) and median ferritin 14 (IIc 140, min 4 max 474). At present 14 patients had neurological evaluation; 6 had neurological symptoms (extrapyramidal tremor was the most frequent, and restless legs syndrome was seen in 1 patient).There were extra-BG Mn deposits in 13 patients (mainly in adenohypophysis). *Conclusion*: Prevalence of BG Mn deposits is high. These individuals have high prevalence of iron deficiency and vascular hepatic lesions. These findings have not been previously reported. We continue evaluating HHT patients to determine whether the latest conditions can be considered risk

non commercial use only

factors for the development of Mn deposits in the CNS. Neurological examination detected extrapyramidal symptoms and will be completed with neuropsychological tests.

C-007
MAGNETIC RESONANCE IMAGING OF THE LIVER IN PATIENTS WITH HEPATIC INVOLVEMENT OF HHT

A Massmann, U Geisthoff, A Buecker, GK Schneider

Saarland University Medical Center Homburg/Saar, Germany, Clinics of City Cologne/Holweide, Germany

Purpose: Evaluation of magnetic resonance tomography and magnetic resonance angiography for detection and characterization of hepatic involvement in HHT. *Methods and Materials:* 256 patients (mean age 46) with confirmed HHT according to Curacao criteria or their first degree relatives underwent a screening examination of the liver. Patients with signs of liver involvement underwent additional non-enhanced and dynamic contrast-enhanced MRI including hepatobiliary phase and MRA after Gadolinium-BOPTA (Multihance, Bracco) 0.05 mmol/kg bodyweight i.v. *Results:* MRI revealed 45 patients (mean age 55.3 years; male 10; female 35) with hepatic and vascular pathologies related to HHT. 14 of 45 patients were associated with PAVM. Hepatomegalia was found in 33 patients. Right-heart-insufficiency (RHI), due to HAVM, was present in 13 patients, who did not suffer from hemodynamically relevant PAVM. Patients with an enlarged diameter of the hepatic artery (HA) showed increased nodular hyperplastic changes of the liver (15 patients), a lower RHI-rate, and a rather normal diameter of the portal vein. *Conclusion:* In HHT 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. HAVM causing hyperplastic nodules, similar to a focal overgrowth in the development of FNH, do not result in direct hemodynamical left-to-right-shunts, while HAVM without hyperplastic nodules is likely to cause RHI.

C-008
PREDICTORS OF DEATH IN PATIENTS WITH HHT, LIVER VASCULAR MALFORMATIONS (LVMS) AND SYMPTOMATIC HEART FAILURE (HF)

LH Young, K Henderson, JS Pollak, RI White Jr, MM Ciarleglio, Y Deng, G Garcia-Tsao

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

Introduction: The most common presentation of LVMs is HF resulting from hepatic artery to hepatic vein shunting, leading to high cardiac output, dyspnea, secondary pulmonary hypertension and right HF. Liver transplantation is an option when standard therapy fails to improve symptoms. Predicting a poor outcome at the time of presentation with HF symptoms is important so that more aggressive therapies and liver transplant evaluation could be initiated earlier in high-risk patients. The aim of this study was to identify predictors of death in patients with HHT, LVMs and symptomatic HF. *Patients and Methods*: A cohort of 41 patients with HHT and symptomatic HF followed at Yale since 1994 was analyzed retrospectively. LVMs were confirmed by imaging studies. Most patients had baseline laboratory tests, cardiac echocardiography and cardiac catheterization around the time of presentation with HF symptoms. Patients were followed until death or February 2013. Complications including severe epistaxis or GI bleeding requiring transfusions, biliary ischemia, severe hypoxemia, atrial fibrillation were recorded. Cox regression was used to identify factors associated with death. Results. Of the 41 patients (36 female, 5 male), genotyping showed 20 with ACVRL1 and 2 with ENG (both with diffuse PAVMs) mutations. Median age at presentation was 60 (34-78) years, including 5 presenting early due to pregnancy (3) or diffuse PAVMs (2). Median (ranges) for cardiac parameters were: NHYA cardiac class: 3 (1-4); LV ejection fraction: 65 (53-80); cardiac output: 9.5 (5.8-19.2) L/min; cardiac index: 5.8 (3.6-11.5) L/min/m2; PCWP: 18 (4-28) mm Hg; PAS 46 (17-92) mmHg. In a median follow-up of 6 (4-8) years, 27/41 (66%) patients died. Median age of death was 69 (34-86) years. Median survival time was 7 years (95% CI: 5.15, 9.67). Cox univariate regression analysis (significant variables) is shown in Table. *Conclusions*: Mortality is relatively high but occurs late in patients with LVMs and advanced symptomatic HF. Clinical, laboratory and hemodynamic variables may predict a poorer outcome and may identify patients who would require more aggressive therapies. Results need to be validated prospectively.

Variable	N	Hazard Ratio	95% CI HR		p
Age at presentation	41	1.055	1.016	1.096	0.0053
Txf-dependent GI bleed	39	2.082	0.959	4.518	0.0637
Any biliary ischemia	39	7.537	2.443	23.255	0.0004
Weight loss	37	2.519	1.025	6.191	0.0440
Pulm artery systolic pressure	30	1.032	1.003	1.062	0.0324
Pulm artery pressure (mean)	30	1.044	0.998	1.092	0.0587
Right ventricular enlargement	27	2.813	0.946	8.365	0.0629
Est RV systolic pressure	25	1.037	0.998	1.078	0.0647
Baseline total bilirubin	22	14.672	2.675	80.476	0.0020

N = number of patients with available data

C-009
MULTIDETECTOR CONTRAST-ENHANCED COMPUTED TOMOGRAPHY IN THE EVALUATION OF SPLENIC INVOLVEMENT IN PATIENTS WITH HEREDITARY HEMORRHAGIC TELANGIECTASIA: A PROSPECTIVE STUDY

M Bensalah, M El Hajjam, J Sellier, S Binsse, T Chinet, J Roume, A Ozanne, I Bourgault, G Lesur, J-H Blondel, A Cordier, S Blivet, C Fagnou, M Bonay, C Karam, A Nicod-Tran, S Chagnon, M Eyries, L Gouya, P Lacombe

non-commercial use only

Consultation Pluridisciplinaire Maladie de Rendu-Osler, Hôpital Ambroise Paré Boulogne, hôpital du Kremlin-Bicêtre. HHT Center, Paris, France

Background: Hereditary hemorrhagic telangiectasia (HHT) is a genetic disease characterized by arteriovenous malformations (AVMs) involving potentially every organ. However, there are limited data in the literature regarding the splenic involvement in HHT. *Purpose:* To evaluate splenic findings in patients with HHT using multidetector contrast-enhanced computed tomography (MDCT). *Materials and Methods:* during a 30-month period, all consecutive patients already diagnosed with HHT underwent MDCT. All MDCT obtained at the arterial and portal phases were evaluated by experienced radiologists. The diameter of the splenic vessels was measured and the presence of aneurysms was recorded. The splenic parenchyma was also carefully evaluated with special emphasis on telangiectases, AVMs, cysts or calcifications. The size and location of identified abnormalities was recorded. The presence of associated liver involvement was also recorded. *Results:* A total of 149 HHT patients (94 women and 55 men, mean age of 44 y.o) were enrolled prospectively in this study. Vascular abnormalities were detected in 49 patients (33%): including splenic artery aneurism in 29 patients (19%), ranging from 5 to 17 mm; intraparenchymal splenic telangiectases in 26 patients (17%) , ranging from 5 to 56 mm; splenic venous enlargement in 14 patients (9 %); splenic cysts in 10 patients (7%), and splenic calcifications in 6 patients (4%). Only 4 cases of splenomegalia were found. In one case of diffuse parenchymal telangiectases in an 11-y.o. girl, a splenectomy was performed. Among patients with splenic involvement, 9 patients (6%) had isolated splenic anomalies without hepatic involvement. No significative correlation was found between splenic abnormalities and the type of mutation. *Conclusion:* Splenic involvement was considered as a rare finding in patients with HHT. With the use of MDCT, vascular and parenchymal splenic abnormalities have been identified in one third of HHT patients. We suggest that the presence of splenic telangiectases should be added in the list of visceral involvement used for the diagnosis of HHT. *Keywords:* HHT; spleen; splenic telangiectasia; splenic artery aneurism

C-010
"ANY MAJOR TREATMENT DECISION REGARDING HHT SHOULD BE DISCUSSED WITH A HHT REFERENCE CENTER": C.A.R.D PROJECT FOR HHT PATIENTS

S Alicante[1], E Buscarini[1], G Manfredi[1], F De Grazia[1], G Lupinacci[1], F Menozzi[1], G Brambilla[1], C Londoni[1], S Crinò[1], A Zambelli[1], P Gazzaniga[2], S Gandolfi[3], PA Forner[4], C Danesino[5], C Olivieri[5], C Canzonieri[5], F Ornati[5], F Pagella[6], M Grosso[7], G Pongiglione[8], E Boccardi[9], on behalf of HHT-NET

[1]*Gastroenterology Dept,* [2]*Cardiology Dept,* [3]*Radiology Dept,* [4]*ENT Dept, Maggiore Hospital, Crema;* [5]*Dipartimento di Medicina Molecolare, Genetica medica, University of Pavia;* [6]*ENT Institute, University of Pavia;* [7]*Radiology Dept, Ospedale S. Croce, Cuneo;* [8]*Paediatric Cardiology Dept, Ospedale Bambin Gesù, Roma;* [9]*Interventional Neuroradiology Unit, Niguarda Hospital, Milan; Italy*

Background and study aims: Also for Hereditary Hemorrhagic Telangiectasia (HHT) the very fact that the disease is rare makes it very difficult to know and appropriately treat it outside the reference centers. This is particularly critical in case of HHT-related emergencies or severe clinical presentations which would require a timely, intensive and appropriate approach. The project is aimed to assist patient management in case of emergent/severe complications of HHT. *Methods:* From October 2011 to June 2012 we recorded 278 phone calls to our HHT center for HHT-related questions; 5 phone calls regarded life-threatening HHT-related complications (2 related to severe hepatic VMs - high output cardiac failure, ischemic cholangitis; 2 hemoptysis for ruptured PAVM; 1 severe GI bleeding); in 2/5 cases a wrong treatment had been done before asking our advice. On the basis of this observation we started the C.A.R.D (Crisis Aid for a Rare Disease) project. For every patient in our database with a definite HHT diagnosis and with a previous clinical and instrumental assessment in our HHT center, we designed a plastic card bearing on the front the patient data: name, surname, date of birth, fiscal code, the diagnosis of HHT, the presence/absence or lack of evaluation of: CAVM, PAVM, HAVM, GI teleangiectases, high output cardiac failure; the need or not for antibiotic prophylaxis; the card back lists general recommendations regarding presentation and treatment of main and most severe HHT complications, and the phone numbers of our HHT center for emergency calls. We agreed with physicians and nurses of our HHT center a 24/7/365 availability to answer to phone calls regarding HHT-related urgent/severe conditions; the name and phone number of patient/physician calling is passed to the HHT-expert physicians who will contact him/her immediately. An appropriate recording of the number and causes of phone calls received, and of patient outcome has been scheduled. *Results:* 486 cards have been so far printed and sent to the patients. Number and causes of phone calls received and patient outcomes will be reported. *Conclusions:* The HHT C.A.R.D. can obtain greater timeliness and appropriateness in the treatment of HHT-related complications outside HHT centers.

C-011
IMPROVEMENT OF HEREDITARY HEMORRHAGIC TELANGIECTASIA RELATED ISCHEMIC CHOLANGIOPATHY FOLLOWING TREATMENT WITH BEVACIZUMAB

PA Vlachou, E Colak, A Koculym, A Kirpalani, TK Kim, GM Hirschfield, ME Faughnan[1]

non commercial use only

Department of Diagnostic Imaging St. Michael's Hospital, Toronto, ON, Canada; Department of Diagnostic Imaging, Toronto General Hospital, Toronto, ON, Canada; Department of Medicine, Division of Gastroenterology, University of Toronto, Toronto, Canada and Centre for Liver Research, Institute of Biomedical Research, NIHR Biomedical Research Unit, University of Birmingham, Birmingham, UK, [1]Department of Medicine, Division of Respirology, Toronto HHT Centre, St. Michael's Hospital, Toronto, Canada and Keenan Research Centre of the Li Ka Shing Knowledge Institute of St. Michael's Hospital, Toronto, ON, Canada

Introduction: HHT-related biliary disease remains a difficult clinical problem with limited medical treatments. Liver transplantation is indicated in patients with ischemic biliary necrosis, intractable high-output cardiac failure (HOCF) or portal hypertension but carries significant morbidity and mortality. Bevacizumab, an anti-VEGF antibody has been shown to improve severe HHT-related anemia and to improve HOCF secondary to hepatic vascular malformations but responses of other HHT-related complications to bevacizumab therapy have not been described. *Methods:* Three patients with severe biliary involvement from florid hepatic HHT leading to significant biliary ischemia were treated with bevacizumab. *Results:* All patients were female, of Caucasian origin, ages 25-43 and presented with symptoms including right upper quadrant pain, weight loss, fatigue, worsening epistaxis, melena and cholestatic liver enzymes. Cross-sectional imaging demonstrated marked intrahepatic biliary strictures and bilomas as well as telangiectasias and arteriovenous shunting. The patients failed to respond to intensive medical therapy, were listed for high-priority liver transplantation and were started on a trial of bevacizumab. All patients showed a dramatic improvement of symptoms from biliary ischemia after 3 months of treatment in two patients and after 8 months in the third patient, obviating the imminent need for liver transplantation. In addition, we observed radiologic evidence of reversal of the ischemic biliary phenotype with striking reduction in biliary duct dilatation, near resolution of bilomas and normalization of arterial flow volume following treatment in all patients. Bevacizumab also appeared to improve other manifestations of the patient's HHT; the severity of epistaxis decreased, gastrointestinal hemorrhaging ceased, and hemoglobin levels were noted to trend towards normal. The first patient experienced resolution of her HOCF and treatment induced reduction in the liver vascularity in all cases. All patients tolerated the treatment well and did not suffer side effects from bevacizumab. The patients remain well one year following initiation of therapy. *Conclusion:* This is the first case series demonstrating significant improvement of biliary complications in HHT patients treated with bevacizumab and lends further support to bevacizumab as an effective treatment modality in hepatic HHT.

C-012
PULMONARY CAPILLARY BLOOD VOLUME/ALVEOLO-CAPILLARY MEMBRANE CONDUCTANCE RATIO IS INCREASED IN HEREDITARY HEMORRHAGIC TELANGIECTASIA PATIENTS WITH LIVER ARTERIOVENOUS MALFORMATIONS

M Dubois, Y Retory, C de Picciotto, J Sellier, M El Hajjam, S Binsse, T Chinet, J Roume, A Ozanne, I Bourgault, G Lesur, J-H Blondel, A Cordier, S Blivet, C Fagnou, C Karam, A Nicod-Tran, S Chagnon, P Lacombe, M Eyries, L Gouya, M Bonay

Consultation Pluridisciplinaire Maladie de Rendu-Osler, Hôpital Ambroise Paré, Boulogne. Hôpital du Kremlin-Bicêtre, HHT Center, Paris, France

Background: The severity of Hereditary Hemorrhagic Telangiectasia (HHT) or Rendu-Osler disease is commonly related to vascular visceral involvement represented by arteriovenous malformations (AVMs). Pulmonary AVMs (PAVMs) induce right-to-left shunting which is classically assessed by contrast echocardiography and arterial blood gas measurements. Pulmonary functions tests (PFTs), completed concomitantly with arterial blood gas measurements, are habitually normal in HHT patients without respiratory comorbidity. Very few studies have evaluated pulmonary gas exchange in HHT patients. The combined diffusing capacity of the lung for carbon monoxide (DLCO) and nitric oxide (DLNO) is a simple test allowing the determination of the 2 components of pulmonary gas exchange: the pulmonary capillary blood volume (Vc) and the alveolo-capillary membrane conductance (Dm). *Methods:* The aim of our study was to compare DLCO and its 2 components Dm and Vc, in HHT patients with [PAVMs, P+Liver AVMs (LAVMs), LAVMs] or without arteriovenous malformations (HHT) and controls (C). *Results:* Sixty three consecutive adult patients with flow expiratory volume in one second/vital capacity ratio >70% (HHT: n=9; PAVMs: n=13; P+LAVMs: n=21; LAVMs: n=20) and controls (n=15) were evaluated in 2010 and 2011, using PFTs, combined DLCO/DLNO, arterial blood gas at rest, contrast echocardiography and enhanced computed tomography scan of the liver and chest. Total lung capacity, alveolar-arterial O2 gradient at rest, DLCO, Vc and Dm (% predicted) did not differ between groups. The proportion of gas transfer conductance due to Vc is proportional to the Vc/DLCO ratio. The Vc/DLCO ratio (C:2.61 0.09; HHT:2.71 0.12; PAVMs: 2.75 0.12; P+LAVMs:2.78 0.20; LAVMs:2.91 0.29; $p<0.01$) and the Vc/Dm ratio (C:1.10 0.10;HHT:1.19 0.10;PAVMs:1.20 0.12; P+LAVMs:1.26 0.20; LAVMs:1.41 0.29; $p<0.01$) were increased in LAVMs as compared with other groups. Interestingly, HHT patients with hepatic artery enlargement (diameter 7mm) evidenced higher Vc/Dm ratio than HHT patients with hepatic artery diameter < 7 mm (1.33 0.24, n=33 vs 1.23 0.19, n=30; p=0.03). *Conclusion:* Our results suggest that pulmonary gas exchanges are modified in LAVMs patients and that high Vc/Dm ratio may be associated with the occurrence of liver arteriovenous malformations.

Non-commercial use only

C-013

FOLLOW-UP OF HHT PATIENTS TREATED WITH BEVACIZUMAB FOR SEVERE HEPATIC VASCULAR MALFORMATIONS AND HIGH CARDIAC OUTPUT (METAFORE CLINICAL TRIAL)

S Dupuis-Girod[1], I Ginon[2], JC Saurin[3], D Marion[4], E Guillot[4], E Decullier[5], MF Carette[6], B Gilbert-Dussardier[7], PY Hatron[8], P Lacombe[9], B Lorcerie[10], S Riviere[11], R Corre[12], S Giraud[13], AE Fargeton[1], S Bailly[14], G Paintaud[15], D Ternant[15], P-J Valette[4], H Plauchu[1], F Faure[16]

[1]*Hospices Civils de Lyon, Hôpital Louis Pradel, Service de Génétique et centre de référence sur la maladie de Rendu-Osler, Bron , Université de Lyon, Faculté de médecine, Université Lyon 1,* [2]*Hospices Civils de Lyon, Centre Hospitalier Lyon Sud, Service de Cardiologie, Pierre-Bénite,* [3]*Hospices Civils de Lyon, Service d'Hépato-gastroentérologie, Hôpital E. Herriot, Lyon,* [4]*Hospices Civils de Lyon, Centre Hospitalier Lyon Sud, Service de Radiologie, Pierre-Bénite,* [5]*Hospices Civils de Lyon, pôle IMER, Lyon, Université de Lyon, Faculté de médecine, Université Lyon 1* [6]*Service de Radiologie, Hôpital Tenon, Paris, Assistance Publique – Hôpitaux de Paris, Université Pierre et Marie Curie (Paris VI) et Centre de Compétence pour la Maladie de Rendu-Osler en Ile de France,* [7]*Service de génétique médicale, CHU La Milétrie, Poitiers, France,* [8]*Service de médecine interne, Université Lille2, CHRU de Lille, Lille, France,* [9]*Hôpital Ambroise Paré, Service de Radiologie, Assistance Publique-Hôpitaux de Paris, Université Paris Ile-de-France Ouest, Boulogne, France,* [10]*Hôpital de Dijon, Service de Médecine Interne,* [11]*Service de Médecine Interne A, Centre Hospitalier Universitaire, Montpellier, France,* [12]*Hôpital Pontchaillou, Rennes, France,* [13]*Hospices Civils de Lyon, Laboratoire de biologie moléculaire, Hôpital E. Herriot, Lyon,* [14]*INSERM, Unité 1036, Biology of Cancer and Infection, Grenoble, France,* [15]*CNRS, UMR 6239; Université François Rabelais de Tours,* [16]*Hospices Civils de Lyon, Hôpital E. Herriot, Service d'ORL, Lyon, France*

Hereditary hemorrhagic telangiectasia (HHT) is a dominantly inherited genetic vascular disorder in which hepatic shunts can be associated with high-output cardiac failure. Twenty five patients have been included between March 2009 and November 2010 in a single-center phase-II trial (Metafore). This trial showed the efficacy of bevacizumab in reducing high cardiac output at 3 and 6 months after the first bevacizumab injection in severe hepatic forms of HHT as well as decreasing epistaxis duration and significantly improving quality of life. Bevacizumab was given at a dose of 5 mg/kg every 14 days with a total of 6 injections. *Objective:* To follow efficacy of bevacizumab in HHT patients 1, 2 and 3 years after the first bevacizumab injection. *Results:* Median cardiac index (CI) at beginning of the treatment was 5.0 l/min/m^2 and significantly decreased at 6 months and 1 year after the beginning of the treatment with a median CI of 4.1 and 4.3 l/min/mV respectively, $p<0.0001$. Median duration of epistaxis, which was 178 min/month (range, 3-947) at inclusion, had significantly decreased at six months (20 min (range, 0-330)) ($p= 0.001$) and one year [24 min (range, 0-307)] ($p=0.0006$). Liver CT scan, skin telangiectasia and pulmonary arteriovenous malformations were not significantly improved. Twenty four patients are alive with a mean follow up of 30.5 months. One patient died 28 months after the first treatment from a non-related complication. Eight patients have been retreated with bevacizumab for high cardiac output 21 to 40 months after the first injection of the first treatment. Among them, 4 had a complete response at 3 months after the second treatment with normalization of CI, 1 had a partial response, 2 did not respond and 1 treatment is ongoing. Tolerance of the second treatment was acceptable. One patient stopped after 2 injections because of articular pain. *Conclusion:* Efficacy of 6 injections of bevacizumab in HHT patients is prolonged in most patients. A second treatment is possible and can be efficient. A maintenance therapy has to be considered.

non commercial use only

Session III
Genetics and genotype/phenotype in HHT

C-014
MUTATION ANALYSIS OF TGF-BETA PATHWAY GENES IN HEREDITARY HEMORRHAGIC TELANGIECTASIA PATIENTS IN JAPAN: GENOTYPE-PHENOTYPE CORRELATIONS IN 119 CASES

H Morisaki, M Komiyama, O Yamada, K Osuga, T Morisaki, and Japan HHT Consortium

Department of Bioscience and Genetics, National Cerebral and Cardiovascular Center Research Institute, Department of Neurosurgery, Osaka City General Hospital, Department of Pediatric Cardiology, National Cerebral and Cardiovascular Center, Department of Radiology, Osaka University Graduate School of Medicine, Department of Molecular Pathophysiology, Osaka University Graduate School of Pharmaceutical Sciences, Japan

Hereditary Hemorrhagic Telangiectasia (HHT) is an autosomal dominant diseasecharacterized by recurrent epistaxis, mucocutaneous telangiectasia and visceral arteriovenous malformations. The majority of cases are caused by mutations in eitherendoglin (ENG) or activin receptor-like kinase 1 (ACVRL1) gene, while mutations in SMAD4 are seen in patients with the combined syndrome of juvenile polyposis and HHT (JP-HHT). We have screened for mutations in a total of 80 unselected Japanese index cases with the suspected diagnosis of HHT. Mutation analysis was performed using direct sequencing of exonic regions and gene dosage analysis with MLPA probes. ENG mutations and ACVRL1 mutations were identified in 47 cases (59%) and 23 cases (29%), respectively. Two cases (3%) were associated with SMAD4 mutations, and 1 case was caused by a mutation in the other TGF-beta signaling molecule. In total, disease causing mutations were identified in 73 index cases (91%). 66% of ENG mutations were predicted to cause premature termination with nonsense, frameshift, or out-of-frame deletion mutations, while 65% of ACVRL1 mutations were missense or in-frame deletion mutations. Family history was positive in 52 index cases; 32 (68%) with ENG mutations, 19 (87%) with ALK1 mutations and 1 with SMAD4 mutation. Subsequent analysis of family members added another 46 mutation-positive cases and genotype-phenotype correlation analysis was performed in a total of 119 genetically defined HHT patients. Pulmonary arteriovenous malformation (PAVF) and cerebral arteriovenous malformation (CAVF) were observed significantly more frequently with ENG mutation carriers than ACVRL1 mutation carriers (PAVF: 85% vs. 30%; CAVF: 33% vs. 11%), while hepatic arteriovenous malformation (HAVF) was significantly more common among ACVRL1 mutation carriers (11% vs. 45%). Epistaxis, telangiectasia in skin, and GI telangiectasia were equally observed between two groups. Pulmonary hypertension was associated only with ACVRL1 mutation carriers. Juvenile polyposis was observed in 3 of 4 SMAD4 mutation carriers, but not among other mutation carriers. This is the first and largest Japanese national study with genetically defined HHT.

C-015
MUTATIONS ON A NEW GENE CAUSE A NEW VASCULAR MALFORMATION DISORDER SIMILAR TO HEREDITARY HEMORRHAGIC TELANGIECTASIA

W Wooderchak-Donahue[1], J McDonald[2], B O'Fallon[1], PD Upton[3], W Li[3], BL Roman[4], S Young[4], P Plant[1], G Tamas[5], C Langa[5], NW Morrell[3], LM Botella[5], C Bernabeu[5], DA Stevenson[6], JR Runo[7], P Bayrak-Toydemir[1,2]

[1]*ARUP Institute for Clinical and Experimental Pathology, Salt Lake City, UT,* [2]*Department of Pathology, University of Utah, Salt Lake City, UT, Department of Medicine, University of Cambridge School of Clinical Medicine, Addenbrooke's Hospital, Cambridge, United Kingdom,* [4]*Department of Biological Sciences, University of Pittsburgh, Pittsburgh, PA,* [5]*Centro de Investigaciones Biologicas, CSIC and Centro de Investigacion Biomedica en Red de Enfermedades Raras (CIBERER), Madrid, Spain,* [6]*Division of Medical Genetics, Department of Pediatrics, University of Utah, Salt Lake City, UT,* [7]*Department of Medicine, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA*

Cutaneous vascular lesions are reported in several vascular malformation syndromes, but in combination with epistaxis only in hereditary hemorrhagic telangiectasia (HHT). Here, we present a new vascular malformation syndrome characterized by epistaxis and telangiectases/capillary malformations (CMs) caused by mutations in a transforming growth factor beta (TGF-β) signaling pathway gene. Mutations were identified in three unrelated patients out of 191 individuals suspected to have HHT, who tested negative for mutations in ENG, ACVRL1, and SMAD4. These three patients had epistaxis and dermal lesions described as telangiectases, but with location and appearance which resembled lesions described in some patients with RASA1-related disorders/CM-AVM (capillary malformation-arteriovenous malformation syndrome). Expression analyses of the mutant proteins, supported by a gene-deficient zebrafish model, suggest that this gene is involved in vasculogenesis and should be considered during evaluation of individuals with dermal telangiectases or CMs and epistaxis.

Non-commercial use only

C-016
COPY NUMBER VARIATION IN ENDOGLIN LOCUS: MAPPING OF LARGE DELETIONS IN SPANISH FAMILIES WITH HEREDITARY HAEMORRHAGIC TELANGIECTASIA TYPE 1

A Fontalba[1], JL Fernández-Luna[1], R Zarrabeitia[2], L Recio-Poveda[3], V Albiñana[3], ML Ojeda-Fernandez[3], C Bernabeu[3], C Alcaraz[4], LM Botella[3]

[1]*Molecular Genetics Unit, Hospital Valdecilla, and Instituto de Formación e Investigación Marqués de Valdecilla (IFIMAV), Santander, Spain,* [2]*HHT Spanish Unit, Hospital Sierrallana and Centro de Investigacion Biomedica en Red de Enfermedades Raras (CIBERER), Torrelavega, Santander, Spain,* [3]*Centro de Investigaciones Biológicas, Consejo Superior de Investigaciones Científicas (CSIC), and Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), Madrid, Spain,* [4]*Bioarray S.L, Crevillente, Alicante, Spain*

Hereditary Haemorrhagic Telangiectasia syndrome (HHT), also known as Rendu-Osler-Weber syndrome is a vascular multiorganic disorder inherited as an autosomal dominant trait. Diagnostic clinical criteria include epistaxis, telangiectases in muco-cutaneous and gastrointestinal sites, arterio-venous malformations (AVMs) most commonly in pulmonary, hepatic and cerebral circulations, and familial inheritance. HHT is transmitted in 90% of the cases as an autosomal dominant condition due to mutations in either Endoglin (ENG), or Activin receptor-like kinase 1 (ACVRL1/ALK1) genes (HHT type 1 or 2, respectively). We have carried out a genetic analysis of four independent Spanish families with clinical criteria of HHT, allowing the identification of new large deletions in ENG gene. These mutations were first detected by MLPA technique and subsequently, the breakpoint for the deletions was mapped using a customized Copy Number Variation microarray. The array was designed to cover the ENG gene and surrounding areas. All tested families carried large deletions ranging from 3-kb to 100-kb, and involving the ENG gene promoter, several exons of ENG, or the two downstream genes FGSH and CDK9. Interestingly, common break points coincident with Alu repetitive sequences were found among these families.

C-017
ENDOGLIN MUTATIONAL MECHANISMS AND GENOTYPE-PHENOTYPE CORRELATIONS IN HEREDITARY HAEMORRHAGIC TELANGIECTASIA

FS Govani, A Giess, IG Mollet, ME Begbie, MD Jones, L Game, CL Shovlin

Imperial College London, UK

Background: Hereditary haemorrhagic telangiectasia (HHT) is most commonly caused by mutations in ENG, ACVRL1 or SMAD4. Mutations include single nucleotide substitutions (nonsense, missense and splice site mutations), and subexon/multiexon insertions and deletions. There are subtle phenotypic differences between different HHT genes, but it is unclear if specific mutational types are associated with further phenotypic variability. *Methods:* HHT-causing ENG mutations from the HHT mutation database were classified into conventional mutational types. Alternate frame reads were used to determine the exact site of the first stop codon generated by out of frame indels. Natural stop codon mutations were modelled using expression constructs. Next generation sequencing of total RNA from seven different confluent cultures of proliferating primary human microvascular endothelial cells was performed. *Results:* 67% [95% confidence intervals 62%, 73%]) of ENG mutations reported on the HHT mutation database were predicted to lead to stop codons, due to frameshifts or direct nonsense substitutions. Of the 111 stop codon-generating mutations, all except one resulted in a premature termination codon (PTC) sited at least 50-55bp upstream of the final exon-exon boundary of L-endoglin. The single natural stop codon mutation disrupted the transmembrane domain suggesting a functional null at a protein level. No HHT-causing mutations corresponded to in vitro generated truncated ENG species that displayed dominant negative activity similar to the S-endoglin isoform, and there was a non-random distribution of ENG stop codons across all three reading frames. Numerous transcribed fragments from ENG intronic regions were consistently detected in endothelial-specific libraries, the majority from the complementary strand. *Conclusions:* These data support the haploinsufficiency model for HHT pathogenesis; explain why final exon mutations have not been detected to date in HHT; emphasise the potential need for functional examination of non PTC-generating mutations; and lead to proposals for an alternate stratification system of mutational types for HHT genotype-phenotype correlations, with key distinctions residing in the generation or non-generation of PTCs, and potential to alter the copy number of intronic transfrags.

Govani, Giess, Mollet, Begbie, Jones, Game, Shovlin. Mol Syndromol 2013;4:184-196.

C-018
CLINICAL EXPRESSION OF HEREDITARY HAEMORRHAGIC TELANGIECTASIA AND DIGESTIVE LESION CHARACTERISTICS IN PATIENTS WITH SMAD4 MUTATION

M Bonjean[1], S Giraud[2], E Decullier[3], JC Saurin[4], P Edery[1], S Dupuis-Girod[1]

[1]*Hospices Civils de Lyon, Service de Génétique et centre de référence sur la maladie de Rendu-Osler, Bron,* [2]*Hospices Civils de Lyon, Laboratoire de biologie moléculaire, Hôpital E. Herriot, Lyon,* [3]*Hospices Civils de Lyon, pôle IMER, Lyon, Université de Lyon, Faculté de médecine, Université Lyon 1,* [4]*Hospices Civils de Lyon, Service d'Hépato-gastroentérologie, Hôpital E. Herriot, Lyon, France*

Background: Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant vascular disorder characterized by epistaxis, telangiectasia and arteriovenous

non-commercial use only

malformations of the lungs, the gastrointestinal tract, the liver and less frequently, the brain. HHT type 1 results from mutations in ENG (coding for endoglin), and HHT type 2 results from mutations in ACVRL1 (coding for activin receptorlike kinase 1). Mutations of either of these two genes account for most clinical cases. In addition, mutations in MADH4 (encoding SMAD4) are responsible of "juvenile polyposis (JP) /HHT" overlap syndrome. JP causes hamartomatous polyps in the gastrointestinal tract and predisposes to gastrointestinal cancer with a risk apparently over 50%. Our aim was to define clinical expression of HHT and digestive lesions in HHT patients with SMAD 4 mutation followed in the French reference center. *Methods:* Restrospective analysis of HHT patients with SMAD4 mutations. Curaçao criterias were used for HHT diagnosis and Jass criterias for JP. *Results:* 14 among 589 patients with identified mutation had SMAD4 mutation (2.3%). Epistaxis and telangiectasia were often present in 13 (93%) and 11 (79%) patients respectively. Nine patients among 13 screened patients had pulmonary arterioveinous malformations (PAVMs) (69%). Among them 4 had diffuse or multiple PAVMs associated with hypoxemia. Three patients among 11 screened patients (27%) had severe hepatic AVM with high cardiac output. Among eleven SMAD4 patients who had digestive endoscopies: 10 (91%) had digestive lesions. Four patients (36%) had a confirmed JP diagnosis, 5 (45%) had upper gastrointestinal tract lesions and 9 (81%) had lower intestinal tract lesions. Lesions were adeno-villous or hyperplasic polyps and one patient had stomach and colon adenocarcinomas and pancreas intraductal papillary mucinous tumour. *Conclusion:* In this study the digestive presentation in patients with SMAD4 mutations is not limited to juvenile polyposis. The HHT phenotype appeared to be more severe for hepatic and pulmonary arteriovenous malformations. This study confirms that any patient with SMAD4 mutation should be screened for JP or digestive tract cancers as well as for HHT complications.

C-019
CLINICAL ANALYSIS OF 42 HHT1 AND 23 HHT2 JAPANESE PATIENTS

M Komiyama[1], T Ishiguro, O Yamada, H Morisaki[2]

[1]*Department of Neurosurgery, Osaka City General Hospital, Osaka, Japan, Departments of Pediatric Cardiology,* [2]*Bioscience and Genetics,* [1]*National Cerebral and Cardiovascular Center, Osaka, Japan*

Purpose: To portray the clinical pictures of the genetically verified Japanese hereditary hemorrhagic telangiectasia (HHT) patients. *Methods:* Between September 2010 and December 2012, 80 patients with suspected HHT or their family members underwent genetic analysis at Osaka City General Hospital, Osaka. Clinical analyses were performed among the genetically verified patients, retrospectively. Principally, they underwent at least brain MR imaging and plain lung CT in addition to an interview and inspection. The other examinations including CECT for the liver, and endoscope for the GI tracts were limited. MR imaging for the spine was least performed. *Results:* 42 HHT1 (M/F: 23/19, age 2-65) and 23 HHT2 patients (M/F: 9/14, age 8-71) were genetically confirmed. In two clinically HHT-definite female patients, genetic loci were not determined. The remaining 13 patients were genetically denied. Nosebleeds were noted in 42/42 (100%) HHT1 and 21/23 (91%) HHT2 patients. Telangiectases were observed in 28/42 (67%) HHT1 and 17/23 (74%) HHT2 patients. Brain arteriovenous malformation/fistulas (AVM/Fs) were detected in 11/39 HHT1 (28%, 9: multiple lesions) and 1/22 HHT2 (5%, 1: multiple lesions) patients. Pulmonary AVFs were noted in 29/39 HHT1 (74%, 25: multiple lesions) and 2/22 HHT2 patients (9%, 2: multiple lesions). Hepatic AV shunts were noted in 5/18 (28%) HHT1 and 14/16 (88%) HHT2 patients. Spinal AVF was detected only in 1 HHT1 symptomatic patient. *Conclusions:* This report is the largest HHT series in Japan. The number of the HHT1 patients was roughly twice as many as that of HHT2 patients in our series. Clinical pictures of nosebleed, telangiectasia, cerebral, pulmonary, and hepatic AVMs were similar to those reported previously. Brain and pulmonary AVM/Fs were predominantly observed in HHT1 while hepatic AV shunts were noted in HHT2. It seemed that ethnicity played a minimal role in the clinical presentation of both HHT1 and HHT2.

C-020
GENOTYPE-PHENOTYPE CORRELATIONS IN HEREDITARY HAEMORRHAGIC TELANGIECTASIA. DATA OF THE FRENCH RENDU-OSLER-WEBER COHORT

C Paez[1], S Giraud[2], G Lesca[2], E Decullier[3], E Babin[4], MF Carette[5], R Corre[6], P Duffau[7], B Gilbert-Dussardier[8], PY Hatron[9], JR Harle[10], P Kaminsky[11], P Lacombe[12], C Lavigne[13], P Lorcerie[14], P Magro[15], S Riviere[16], P Edery[1], S Dupuis-Girod[1]

[1]*Hospices Civils de Lyon, Service de Génétique et centre de référence sur la maladie de Rendu-Osler, Bron ,* [2]*Hospices Civils de Lyon, Laboratoire de biologie moléculaire, Hôpital E. Herriot, Lyon, ,* [3]*Hospices Civils de Lyon, pôle IMER, Lyon, , Université de Lyon, Faculté de médecine, Université Lyon 1, ,* [4]*Hôpital Côte de Nacre, Service d'ORL, Caen, France,* [5]*Hôpital Tenon, Service de Radiologie, Paris, Assistance Publique – Hôpitaux de Paris, Université Curie (Paris VI),* [6]*Centre Hospitalier Universitaire, Hôpital Pontchaillou, Service de Pneumologie. Rennes, France,* [7]*Hôpital Haut-Lévêque – Centre François Magendie Service de Médecine Interne, Pessac, France,* [8]*Centre Hospitalier Universitaire La Milétrie, Service de Génétique Médicale, Poitiers, France,* [9]*Université Lille2, CHRU de Lille, Hôpital Jeanne de Flandre Service de médecine interne, Lille, France,* [10]*Centre Hospitalier Universitaire de Marseille, Hôpital de la Conception, Service de Médecine Interne, Marseille, France,* [11]*Centre Hospitalier Universitaire de Brabois Service de Médecine Interne, Vandoeuvre-lès-Nancy, France,* [12]*Hôpital Ambroise Paré, Service de Radiologie, Assistance Publique-Hôpitaux de Paris, Université Paris Ile-de-France Ouest, France,* [13]*Centre Hospitalier Universitaire d'Angers Service de Médecine Interne, Angers, France,* [14]*Centre Hospitalier*

non commercial use only

Universitaire de Dijon, Service de Médecine Interne, Dijon, France, [15]*Centre Hospitalier Régional et Universitaire Bretonneau, Service de Pneumologie, Tours, France,* [16]*Centre Hospitalier Universitaire, Hôpital Saint Eloi, Service de Médecine Interne A, Montpellier, France*

Introduction: Hereditary haemorrhagic telangiectasia (HHT) is a dominantly inherited genetic vascular disorder characterized by recurrent epistaxis, cutaneous telangiectasia and visceral arteriovenous malformations (AVM) that affect many organs, including the lungs, gastrointestinal tract, liver and brain. *AIMS:* To study the relationship between the phenotype and genotype in patients with a proven mutation in either ENG, ACVRL1, or less frequently MADH4. *Method:* We used the French HHT database (CIROCO) developed for the network, which contains detailed clinical features registered from 2005 to 2013. *Results:* A total of 1534 patients with a proved mutation were analysed. Among them, the mutated gene was ACVRL1 in 58.4%, ENG in 39.9% and MADH4 in 1.7% of patients. The nose-bleeding event appears to be a predominant characteristic for each of the HHT populations studied: this symptom was present in 92.4, 93.4 and 88.5% of the cases of patients carrying the ENG, ACVRL1 and MADH4 mutations, respectively. However, the severity of the nose bleeding was similar once the patient reached middle age. Telangiectasia identification during the first consultation resulted to be predominantly characteristic in patients with a probed mutation for the different genes ACVRL1 (92.7%), ENG (90.6%) or SMAD4 (76%). Patients with ENG mutations showed a higher prevalence of pulmonary arteriovenous malformations (PAVM) (72.4%) as well as a marked prevalence of cerebral arteriovenous malformations (CAVM) (24.5%). In contrast, the hepatic malformations (HAVM) manifested to be more often related to the presence of the ALK1 mutation (66.2%). Structurally, ENG mutations showed to be widely distributed through the gene. In contrast, ACVRL1 mutations occur preferentially in exons 3 and 7. *Conclusions:* This study on a large cohort shows major differences linking the syndrome and the mutated gene. In general, patients expressing an ENG mutation present a distinct and more severe form that those that expressed an ACVRL1 mutation. Prevention, diagnosis and treatment can be applied distinctively and properly for patients carrying the different HHT mutations.

C-021
"THE ITALIAN JOB": OUR EXPERIENCE IN HHT MANAGEMENT

C Olivieri[1], C Canzonieri[1], F Ornati[2], F Pagella[3], E Buscarini[4], L Lanzarini[2], G Manfredi[4], E Matti[3], F Chu[3], P Gazzaniga[5], S Gandolfi[6], PA Forner[7], M Grosso[8], G Pongiglione[9], E Boccardi[10], C Danesino[1], on behalf of HHT-NET

[1]*General Biology and Medical Genetics, Dept of Molecular Medicine, University of Pavia,* [2]*Cardiology Dept., IRCCS Fondazione "Policlinico S. Matteo", Pavia,* [3]*ENT Dept, IRCCS Fondazione "Policlinico S. Matteo" and University of Pavia,* [4]*Gastroenterology Dept,* [5]*Cardiology Dept,* [6]*Radiology Dept,* [7]*ENT Dept, Maggiore Hospital, Crema,* [8]*Radiology Dept, Ospedale S Croce, Cuneo,* [9]*Paediatric Cardiology Dept, Ospedale Bambin Gesù, Roma,* [10]*Interventional Neuroradiology Unit, Niguarda Hospital, Milan; Italy*

In the late 90's we have introduced for the first time in Italy mutation analysis in HHT patients. The General Biology and Medical Genetic research group begun a tight collaboration with two clinical centers, which were later identified as "Clinical Reference Italian Centers for HHT", the Gastroenterological Unit in Crema (dott.ssa Buscarini and collaborators) and the ENT Unit in Pavia (dott. Pagella and collaborators). The patients undergo to clinical routine HHT analyses in the clinical centers, then a blood sample is referred to the genetic lab for molecular analyses. A genetic counseling is offered to the patients before blood sample is collected and an informed written consent is requested. We have collected till now more than 1500 DNAs from HHT patients and relatives, belonging to more than 500 different families from all Italian regions. Moreover, we have samples of patients from other European countries. The patients are diagnosed as having definite, possible or unlike HHT according to the international diagnostic criteria. One subject from each family is chosen to be the Index Case included in molecular screening. After the familiar mutation is found, all the at risk relatives are tested. We have analyzed more than 350 Index Cases. We have found a disease causing mutation in more than 260 of them. We have observed a notable difference in mutation distribution within the two genes, with ACVRL1 (and so HHT2) being involved in more than 70% of the families. We have confirmed our previous observation on an high percentage of mutation involving ACVRL1 exon 3 in our population: about 40% of mutations in ACVRL1; about 30% of the sum of mutations considering both genes. We have observed an important difference in mutation founding rate when considering subjects with a "definite" diagnosis if compared to "possible" or "unlike". This last data confirms and underlines the importance of a continuous and deep collaboration between the clinical centers and the molecular laboratories in order to obtain as much information on the disease as possible but also to offer the patients the most complete care giving.

Non-commercial use only

C-022
DOES GENETIC STATUS MODIFY PULMONARY ARTERIOVENOUS MALFORMATION PHENOTYPES?

A Khalil[1,2,3], B Monod[1,3], M Eyris[3,4], J Cadranel[2,5,6], F Lebrin[2,3], MF Carette[1,3,6]

[1]*AP-HP, HUEP, Tenon Hospital, Radiology department,* [2]*Collège de France, CNRS UMR 7241/INSERM U1050, Early Development and Pathologies Center for Interdisciplinary Research in Biology,* [3]*Competent Center for HHT in Ile de France; Paris- France,* [4]*AP-HP, Ptié Salpétrière Hospital, Molecular Genetic department,* [5]*AP-HP, HUEP, Tenon Hospital, Pneumology department,* [6]*Pierre and Marie Curie University, 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:* Ninety nine consecutive patients with PAVMs identified from a prospective register (March 1993 to January 2012) including all patients referred for PAVMs' vaso-occlusion or evaluated for HHT in Tenon hospital, a recognized Competent Center for HHT in Paris, were included in this study. HHT were selected on Curacao criteria. We analyzed the distribution and the architecture of PAVMs (619) according to findings at multidetector or helical monodetector CT-scan or pulmonary angiography. *Results:* They 76 (49F, 27M; mean age 41.8 yrs) HHT patients and 23 (16F, 7M; mean age 50 yrs) non-HHT patients (18 with negative research for mutation) are included in this study. Of 76 HHT patients, 71 had a genetic test (ENG mutation (n=45), ACVRL1 mutation, (n=17), MADH4 mutation (n=2) and no mutation (n=7)). Eighteen (78%) out of 23 patients had genetic testing results that negative for the two most common genes predisposing to HHT, ENG and ACVRL1. A total of 619 PAVMs were identified. They were more prevalent among HHT patients (means of 7.8/patient for HHT vs 1.2/patient for idiopathic). The prevalence of PAVM was different according to each subgroup of HHT-patients especially the difference between patients with ENG (mean 10.6 per patient) and ACRVL1 (mean 1.6 per patient) mutation. PAVMs were found to be disseminated or diffuse in 13 patients of the HHT group and especially in patients with ENG mutation (10/45: 22%) comparing to no patient with ACRLV1 mutation. Small and tiny PAVMs are more frequent in HHT patients than in non-HHT patients (408/591 versus 5/28: $p<0.001$). Diffuse or disseminated disease was observed in 14 patients, one of them was a non-HHT patient. Isolated complex PAVM are more frequent in non-HHT patients (6/8 patients versus 7/34 patients: $p = 0.006$). Telangiectases (n=19) were found in 10 HHT patients, and none in non-HHT patient. *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.

Session IV: Cellular and molecular involvement in HHT and related pathologies

C-023
ROLE OF MACROPHAGES IN HHT PATHOGENESIS

YH Kim, S Choe, E-J Choi, SP Oh

Department of Physiology and Functional Genomics, College of Medicine, University of Florida, FL, USA

Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant vascular disease affecting about 1 in 5000 people worldwide due to mutations in ENG, ALK1 or SMAD4. Mechanisms underlying AVM formation are still largely unknown, and treatment options for HHT are limited. Here, we investigated the role of macrophages in HHT pathogenesis to develop novel therapeutic options for epistaxis caused by nasal telangietases. Utilizing $ROSA26^{CreER}$ and Alk1-conditional knockout mice, we have previously developed a mouse model of HHT. Tamoxifen treatment on $ROSA26^{CreER}$; $Alk1^{f/2f}$ mice (Alk1-iKO) induces skin AVMs responding to wounds in addition to visceral AVMs. We also established pulmonary endothelial cells (pECs) from $ROSA26^{CreER}$; $Alk1^{2f/2f}$ mice for an in vitro model, in which Alk1 gene deletion can be induced by treatment with 4 hydroxyl-tamoxifen. Microarray and qRT-PCR analysis showed elevated transcript levels of Ccl5 and Cxcl10, chemoattractant cytokines for macrophages, in Alk1-null pECs. CCL5 and CXCL10 protein levels were also increased in the culture media of Alk1-null pECs. Conditional media from Alk1-null pECs enhanced migration properties of macrophages in vitro transwell assay. Consistent with these in vitro findings, a higher number of F4/80-positive macrophages were detected in perivascular regions of skin wounds in Alk1-iKO mice. In order to elucidate the role of macrophages in the development of AVMs, we examined whether Clodro-LIPO mediated macrophage depletion affects de novo AVMs in the Alk1 iKO model. Clodro-LIPO treatment effectively removed F4/80-positive macrophages in the wound areas, and resulted in almost complete prevention of de novo AVMs forming in wounded-skins and ears, indicating that macrophages are necessary for AVM development in this model. In addition, treatment with Met-Rantes, a CCL5 antagonist, significantly reduced wound-induced AVM formation. Taken together, these results suggest that macrophages and the cytokines involved in recruiting macrophages can be novel therapeutic targets for the inhibition of intranasal AVM development in HHT patients.

Non-commercial use only

C-024
CHARACTERIZATION OF A MYELOID SPECIFIC ENDOGLIN KNOCK-OUT MOUSE: THE ROLE OF ENDOGLIN IN THE INNATE IMMUNE RESPONSE

ML Ojeda-Fernandez, L Recio-Poveda, P Lastres, HM Arthur, C Bernabeu, LM Botella

Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), Spain, Centro de Investigaciones Biológicas, Consejo Superior de Investigaciones Científicas (CSIC), Madrid, Spain, Institute of Human Genetics, International Centre for Life, Central Parkway, Newcastle University, UK

Endoglin, a transmembrane protein that acts as an auxiliary receptor for TGF β, is expressed in vascular endothelial cells, smooth muscle cells and different hematopoietic subsets. Endoglin is also upregulated during in vitro activation of cultured human peripheral blood monocytes, and is expressed in tissue-resident macrophages. However, the role of endoglin in macrophages has been poorly studied, and is not well understood. We have evaluated the endoglin levels expressed by murine resident and inflammatory macrophages. Moreover, an endoglin myeloid lineage specific knock-out mouse has been developed to address the involvement of endoglin in the immune response. The KO was obtained in a C57Bl/6 background, by inter-crossing endoglin bifloxed mice (eng2fl/2fl) with a strain expressing Cre recombinase under the control of Lysozyme promoter (LyzCre). Endoglin knock-out mice (eng2fl/2fl LyzCre) are viable, present a normal development, but exhibit an immunodeficient phenotype characterized by recurrent infections caused by opportunistic bacteria and sporadic infections by rotavirus. In vivo assays reveal a higher survival rate of KO mice to a septic shock, suggesting an impaired immune response. Comparative studies show that endoglin expression is related to the levels of TLR2 expression, with a significant decrease of TLR2 levels on the peritoneal macrophages from KO mice compared to control mice. A comparison of the phagocytic function by peritoneal macrophages from KO versus wild type mice, and the possibility of proinflammatory cytokine differential expression between KO and wild type peritoneal macrophages is currently under investigation. Altogether, the data from the KO mice is compatible with an impaired innate immune response, which might be related with the higher infection rates, by opportunistic bacteria, described in a retrospective study of HHT patients (Dupuis-Girod S et al. Clin Infect Dis 2007). Thus, the endoglin-myeloid KO mouse model may be a useful tool to elucidate the endoglin role in macrophages, and would help to throw light on the controversial immune profile of HHT patients discussed in recent years.

C-025
NO LINK BETWEEN CXCR4/SDF-1 ABNORMALITIES ON MONONUCLEAR LEUCOCYTES AND HISTORY OF SEVERE INFECTION IN HHT

A Guilhem[1], S Dupuis-Girod[2], T Vincent[3], P Portales[3], D Cerrutti[1], P Guilpain[1], A Le Quellec[1], S Riviere[1]

[1]*Service de Médecine Interne et maladies multiorganiques, CHU Montpellier, France,* [2]*Service de génétique, Hospices civils de Lyon, France,* [3]*Laboratoire d'immunologie, CHU Montpellier, France*

Background: In hemorrhagic hereditary telangiectasia (HHT), a high rate of infectious has been reported. SDF-1 (a circulating agent), CXCR4 (his related cellular receptor) and CD26 (his inhibitor) form a specific chemotactic pathway involved in cell's trafficking and responsible for two rare immunodeficiency disease. Recently, abnormalities of SDF1/CXCR4 axis have been reported on HHT mononuclear leucocytes that could be relevant to explain the high rate of severe infections observed in HHT. *Main objective:* We hypothesized that the degree of the CXCR4/SDF-1 axis impairment on circulating mononuclear cells is related to the risk of severe infection in HHT. *Patients and method:* From January to October 2012, we prospectively included patients with definite HHT (Curaçao criteria) and controls. Patients were classified into 3 groups matched in age and sex. The first was HHT patients with a severe infectious disease's history (IH), the second, HHT without infectious history (CH) and the third group was 18 healthy controls. A whole blood flow cytometry protocol was tuned to assess the CXCR4, CD26 and endoglin (CD105) mean fluorescence intensity on monocytes, NK cells and T4/T8 lymphocytes together with their activated and naive/memory subsets. Migration test with SDF1 were done for 21 subjects. *Results:* Compare to healthy controls, we observed an under-expression of CXCR4 in HHT patients on T4 lymphocytes (p= 0,006), a T4 lymphopenia (p= 0,002) and an under expression of CD105 on monocytes (p= 0,038). Clear trends were observed towards an over-expression of CXCR4 on monocytes (8,3 versus 3,6 p=0,051). Migration test with SDF1 was normal. However, none of these specificities were significantly different neither between the IH and CH groups nor between endoglin and ALK1 genotypes. *Conclusion*: The level of CXCR4 under-expression on circulating T4 lymphocytes is not linked to the risk of severe infectious events in HHT.

C-026
THE POTENTIAL ROLE OF ENDOGLIN IN REGULATING MYELOID CELLS DURING RESOLUTION OF INFLAMMATION

M Jerkic, M Peter, D Douda, V Sotov, DS Ardelean, N Palaniyar, M Letarte

Molecular Structure & Function Program, and Physiology & Experimental Medicine Program, Hospital for Sick Children; Department of Immunology, and Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Canada

Non-commercial use only

Endoglin, a co-receptor of the TGF-β superfamily, is mostly expressed in endothelial cells but is also present on some hematopoietic and myeloid cells and could therefore act as a modulator of immune responses. We previously demonstrated that Endoglin heterozygous (Eng+/-) mice, subjected to the dextran sulfate sodium model of experimental colitis, showed a similar acute inflammatory response to that of wild type mice. However, Eng+/- mice manifested delayed recovery, marked by persistent gut inflammation and epithelial ulceration, while Eng+/+ mice recovered. Our aim was to assess the contribution of myeloid cells (distribution, number and function) to the prolonged inflammatory response observed in Eng+/- mice. Using flow cytometry on immune cells isolated from the lamina propria, we demonstrated in both groups a shift in distribution from resident gut macrophages to infiltrating monocytes and neutrophils with colitis progression. However, only a slight increase in the overall number of macrophages and neutrophils was observed in Eng+/- versus control mice despite more severe disease. We also assessed the distribution and number of myeloid subsets in the spleen and peripheral blood and found no impairment in recruitment from the bone marrow in Eng+/- versus control mice. Interestingly, we observed lower levels of the myeloid reactive oxygen species generating enzymes, Nox2 and myeloperoxidase, in the colons of colitic Eng+/- relative to Eng+/+ mice. These data suggest a functional defect in subset(s) of myeloid cells in colitic Eng+/- mice that may contribute to impaired resolution of inflammation. We are currently determining by immunostaining and confocal microscopy whether neutrophils and/or macrophages are responsible for the lack of recovery from inflammatory disease in Eng+/- mice. These findings suggest that endoglin expression might be critical for proper function of myeloid cells in the resolution of inflammation.

C-027
THE ENDOGLIN OVEREXPRESSION COMPROMISES THE IMMUNE RESPONSE IN MYELOID CELLS. NOVEL INSIGHTS FOR HEREDITARY HEMORRHAGIC TELANGIECTASIA.

FJ Blanco, ML Ojeda-Fernandez, M Aristorena, LM Botella, C Bernabeu

CIBER de Enfermedades Raras (ISCIII), and Centro de Investigaciones Biológicas (CSIC), Madrid, Spain

Endothelial cells are the main scenario where endoglin has been functionally studied since it is markedly induced during angiogenesis. In addition, endoglin expression is up-regulated also during the monocyte to macrophage differentiation, but little is known about its role in this myeloid context. To investigate the function of endoglin in monocytes, transfectants overexpressing two different endoglin isoforms in the promonocytic human cell line U937 were generated. The differential gene expression fingerprinting of these endoglin transfectants using DNA microarrays (4x44K) and further analysis with Ingenuity™ software showed a clear alteration in the groups "Cellular Movement" and "Hematological System Development and Function". Interestingly, these cellular functions are highly dependent on adhesion molecules, including integrins 1 (CD49a, *ITGA1* gene), L (CD11a, *ITGAL* gene) and 2 (CD18, *ITGB2* gene) and the chemokine receptor CCR2 (CD192, *CCR2* gene), which are down-regulated in endoglin transfectants. Moreover, activin A (INHBA gene), a TGF-β superfamily member involved in macrophage polarization, was distinctly affected in each endoglin transfectant. All these data were confirmed by qRT-PCR, flow cytometry and functional tests. Cell adhesion and transmigration assays confirmed that endoglin overexpression inhibits these processes, suggesting that endoglin plays a critical role in the immune response mediated by monocyte and its differentiation to macrophages. Together, these results provide a new insight for understanding the physiopathology of HHT, where macrophages may play a key role in vascular remodeling.

C-028
ENDOGLIN DEFICIENCY LEADS TO INCREASED ENDOTHELIAL CELL PERMEABILITY

M Jerkic, ZA Liang, M Letarte

Molecular Structure & Function Program, and Department of Immunology, University of Toronto, Toronto, Canada

Endoglin, a component of the TGF-β receptor complex, is critical for endothelial homeostasis. Embryos deficient in endoglin display numerous cardiovascular lesions, including hemorrhage and leaky vasculature, leading to lethality at mid-gestation. Endoglin has been shown to interact with several proteins including integrins, zyxin and VE-Cadherin critically involved in cell adhesion and vascular permeability. Therefore we tested permeability of endothelial cell (EC) lines established from cells isolated from endoglin null (Eng-/-) or normal embryos (Eng+/+) ad days 8-9 of gestation. EC were cultured on Transwell filters and permeability was measured on confluent monolayers using FITC-labelled dextrans (4 and 40 kDa) and the fluorescence recovered in the lower chambers after two hours was estimated. Permeability was markedly increased through the Eng-/- monolayer compared with the Eng+/+ monolayer. Increasing the cell starvation period from 4 to 21 hours did not change the permeability of control cells but increased that of Eng-/- cells by 4-fold, suggesting a more unstable monolayer under stress. To investigate EC integrity and paracellular transmigration, neutrophils were isolated from bone marrow, labelled with calcein AM, and tested in the transwell assay. Neutrophils transmigrated faster through Eng-/- than Eng+/+ EC monolayers, in agreement with potentially impaired cell junctions. To assess the mechanisms responsible for the increased permeability and/or instabilily of Eng null monolayers, we explored the role of RhoA, a small GTPase primarily involved in regulation of endothelial barrier function. Using a high-throughput luminescence-based mammalian interactome mapping assay, we had shown previously that endoglin interacts with several GTPases including RhoA. We now performed RhoGST pulldown assays to estimate RhoA activa-

Non-commercial use only

tion under basal conditions. Our preliminary results reveal that RhoA is constitutively active in Eng-/- cells suggesting that endoglin regulates EC permeability at least partly through RhoA activation. We are currently exploring effects of VEGF and TGF-β1 treatment on RhoA activation and EC permeability. Our findings imply that expression of endoglin in endothelial cells might be critical for their proper barrier function and regulation of leukocyte transmigration.

C-029
ALK1 AND ENDOGLIN REGULATION OF ENDOTHELIAL GAP JUNCTION EXPRESSION

D Phan[1], J-H Kim[1], CCW Hughes[1,2,3]

[1]*Department of Molecular Biology & Biochemistry,* [2]*Department of Biomedical Engineering,* [3]*Edwards Lifesciences Center for Advanced Cardiovascular Technology. University of California Irvine, Irvine CA, USA*

ALK1 is a member of the TGFβ/BMP receptor family and is expressed predominantly by arterial endothelial cells (EC). Endoglin is a TGFβ/BMP co-receptor that is expressed throughout the vascular tree and is up-regulated in angiogenic blood vessels. Mutations in these genes are responsible for Hereditary Hemorrhagic Telangiectasia Type 2 (HHT2) and Type 1 (HHT1), respectively. HHT is characterized by fragile vessels, capillary overgrowth, and arterio-venous malformations (AVMs) in multiple organs, however, despite our growing understanding of the basic signaling pathways downstream of Alk1 and endoglin the precise mechanisms underlying the vascular defects in HHT are not understood. Using an in vitro angiogenesis assay that recapitulates the dependence of vascular sprouting on interactions with stromal and perivascular cells we have investigated these interactions using wild-type EC, or EC lacking Alk1 or endoglin. We identified several gap junction proteins as being targets of Alk1 and endoglin signaling in EC, with connexins 40, 43 and 45 all reduced in arterial EC when Alk1 or Endoglin were knocked down by siRNA. Interestingly, knockdown of Cx40 in EC disrupts in vitro vascular sprouting. As connexins mediate both EC-EC and EC-smooth muscle cell communication, our data suggest that disrupted intercellular communication in the vessel wall may contribute to disease pathology.

C-030
LOSS OF ENDOTHELIAL ENDOGLIN WEAKENS THE ENDOTHELIAL BARRIER TO CANCER CELL TRANSMIGRATION AND LEADS TO INCREASED METASTASES

Z Zhai, RRS Tual-Chalot, HM Arthur

Institute of Genetic Medicine, Centre for Life, Newcastle University, UK

Tumour growth and metastasis depend on the vascularization of tumours by angiogenesis and is regulated by the combined action of several growth factors that are secreted by the growing tumour. Endoglin, an endothelial co-receptor for members of the TGF-β superfamily, has been shown to be important for angiogenesis and may provide a target for anti-cancer therapies. Indeed, antibodies targeting endoglin are currently in clinical trials. However, the effect of targeting endoglin on metastasis has not been investigated in detail. To address the role of endothelial endoglin on tumour growth and metastasis, we used a conditional endoglin knockout mouse model that was generated by combining a floxed endoglin allele with a tamoxifen- inducible vascular specific Cre (Cdh5 (PAC)CreERT2). Angiogenesis was first tested using the matrigel subdermal plug assay and was significantly reduced in endoglin-deficient adult mice compared with tamoxifen treated control mice. Subsequently, angiogenesis and metastasis were investigated using a subdermal lewis lung carcinoma (LLC) model. The growth of the primary tumours was initially reduced, suggesting that targeting endoglin may delay tumour progression at an early stage. However, there was no significant effect of endoglin loss on primary tumour growth at later stages of tumour progression. Furthermore, loss of endothelial endoglin resulted in a significant increase in lung metastases, which was also associated with a reduction in the ability of endothelial cells to restrict cancer cell transmigration both in vivo and in vitro. We are currently investigating possible mechanisms to explain these findings.

C-031
ENDOGLIN EXPRESSION INCREASES THE PRO-ANGIOGENIC POTENTIAL OF TRANSPLANTED CDCS FOLLOWING MYOCARDIAL INFARCTION IN MICE

R Redgrave, B Davison, M Amirrasouli, B Keavney, A Blamire[1], HM Arthur

Institute of Genetic Medicine, Newcastle University, Central Parkway, Newcastle upon Tyne, UK. [1]*Institute of Cellular Medicine, Newcastle Magnetic Resonance Centre, Campus for Ageing and Vitality, Newcastle University, UK*

Cardiosphere derived cells (CDCs) have been shown to promote cardiac repair *in vivo*, however the precise mechanisms involved are not yet understood. Endoglin, a TGFβ co-receptor, is expressed in several progenitor cell types that have been successful in improving cardiac function following injury, including EPCs, MSCs and CDCs. Human mononuclear cells (MNCs) heterozygous for Endoglin promote cardiac repair in a mouse myocardial infarction (MI) model with reduced efficacy relative to wild-type controls. We hypothesise that Endoglin acts as a key marker and functional regulator of the pro-angiogenic properties of cardiac repair cells and the aims of this study were to confirm that CDCs significantly improve cardiac function and augment neovascularisation following MI and to test the effect of Endoglin depletion on this process. Genetically-tagged CDCs were derived from Engfl/fl;Rosa26-CreERT2;CAG-GFP neonatal mice. FACS analysis demonstrated that Endoglin was expressed by the majority of passage 2 cells, whilst the putative stem cell marker, cKit and endothelial marker, CD31

non-commercial use only

were expressed in smaller subpopulations. CDCs were treated with 4-hydroxy-tamoxifen in vitro to knock down Endoglin expression (Eng-KO) using inducible Cre/loxP technology. Acute MI was induced in adult C57Bl/6 mice by permanent ligation of the left anterior descending coronary artery and 106 control or Eng-KO CDCs were immediately delivered via direct intramyocardial injection into the infarct border zone. At 28 days post injury cine cardiac MRI revealed that both control- and Eng-KO CDC recipient groups showed a marked increase in ejection fraction (12.4% and 16.7% respectively (versus PBS-recipient infarcted control animals)) and reduced left ventricular volumes suggesting attenuated adverse left ventricular remodelling. Furthermore, injection of control-CDCs led to an increased angiogenic response at 4 weeks, which was significantly reduced when Eng-KO cells were transplanted. Very few GFP-tagged donor cells could be identified at 4 weeks indicating that the beneficial effects of CDC-transfer were mediated via paracrine mechanisms. Initial data suggests that Endoglin expression is dispensable for CDC-mediated augmentation of cardiac function in injured hearts; however it is essential for stimulating enhanced angiogenesis. Future longer term studies will reveal if this increased Endoglin-dependent pro-angiogenic response will protect against progression to heart failure.

C-032
SHEDDING OF SOLUBLE ENDOGLIN IS REGULATED BY OXYSTEROLS AND IS INVOLVED IN HYPERTENSION

AC Valbuena-Diez[1], FJ Blanco[1], B Oujo[2], C Langa[1], M Gonzalez-Nuñez[2], E Llano[2,3], AM Pendas[3], M Díaz[4], A Castrillo[4], JM Lopez-Novoa[2], C Bernabeu[1]

[1]*Centro de Investigaciones Biológicas, Consejo Superior de Investigaciones Científicas (CSIC), and Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), Madrid, Spain;* [2]*Unidad de Fisiopatología Renal y Cardiovascular, Departamento de Fisiología y Farmacología, Universidad de Salamanca (USAL), Campus Miguel de Unamuno and Instituto de Investigación Biomédica de Salamanca (IBSAL), Salamanca, Spain;* [3]*Centro de Investigación del Cancer (CSIC-USAL), Campus Miguel de Unamuno, Salamanca, Spain;* [4]*Instituto de Investigaciones Biomédicas "Alberto Sols" CSIC-Universidad Autonoma de Madrid and Unidad Asociada de Biomedicina IIBM CSIC-Universidad de Las Palmas de Gran Canaria, Spain*

A soluble form of endoglin (sEng) has been detected in plasma, serum, and urine from patients with different pathologies, including preeclampsia and cancer, but the regulatory mechanisms of sEng release are largely unknown. Ischemia in the placenta is considered as the base of the pathogenesis of preeclampsia, a pregnancy-specific syndrome where sEng is a prognostic marker and plays a pathogenic role. We have investigated the effects of hypoxia and the downstream pathways in the release of sEng. Under hypoxic conditions, the trophoblast-like cell line JAR showed an increase of sEng parallel to an elevated formation of reactive oxygen species (ROS). Because ROS are related with the formation of oxysterols, we assessed the effect of 22-(R)- hydroxycholesterol (22-R), a natural ligand of the liver X receptor (LXR) and the LXR synthetic agonist, T09. Treatment of JAR cells or human placental explants with 22-R or T09 resulted in a clear increase of sEng that was dependent on LXR. These LXR agonists induced an increased MMP-14 expression and activity as well as a significant reduction of its endogenous inhibitor TIMP-3. Also, mice treated with LXR agonists underwent an increase in the plasma sEng levels, concomitant with an increase in blood pressure (AP). Moreover, transgenic mice overexpressing sEng displayed high blood pressure. Finally, administration of an endoglin peptide containing the consensus MMP-14 cleavage site Glycine-Leucine prevented the oxysterol-dependent increase of AP and sEng levels in mice. These studies provide a clue to understand the involvement of the LXR pathway in the sEng release and its contribution to pathogenic role in vascular disorders such as preeclampsia. *Reference:* Valbuena-Diez et al. (2012) *Circulation* 126(22): 2612-2624.

non commercial use only

Session V
Central nervous system involvement and treatment in HHT

C-033
MALFORMATIONS OF CORTICAL DEVELOPMENT AND BRAIN VESSELS IN PATIENTS WITH HEREDITARY HAEMORRHAGIC TELANGIECTASIA

J-F Bergerot[1], S Dupuis-Girod[3,4], Y Berthezene[1], T-H Cho[2,3,5], F Tahon[1], J Honnorat[3,5], H Plauchu[3,4], M Hermier[1,2,3]

[1]*Service de Radiologie & IRM, Hôpital Neurologique et Neurochirurgical Pierre Wertheimer, Hospices Civils de Lyon, Lyon, France,* [2]*CREATIS, UMR CNRS 5220, U1044 INSERM, Lyon, France,* [3]*Université de Lyon, Université Claude-Bernard Lyon-I, Lyon, France,* [4]*Service de Génétique Clinique, Centre de Référence National pour la maladie de Rendu-Osler, Hospices Civils de Lyon, Hôpital Louis Pradel, Lyon, France,* [5]*Service de Neurologie, Hôpital Neurologique et Neurochirurgical P. Wertheimer, Lyon, France*

Background and purpose: Experimental data support the hypothesis that impaired angiogenesis may lead to disorders of cortical development. Impaired angiogenesis is a hallmark of hereditary haemorrhagic telangiectasia (HHT). We observed focal areas of polymicrogyria at magnetic resonance imaging (MRI) in patients with HHT. Polymicrogyria has been reported previously in the setting of other vascular dysplasias, and in a single patient with HHT. We tested the hypothesis that HHT could be associated with malformations of the cerebral cortex. *Methods:* Patients with a definite clinical diagnosis of HHT were retrospectively (n=72) or prospectively (n=90) included. They underwent neurological evaluation, and screening for HHT manifestations and mutations. Screening for any disorder of cortical development was performed using high-resolution MRI. Intracranial vascular anomalies were sought with MR angiography and contrast-enhanced MRI. *Results:* MRI demonstrated malformations of cortical development (MCDs) in 13 out of 162 patients. Areas of polymicrogyria were observed in 12, predominantly located in the perisylvian areas, without specific pattern. One patient had focal cortical dysplasia. MCDs were observed in both HHT types 1 and 2. MRI and MRA further showed that HHT was associated not only with a high rate (22/162 patients) of intracranial vascular malformations at risk of bleeding (i.e. saccular aneurysms, n=9; arteriovenous malformations/telangiectasia,n=18; cavernoma, n=1) but also with a high rate (21/162) of unusual anatomic variants of cerebral arteries, including uncommon branching patterns of middle cerebral arteries (MCA),unusual course or diameter of MCA branches, segmental duplication of insular branches, accessory MCA, basilar artery fenestration, persistent trigeminal artery. 18 patients had developmental venous anomalies. Overall, vascular malformations and variants,although nonspecific, were unusually frequent, and may be the consequence of an impairedangiogenetic process. Polymicrogyria was associated with ipsilateral dysplastic arterial abnormalities in 6 patients, and with developmental venous anomalies in 6. We suggest that MCD may be considered as a potential, nonspecific, additional marker of HHT. MCD should be regarded as a possible aetiology of neurological symptoms in HHT patients. An inappropriate adaptation to tissular hypoxia in HHT may play a role through an impaired imbalance between vascular and/or neural trophic and pro-apoptotic factors during cortical development.

C-034
CEREBRAL ABSCESSES AS A FIRST SYMPTOM OF HHT AMONG DANISH HHT PATIENTS

AD Kjeldsen[1], PM Tørring[2], H Nissen[3], PE Andersen[4]

Odense University Hospital, [1]*Department of Otorhinolaryngolog,* [2]*Department of Clinical Genetics,* [3]*Department of Cardiology,* [4]*Department of Interventional Radiology, Denmark*

Conflicts of interest: none The full manuscript has been submitted for publication Abstract *Background:* It is well know that HHT patients have increased risk of cerebral abscess. Prevalence studies has however not been performed previously. Especially patients with PAVM seems to be at risk. *Objective:* To estimate the risk of CA among HHT patients. Methods: Since 1995 all HHT patients referred to the Danish HHT centre have been offered screening for PAVM and have been clinically evaluated for the presence of neurological symptoms and history of previous CA. *Setting:* Odense University Hospital, HHT centre *Subjects:* All HHT patients included in the Danish HHT data base, between January 1995 and October 2012. *Results:* A total of 337 HHT Patients have been included in the Danish database. Of these 264 were screened for the presence of PAVM. In 117 patients a PAVM was diagnosed, among these we identified 9 patients with a history of CA. The prevalence of CA among HHT patients with PAVM was therefore 7.8 %. The patients with a history of CA were genetically evaluated and seven had ENG mutations, one had an ALK1 mutation and in one case a mutation could not be identified. *Conclusion:* Patients with untreated PAVM have a considerable risk of sustaining cerebral abscesses. A CA may be the first symptom leading to an HHT diagnosis. Patients with unexplained CA should be evaluated for HHT and PAVM.

C-035
MRI AND MRA FOR THE DETECTION OF CAVM IN PATIENTS WITH HHT

A Massmann, U Geisthoff, A Buecker, GK Schneider

Saarland University Medical Center, Homburg/Saar, Germany, Clinics of City Cologne/Holweide, Germany

Purpose: Evaluation of magnetic resonance imaging for CAVM in patients with HHT. *Methods and Materials:* 302 patients (mean age 46; male 127; female 175) with confirmed HHT according to Curacao criteria underwent screening cerebral MRI (cMRI) for the presence of

Non-commercial use only

CAVM 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 definite or questionable CAVM were referred for further non-contrast and contrast-enhanced MRA for evaluation of angioarchitecture of CAVM for possible embolization therapy or surgical treatment. *Results:* MRI revealed 15/302 (5.0%) patients (mean age: 48; male 9; female 6) with possible or definite arteriovenous malformations. 9/15 (male 5; female 4) 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:* In our large patient cohort CAVMs area very rare. For screening purpose a high-resolution MRI without contrast media is suitable to identify clinically relevant CAVMs. Detailed characterization of angioarchitecture is performed by CE-MRA for a complete diagnostic work-up for therapy planning and monitoring.

C-036
MICRO BRAIN VASCULAR MALFORMATIONS ASSOCIATED WITH HEREDITARY HEMORRHAGIC TELANGIECTASIA: ARTERIOVENOUS MALFORMATIONS AND CAPILLARY MALFORMATIONS

T Nishida[1,2,3], K terBrugge[2], T Krings[2], K Henderson[1], RI White Jr.[1]

[1]*Yale HHT Center, Department of Diagnostic Radiology, Yale University School of Medicine, New Haven, CT, USA,* [2]*Department of Medical Imaging, Devision of Neuroradiology, Toronto Western Hospital, University of Toronto, Toronto, ON, Canada,* [3]*Department of Neurosurgery, Osaka University School of Medicine, Suita, Osaka, Japan*

Objective: To demonstrate a spectrum of micro (<10mm) brain vascular malformations in patients with hereditary hemorrhagic telangiectasia (HHT), to propose their subclassification, and to compare their image characteristics on magnetic resonance (MR) and digital subtraction angiography (DSA). *Methods:* Institutional review board approvals were obtained with waiver of informed consent for this retrospective HIPAA-compliant study. From our databanks of 127 patients with HHT and brain vascular malformations collected from two institutions, 36 micro brain vascular malformations in 20 consecutive patients were registered. Their images and patient records were reviewed. Micro brain vascular malformations were categorized into 2 sub-types based on the presence of shunting flow, seen on DSA. Their MR findings were compared, and sensitivity and specificity of MR findings (high signal on time-of-flight[TOF] sequence, flow voids on T1 and T2-weighted images) for "true AVM" were also calculated. *Results:* Thirty-six lesions were categorized into 23 AVMs and 13 Capillary Malformations with the mean (SD) size of 6.0mm (2.1mm) and 4.9mm (1.4mm), respectively. High signal on TOF and flow voids on T1WI were recognized only in true AVMs, though their sensitivities were 44% (4/9) and 29% (6/21), respectively. *Conclusion:* We demonstrated two sub-types of micro brain vascular malformations in patients with HHT. Based on MR characteristics alone they cannot be differentiated. DSA may still be required to correctly diagnose and classify these lesions in patients with HHT. Further clinical correlation will be required to evaluate the significance of this sub-classification.

C-037
COINCIDENTAL AND ACQUIRED NEUROVASCULAR MALFORMATIONS AND SHUNTS ASSOCIATED WITH HHT DISORDER

K terBrugge, T Nishida, T Krings

University of Toronto, Toronto, Canada; University of Osaka, Osaka, Japan

Among 42 patients with known HHT disorder managed at the Toronto Western Hospital because of possible HHT involvement of the central nervous system (CNS)there were 6 patients which showed associated vascular malformations and shunts other then the known CNS phenotypes of HHT disorder. One of these had a Vein of Galen Malformation , one a proleferative angiopathy and 2 patients had capillary telangiectasias. In addition there were 2 HHT patients with AVS of the spinal cord and brain that following curative treatment of their condition with surgery and embolization developed de novo dural arterio-venous shunts. The incidence of these associated vascular disorders appears to be much higher then the know incidence in the general population. This may have an impact on the screening and follow up of HHT patients investigated and actively managed for their CNS involvement.

C-038
A COMPARISON OF HEMORRHAGE AND NONHEMORRHAGE IN PATIENTS WITH CCM1 COMMON HISPANIC MUTATION

L Morrison[1,2], B Hart[3], B Baca[1], Y Khan[1], J Nelson[4], H Choquet[4], A Akers[5], H Kim[4]

Departments of Neurology[1], Pediatrics[2], Radiology[3] at the University of New Mexico, Albuquerque, NM, Center for Cerebrovascular Research, Department of Anesthesiology and Perioperative Care, University of California at San Francisco, CA, Angioma Alliance, Durham, NC, USA

Objective: Brain vascular malformations are characterized by intracranial hemorrhagic and nonhemorrhagic neurological disability. *Methods:* We evaluated 197 patients six years of age and older with CCM1 common Hispanic mutation (CCM1-CHM) at the University of New Mexico as part of the BVMC NINDS grant. There were 65% women, and mean age was 38.7±19.8 years.

non commercial use only

The mean number of lesions on 3T MRI with counted on SWI was 59.3±113.0. Subjects were divided into nonhemorrhagic (N) and hemorrhagic (H) groups. *Results:* Seizures (29% in N and 56% in H, p-value <0.001) and headaches (52% in N and 68% in H, p-value 0.044) were more common in the H group. Of the comorbidities, renal disorders were higher in the H group (6% in the N group and 19% in the H group, p-value 0.009). Lab values including Hg A1C, and lipid panels did not differ, however there was a trend toward high sensitivity C-reactive protein to be above normal (>=3) in the N group with logistic regression (OR: 0.50, 95% CI: 0.22, 1.11; p=0.088). Modified Rankin scores were higher in the H group. Total lesion numbers (53.6±100.6 in N group and 71.6±135.9 in the H group) showed a trend toward being increased in the H group. *Conclusions:* CCM1-CHM patients with hemorrhage have a higher risk of neurological disability including seizures, headaches and neurological impairment on the modified Rankin score. There were no significant differences in laboratory markers or comorbidities including hypertension, hyperlipidemias, and diabetes with the exceptions of obesity (higher in the N group) and renal disorders (higher in H group). A trend toward higher risk of hemorrhage was found in patients with higher overall lesion counts and a trend toward nonhemorrhage with elevated CRP.

Session VI
Molecular diagnostics, markers and epidemiology for HHT

C-039
MIR-205 IS A NOVEL BIOMARKER FOR HEREDITARY HEMORRHAGIC TELANGIECTASIA WITH ANTIANGIOGENIC FUNCTION

SP Tabruyn[1], S Hansen[1], ML Ojeda-Fernandez[2], R Zarrabeitia[3], L Recio-Poveda[2], N Bovy[1], C Bernabeu, JA Martial[1], LM Botella[2], I Struman[1]

[1]*Unit of Molecular Biology and Genetic Engineering, GIGA, University of Liège, Sart-Tilman, B-4000 Liège, Belgium,* [2]*Centro de Investigaciones Biológicas (CIB), Consejo Superior de Investigaciones Científicas (CSIC) and Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), Madrid, Spain, 3Department of Internal Medicine. Hospital de Sierrallana, Torrelavega, Spain*

Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant disorder characterized by arteriovenous malformations and hemorrhage. This vascular disease results mainly from mutations in 2 genes involved in the TGF-β pathway (ENG and ACVRL1) that are exclusively expressed by endothelial cells. The present study identified miR-27a and miR-205 as two plasma circulating miRNAs differentially expressed in HHT patients. The plasma level of miR-27a is increased while plasma level of miR-205 is reduced in both HHT1 and HHT2 patients compared to healthy controls. The role of miR-205 in endothelial cells was further investigated. Our data indicate that miR-205 expression displaces the TGF-β balance towards the anti-angiogenic side by targeting Smad1 and Smad4. In line, expression of miR-205 in endothelial cells reduces proliferation, migration and tube formation. This study not only suggests that detection of circulating miRNA (miR-27a and miR-205) could help for the screening of HHT patients but also provides a functional link between the deregulated expression of miR-205 and the HHT phenotype.

C-040
CLINICAL UTILITY OF A NEXT GENERATION SEQUENCING PANEL IN THE DIAGNOSIS OF HEREDITARY HEMORRHAGIC TELANGIECTASIA (HHT) AND OTHER SYNDROMES FEATURING VASCULAR MALFORMATIONS

W Wooderchak-Donahue[1], B O'Fallon[1], T Lewis[1], J McDonald[2], J Stocks[1], P Plant[1], DA Stevenson[3], JF Grimmer[4], P Bayrak-Toydemir[1,2]

[1]*ARUP Institute for Clinical and Experimental Pathology, Salt Lake City, UT,* [2]*Department of Pathology, University of Utah, Salt Lake City, UT, Department of Medicine,* [3]*Division of Medical Genetics, Department of Pediatrics, University of Utah,* [4]*Division of Otolaryngology, Department of Surgery, University of Utah*

non commercial use only

Vascular malformations are localized structural defects of the vasculature named for the type of vessel affected such as venous malformations (VM) and capillary malformations (CM) or a combination of two different vessels such as in arteriovenous malformations (AVMs). Although most vascular malformations are sporadic, syndromic and inherited forms exist. Inherited disorders featuring vascular malformations such as hereditary hemorrhagic telangiectasia (HHT) and RASA1-related disorders often have overlapping phenotypes and can be difficult to distinguish clinically. HHT, the most common inherited vascular malformations disorder with an incidence of 1 in 10,000 individuals, is a multigenic autosomal dominant disorder caused by mutations in three transforming growth factor beta (TGF-β) signaling pathway genes (ENG, ACVRL1, and SMAD4). Because of the genetic complexity of HHT and the phenotypic overlap of other disorders featuring vascular malformations, we developed a custom designed next-generation sequencing (NGS) panel assay using SureSelect hybridization capture to rapidly identify mutations in 10 vascular malformation-causative genes (ENG, ACVRL1, SMAD4, RASA1, PTEN, TIE2/TEK, GLMN, KRIT1/CCM1, CCM2, and CCM3). Unlike traditional molecular approaches such as Sanger sequencing, this NGS assay is more cost-effective and eliminates repeated or non-essential medical evaluations because the molecular diagnosis can be obtained rapidly and used effectively to guide patient care. Here, we present the validation of the vascular malformations clinical NGS panel assay and its complementary comparative genomic hybridization (CGH)-array assay used to detect the presence of large deletions or duplications in the same genes. The clinical sensitivity of this new vascular malformations panel assay will be discussed.

C-041
MULTIPLE DELETERIOUS MUTATIONS IN ANGIOGENESIS-RELATED GENES GENERATE SYMPTOMS INDISTINGUISHABLE FROM HEREDITARY HEMORRHAGIC TELAGIECTASIA (HHT)

B O'Fallon, W Wooderchak-Donahue, A Wilson, J McDonald, P Bayrak-Toydemir

ARUP Institute for Clinical and Experimental Pathology, ARUP Labs, Salt Lake City, UT, USA

While some 80% of individuals with hereditary hemorrhagic telangiectasia (HHT) have a causative mutation in the ENG, ACVRL1, or SMAD4 genes, the genetic etiology remains poorly understood in the remaining individuals. Identifying genetic factors responsible for HHT development in these individuals has proven challenging in part due to the variable and age-dependent presentation of the phenotype. In this study we examine full exome sequences from 42 unrelated individuals diagnosed with three- or four-criteria HHT and without causative mutations in ENG, ACVRL1, or SMAD4. We demonstrate that our sample group is significantly enriched for multiple deleterious mutations in angiogenesis-related genes when compared to control data obtained from the 1000 Genomes project and the Complete Genomics diversity panel. Our detection method controls for the presence of false positive variant calls in the samples, and the enrichment finding is robust to the algorithm and threshold used to predict deleteriousness. Among all variants identified, the eight most significantly enriched exist in five genes, and each of these five genes interacts strongly with VEGF, an important regulator of angiogenesis. In addition, we demonstrate that the severity of epistaxis is significantly higher in individuals with greater numbers of deleterious mutations. Together, our results indicate that a collection of deleterious mutations in genes influencing angiogenesis and vascular development, in particular those interacting with VEGF, may be sufficient to generate symptoms indistinguishable from classical HHT.

C-042
COMBINED GENETIC, IN-SILICO AND FUNCTIONAL TOOLS FOR INTERPRETATION OF THE PATHOGENIC SIGNIFICANCE OF ACVRL1 MISSENSE MUTATIONS

S Giraud[1], C Vercherat[2], C Auboiroux[1], S Bailly[3], G Lesca[1], JY Scoazec[2], A Calender[1]

[1]Hospices Civils de Lyon, Service de Génétique, Hôpital E. Herriot, Lyon, France, [2]INSERM 1052, UMR CNRS 5286, Université Lyon 1, Faculté de médecine Laennec, Lyon, France, [3]INSERM U1036, Université Joseph Fournier, CEA Grenoble, France

Introduction: Hereditary Hemorrhagic Telangiectasia (HHT) is a genetic disorder of the blood vessels, due to mutations of ENG, ACVRL1 and SMAD4 genes. Mutations of the ACVRL1 gene coding for the ALK1 (Activin receptor-Like Kinase 1) protein are responsible for the HHT2 form. ALK1 is a protein that functions as a receptor inserted through the membrane of endothelial cells; its ligand is BMP9 (Bone Morphogenetic protein 9). In 2010 Ricard & al described functional analysis of the BMP9 response of ALK1 mutants as a diagnostic tool for novel mutations. Since ten years, our laboratory has been implicated in HHT genetic testing and identified several new missense mutations. Assessing pathogenicity of mutations is critical to propose genetic testing and clinical follow-up of carriers in families. *AIMS:* the aim of the study was to evaluate 36 ACVRL1 missense mutations for which pathogenic significance has not been previously documented. *Method:* when DNA of several relatives was available, we studied the cosegragation of the missense variants with the phenotype. To assess the potential impact of the mutations we used in-silico prediction tools (Alamut software) for aminoacidsubstitutions. In addition, we generated ALK1 mutants and tested their consequences with a Smad1/5 reporter gene in response to BMP9. ALK1 mutant constructs were transfected in mouse 3T3 fibroblast cells that do not express endogenous ALK1 and tested for ALK1 activity, using the Smad1-responsive transcriptional reporter, BRE4-luciferase. We measured the basal activity and the activity in response to BMP9. *Results:* cosegregation analysis could be established for nine missense variants. Functional analysis revealed an absence of response to BMP9 for 29 variants while normal response was found for 7 variants including 5 patients that carried another mutant of ENG or ACVRL1. In silico and functional analy-

non-commercial use only

ses were discordant for a minority of variants. *Conclusions:* combined genetic and functional studies allowed us to assess a pathogenic role for 29/36 missense ACVRL1 mutations; it was not possible to conclude for the effect of 2 missense. Five were probably polymorphisms.

C-043
ESTABLISHMENT OF AN IN VITRO FUNCTIONAL TEST TO SCREEN NOVEL ENDOGLIN MUTATIONS FROM HHT1 PATIENTS

K Lamribet, S Giraud[1], C Mallet, JJ Feige, S Bailly, E Tillet

INSERM U1036, Université Joseph Fourier, CEA Grenoble, France, [1]Service de Génétique Moléculaire et Clinique, Hôpital Edouard Herriot, Lyon, France

Hereditary haemorrhagic telangiectasia (HHT) is an autosomal dominant genetically inheritable vascular dysplasia caused by mutations in genes encoding either endoglin (ENG; HHT1), or activin receptor-like kinase-1 (ALK1; HHT2). We have previously described a cellular assay using the BMP9-induced BRE (BMP Response Element) that can be used as a diagnostic tool for ALK1 mutations in HHT2. Here we tested whether we could use a similar approach to study the functional significance of mutations found in the co-receptor endoglin. We first set-up experimental conditions, where the addition of WT endoglin enhanced the ALK1 response to low doses of BMP9 using the BRE-luciferase reporter. We next generated, by site directed-mutagenesis, 32 missense ENG mutations that have been identified in Lyon (28 were new variants). We found that 16 of these mutants showed no defects in endoglin expression and translocation to the cell surface, nor in their capacity to enhance ALK1 response to BMP9, thus suggesting that these variants represent polymorphism of endoglin. Five mutants could not be detected at the cell surface and are retained intracellularly as shown by flow cytometry and immunofluorescence and therefore did not respond to BMP9. Interestingly, one mutant was correctly exported to the cell surface but has lost its ability to bind BMP9. The other mutants were expressed at the cell surface but displayed only a partial response to BMP9 and further work will be necessary to understand the underlying mechanisms of these mutants. These data demonstrate that different mechanisms are involved in mutant endoglin's loss of function and enabled us to identify amino acids important for membranous expression or BMP9 binding. Altogether, our work demonstrates that we have set-up a cellular assay that can be can be used as a diagnostic tool by geneticists confronted with novel or conflicting ENG mutations discriminating pathogenic versus polymorphic mutations.

C-044
THE PREVALENCE OF HEREDITARY HAEMORRHAGIC TELANGIECTASIA IN THE UK AND ASSOCIATIONS WITH SEX, REGION OF RESIDENCE AND SOCIOECONOMIC STATUS: A POPULATION-BASED STUDY

JW Donaldson[1], TM McKeever[1], IP Hall[2], RB Hubbard[1], AW Fogarty[1]

[1]*Division of Epidemiology and Public Health, University of Nottingham, UK,* [2]*Division of Therapeutics and Molecular Medicine, University of Nottingham, UK*

Objective: Most prevalence studies of Hereditary Haemorrhagic Telangiectasia (HHT) do not consider the impact of demographics (such as sex, socioeconomic status and region of residence) as risk factors for a diagnosis of HHT. We examined the prevalence of a diagnosis of HHT in the United Kingdom and its association these demographic factors in order to understand more about what influences the presentation of this disease. *Methods:* We used a large computerised general practice research database (The Health Improvement Network - THIN) covering 5% of the United Kingdom population to calculate prevalence estimates for the disease stratified by age, sex, socioeconomic status and geographical location. Socioeconomic status was determined using the Townsend score and region of residence grouped by UK health authority. *Results:* The point prevalence for HHT in 2010 was 1.06 per 10,000 person years (or 1 in 9400) [95% confidence interval (CI) 0.95-1.17]. The diagnosed prevalence of HHT was significantly higher in females compared to males [adjusted prevalence rate ratio 1.53, 95% CI 1.24-1.88] and in those from the most affluent socioeconomic group [adjusted prevalence rate ratio 1.74, 95% CI 1.14-2.64] (Table1). The adjusted prevalence rate ratio varied between different regions of the country [most prevalent area compared to least prevalent 1.86, 95% CI 1.61-2.15]. *Conclusion:* HHT is much more common in the United Kingdom than previous estimates suggest. It is more frequently diagnosed in females compared to males which may represent a true biological difference or alternatively reflect their differing rates of access to primary care services. There is a significant variation in the prevalence of diagnosis between different socioeconomic groups and geographical regions across the UK that requires further investigation.

Table 1. Crude prevalence rates and prevalence rate ratios of HHT derived from Poisson regression modelling using the THIN dataset in 2010
*Adjusted for sex, age group, Townsend score and health authority
†p-trend across age categories

	Crude Prevalence rates (95% CI) per 10,000 person-years	Crude prevalence rate ratios (95% CI)	Mutually adjusted prevalence rate ratios (95% CI)*
Sex			
Male	0.84 (0.70-0.98)	1.00	1.00
Female	1.28 (1.11-1.44)	1.56 (1.25-1.95)	1.53 (1.24-1.88) P=0.0001
Age group (years)			
<15 years	0.61 (1.15-1.77)	1.00	1.00
15-50 years	0.84 (0.71-0.98)	1.39 (0.88-2.19)	1.39 (0.96-2.02)
>50 years	1.58 (1.35-1.81)	2.62 (1.69-4.07)	2.53 (1.76-3.63) p<0.0001 p=0.29†
Townsend Score			
1 (Least deprived)	1.31 (1.07-1.55)	1.93 (1.29-2.89)	1.74 (1.14-2.64)
2	1.05 (0.81-1.29)	1.55 (1.701-2.38)	1.36 (0.88-2.11)
3	1.10 (0.85-1.35)	1.62 (1.03-2.55)	1.50 (0.97-2.31)
4	0.87 (0.63-1.10)	1.28 (0.79-2.08)	1.23 (0.78-1.94)
5 (Most deprived)	0.68 (0.43-0.93)	1.00	1.00
9 (Missing values)	1.34 (0.77-1.91)	1.98 (1.12-3.52)	2.20 (1.25-3.88) P=0.026

Non-commercial use only

C-045
URINARY ANGIOGENESIS BIOMARKERS IN STURGE-WEBER SYNDROME: UPDATE IN A LONGITUDINAL STUDY

CD Bachur[1], KE Lanier[1], AS Curatolo[2], SM Connors[2], MA Moses[2,3*], AM Comi[1,4,5*]

[*]Drs. Moses and Comi contributed equally to this abstract, [1]Department of Neurology and Developmental Medicine, Kennedy Krieger Institute, Baltimore, MD, [2]Vascular Biology Program, Boston Children's Hospital, Boston, MA, [3]Department of Surgery, Harvard Medical School, Boston, MA, [4]Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, [5]Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, MD, [5]Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Sturge-Weber Syndrome (SWS) is sporadic disorder consisting of a capillary-venous vascular malformation of the brain, skin and eye which results in neurologic deterioration with seizures, strokes and cognitive impairment. We have an ongoing longitudinal study of urine biomarkers funded through the Brain Vascular Malformation Consortium to study the association of bFGF, VEGF, and MMPs in the urine of subjects with SWS and their clinical and neurologic status. MMP2, MMP9 and abnormally high levels of bFGF are more likely to be detected in the urine of SWS subjects compared to controls. MMP levels are positively correlated with neurologic and disease severity while higher bFGF levels in the urine are associated with better neurologic status over time. These results suggest that MMP-2 and MMP-9 levels may be useful in assessing SWS progression as well as indicating which patients might benefit from more aggressive treatment, while bFGF levels may be useful in judging the efficacy of neurologic treatment in SWS.

Session VII: Antiangiogenic therapies in HHT and outcomes

C-046
ELLIPSE STUDY: A PHASE-1 STUDY EVALUATING THE TOLERANCE OF BEVACIZUMAB NASAL SPRAY TO TREAT EPISTAXIS IN HEREDITARY HAEMORRHAGIC TELANGIECTASIA

AE Fargeton[1], F Faure[2], A Ambrun[2], E Decullier[3], F Chapuis[3], F Disant[2], G Samson[3], C Rioufol[4,7], V Schwiertz[4], Y Donazzolo[5], G Paintaud[6], S Dupuis-Girod[1].

[1]Hospices Civils de Lyon, Hôpital Louis Pradel, Service de Génétique et centre de référence sur la maladie de Rendu-Osler, Bron, [2]Hospices Civils de Lyon, Hôpital E. Herriot, Service d'ORL, Lyon, [3]Hospices Civils de Lyon, pôle IMER, Unité de Recherche Clinique, Lyon, [4]Hospices Civils de Lyon, Centre Hospitalier Lyon Sud, Unité de Pharmacie Clinique Oncologique, Pierre-Bénite, [5]Eurofins-Optimed, Centre Hospitalier Lyon Sud, Pierre-Bénite, [6]CHRU de Tours, Laboratoire de Pharmacologie-Toxicologie, Tours, , [7]EMR 3738 CTO Ciblage Thérapeutique en Oncologie, UFR Lyon Sud, Pierre-Bénite, France

Background: Epistaxis is the most visible manifestation of HHT, with spontaneous, frequent and severe episodes justifying continuous martial treatment and sometimes multiple red blood cell transfusions. Management of this symptom has no standard and local treatments are often aggressive, their efficacy is variable and has not been proven. Antiangiogenic drugs, such as bevacizumab, are a new treatment strategy. Its systemic administration in patients with HHT improves liver damage-related symptoms and epistaxis. To limit the systemic adverse effects of bevacizumab and to ease administration, a local administration seems suitable. Clinical case reports recently showed the benefits of bevacizumab nasal spray in these patients. However no phase I study had been performed. *Objectives:* Primary objective was to evaluate the tolerance of increasing doses of bevacizumab administered as a nasal spray in patients with HHT-related epistaxis. Secondary objectives were to study bevacizumab bioavailability and efficacy against epistaxis when given as nasal spray. *Methodology:* This phase-1, randomized, double-blind, placebo-controlled, monocentric study was carried out sequentially (dose escalation) on 5 groups of 8 patients. Each group was made up of 6 verum and 2 placebos. Five increasing doses of bevacizumab nasal spray (25mg/mL) were evaluated: 12.5 mg, 25 mg, 50 mg, 75 mg and 100 mg. Each test dose was a single dose. To escalate to a higher dose level, eight patients of each dose level should have completed 14 days of follow-up with no dose-limiting toxicity. At each dose level a safety assessment was carried out by a scientific committee. If needed, some dose levels could be duplicated. *Statistical analysis:* Baseline characteristics will be described. Number of patients, treatment received and adverse

non commercial use only

events will be listed for each dose level. Efficacy will be assessed by comparing average time monthly epistaxis, hemoglobin, serum ferritin and number of transfusion before treatment and after treatment using paired tests. Pharmacokinetics will be studied by compartmental and non-compartmental modelling. *Results:* A total of 40 patients were included between October 2011 and October 2012. Bevacizumab nasal spray was well tolerated in all patients. No dose limiting toxicity was observed. Trial Registration: ClinicalTrials.gov Identifier #NCT01507480

C-047
BEVACIZUMAB IN HHT: A RETROSPECTIVE STUDY OF 24 PATIENTS

S Riviere[1], A Guilhem[1], A-C Simon[2], P Duffau[3], MF Carette[4], B Gilbert-Dussardier[5], O Bletry[6], J-R Harle[7], P Kaminsky[8], B Lorcerie[9], N Lerolle[10], C Lavigne[11], JC Saurin[12], A Lequellec[1], S Dupuis-Girod[13]

[1]*Service de medecine interne et maladies multiorganiques, CHU Montpellier,* [2]*Service de pneumologie, CHU Poitiers,* [3]*Service de medecine interne, CHU Bordeaux,* [4]*Service de radiologie, Hopital Tenon, APHP,* [5]*Service de génétique, CHU Poitiers,* [6]*Service de medecine interne, Hopital Foch, Suresnes,* [7]*Service de medecine interne, AP hopitaux de Marseille,* [8]*Service de medecine interne, CHU Nancy,* [9]*Service de medecine interne, CHU Dijon,* [10]*Service de medecine interne, CHU Bicêtre,* [11]*Service de medecine interne, CHU Angers,* [12]*Service de gastro-enterologie, hospices civils de Lyon,* [13]*Service de genetique, hospices civils de Lyon, France*

Bevacizumab (BVZ), a vascular endothelial growth factor inhibitor, has been reported helpful to reduce high cardiac output (HCO), epistaxis and gastrointestinal bleeding in HHT patients. The aim of our study was to report cases of HHT patients, not included in a BVZ trial, but treated by BVZ in our HHT network. *Method:* HHT patients who were treated by BVZ until 12/2012 were retrospectively included. We fullfiled a standardized questionnaire for indication, dosage, efficacy and adverse events (AE) of BVZ. Standard therapy was definied by 5 mg/kg each 15 days for 6 times. Physicians classified improvement in 3 groups: major, moderate or none. *Results:* 24 medical records were analyzed. All patients had definite HHT according to Curaçao criteria.Thirteen patients were treated for HCO related to hepatic involvement with a sex ratio of 3/10, a mean age of 68.8 years. Standard therapy was applied to 8 patients. Improvement was observed in 53.8% of patients (7/13). Mean duration of improvement was 7 months. Four patients had no change and 3 died. Recorded AE were ischemic cholangitis (1), polyarthritis (1), infection (1) and gout (1). One patient was treated with BVZ each 21 days for 45 months with a good tolerance and efficacy. Six patients were treated for severe gastrointestinal bleeding (sex ratio 3/6, mean age 71.5 years). Standard therapy was applied to 5 patients. Major improvement concerned 66.6 % of these patients (4/6). Mean duration of improvement was 6 months. One patient had 18 infusions for 12 months with good tolerance and efficacy. AE were: abdominal pain (1), confusion (1) and trophic disorder (1).Eleven patients were treated for severe epistaxis (sex ratio 2/11, mean age 69.2). Standard therapy was applied to 9 patients. Improvement was observed in 72.7% of patients (8/11). Mean duration of improvement was 9.4 months. Two patients had a second course because of relapse. AE were: neutropenia and paresthesia. *Conclusion:* BVZ can be hepful to manage severe bleedings and HCO in HHT. However efficacy disappeared after a few months. A maintenance therapy could be an option but has to be evaluated. Otherwise, some patients are not improved by BVZ.

C-048
OUTCOMES OF BEVACIZUMAB PLUS LASER IN THE TREATMENT OF HHT RELATED EPISTAXIS

AB Whitehouse, I Ortega, JR Gossage

Georgia Regents University, Augusta, GA, USA

Objective: To determine the effectiveness of combined intranasal submucosal injection of bevacizumab and KTP laser for the treatment of epistaxis in hereditary hemorrhagic telangiectasia (HHT). *Methods:* Eighteen patients were interviewed after intranasal injection of bevacizumab (50 mg in each side) combined with KTP laser of telangiectasias. The data collected included frequency and duration of nosebleeds, nosebleed severity, medical therapy prior to treatment, presence of anemia, red blood cell transfusion, hemoglobin level, iron infusions, emergency department (ER) visits, epistaxis severity score (ESS), and duration of benefit (≥50% subjective improvement in epistaxis). Data were collected prospectively for recently treated patients and retrospectively for distantly treated patients. Data were collected for the 3 month period prior to intervention (baseline), and at 1, 3, 6, and 12 months after intervention. Data were analyzed by paired t test.*Results:* Data were available for 18 patients at 1 and 3 months, 17 patients at 6 months, and 9 patients at 12 months. The ESS improved from 5.8 at baseline to 2.6 at 1 month ($p<0.05$), 3.3 at 3 months ($p<0.05$), 4.4 at 6 months ($p<0.05$), and 4.8 at 12 months (p=NS). In the 3 months prior to intervention, 28% of patients required RBC transfusion, compared to 28, 47, and 44% at 3, 6, and 12 months respectively. Thirty-three percent had ER visits for epistaxis during the baseline period compared to 6 and 13% at 3 and 6 months, respectively. During the baseline period 50% of patients had at least one blood transfusions, iron infusion, or ER visit, compared with 28, 47, and 67% at 3, 6, and 12 months respectively. No side effects were reported from the use of bevacizumab. *Conclusions:* The combination of intranasal bevacizumab submucosal injection and KTP laser may be an effective alternative for the treatment of HHT related epistaxis. It significantly reduced the ESS during the first 6 months after treatment, reduced ER visits at 3 and 6 months, and reduced the composite endpoint of blood transfusions, iron infusions, or ER visits at 3 months.

Non-commercial use only

C-049
EFFICACY AND SAFETY OF THALIDOMIDE FOR TREATMENT OF CHRONIC SEVERE GI BLEEDING IN HEREDITARY HEMORRHAGIC TELANGIECTASIA

G Manfredi[1], E Buscarini[1], F De Grazia[1], G Lupinacci[1], F Menozzi[1], G Brambilla[1], C Londoni[1], S Alicante[1], S Crinò[1], A Zambelli[1], P Gazzaniga[2], S Gandolfi[3], PA Forner[4], C Danesino[5], C Olivieri[5], C Canzonieri[5], F Ornati[5], M Grosso[6], G Pongiglione[7], E Boccardi[8], on behalf of HHT-NET

[1]*Gastroenterology Dept,* [2]*Cardiology Dept,* [3]*Radiology Dept,* [4]*ENT Dept, Maggiore Hospital, Crema;* [5]*Dipartimento di Medicina Molecolare, Genetica medica, University of Pavia;* [6]*Radiology Dept, Ospedale S Croce, Cuneo;* [7]*Paediatric Cardiology Dept, Ospedale Bambin Gesù, Roma;* [8]*Interventional Neuroradiology Unit, Niguarda Hospital, Milan, Italy*

Background and study aims: Preliminary data shows the effectiveness of thalidomide in treating GI bleeding from teleangiectases. This treatment protocol is aimed to evaluate thalidomide efficacy and safety in the treatment of chronic severe GI bleeding from teleangiectases in HHT. *Methods:* The treatment protocol, approved by our Institutional Review Board, dealt with HHT patients with severe chronic anaemia from GI bleeding, requiring more than 1 blood unit transfusion/month and refractory to standard therapies and endoscopic treatment. Pregnant females, pre-menopausal females and sexually active males rejecting contraceptive measures were excluded. The initial thalidomide dosage of 50 mg/day was to be increased to 100 and 200 mg/day after 4 and 6 weeks, respectively, in case of partial/no response. If treatment was effective and well tolerated a maintenance dose of 50 mg/day was scheduled after initial 24 weeks. Blood cell count, transfusion requirement, serum iron/ferritin, liver and kidney function tests, ECG, echocardiography, neurological evaluation were performed before, during and after treatment end. Thalidomide efficacy was judged upon NCCN classification of anemia severity (grades 1 to 4), and blood transfusion requirement in PRBC units/month. Complete response to treatment was defined as a mean Hb > 10 g/dl with no blood transfusion requirement. Partial response to treatment was defined as grade shift of anemia severity from 4 to 3 or 2 and/or a >50% reduction of blood transfusion requirement. Adverse event type, severity and outcome were recorded. *Results:* Nine patients (age 59-77, 7 m) have been so far treated, for a mean treatment duration of 35.4 months (range 3-57). Response to treatment was complete in 1 case, partial in 7, absent in 1. Average hemoglobin value in the 6 months preceding treatment was 6.8 gr/dl (range 4.2-7.8); during treatment it was 9.0 gr/dl (range 6.2-12.2); mean blood transfusion requirement/pt/month before treatment was 6.3 and during treatment was 1.9. Thalidomide was stopped in 4 patients to month 3, 4, 23 and 48 for adverse events, which were respectively arterial thromboembolism, severe limb edema, stroke, peripheral neuropathy. Conclusions: Thalidomide treatment seems a reasonable option for HHT patients with severe chronic GI bleeding; the high rate of adverse events is to be weighed.

C-050
BENEFICIAL EFFECTS OF ANTI-VEGF THERAPY IN THE PULMONARY VASCULATURE OF ENDOGLIN AND ALK1 HETEROZYGOUS MICE

DS Ardelean, M Jerkic, M Peter, M Letarte

Molecular Structure and Function, Hospital for Sick Children and Department of Immunology, University of Toronto, Toronto, ON, Canada

HHT is caused by mutations in endoglin (ENG) and ALK1 genes that lead to the generation of arteriovenous malformations (AVMs) in multiple organs. Our laboratory established many years ago that haploinsufficiency was the underlying mechanism of disease. The current view is that expression of a single allele of ENG or ALK1 causes endothelial dysfunction that predisposes to formation of vascular lesions upon exposure to a second hit, such as an increased in blood flow or an angiogenic stimulus. We have been studying heterozygous (Eng+/- and Alk1+/-) mice to characterize potential alterations in their vascular endothelium and changes in their angiogenic profile relative to control mice. As demonstrated previously, these mouse models of HHT develop with age an abnormal lung phenotype, characterized by extensive vascular remodeling leading to increased resistance and right ventricular hypertrophy (RVH). To determine whether these changes were associated with dysregulated angiogenesis and whether anti-VEGF treatment was beneficial, we assessed peripheral microvascular density, RVH and several angiogenic factors in Eng+/- and Alk1+/- mice treated with an antibody to mouse VEGF or vehicle and compared to control mice. Administring 4 i.p. injections (5mg/kg; 7 days apart) of the G6-31 monoclonal antibody to 15 week-old mice led to high levels of circulating antibody-bound VEGF (5-6 days after last injection) and to reduced VEGF levels in lungs of Eng+/- and Alk1+/- mice. The treatment paradoxically increased the number of peripheral lung vessels and attenuated RVH. We showed that the basal pulmonary levels of the angiostatic factor TSP-1 were 4-fold higher in Eng+/- than control mice and were normalized by anti-VEGF treatment. In Alk1+/- mice, angiopoietin-2 rather than TSP-1 was increased under basal conditions and normalized by treatment. Our findings suggest that the mechanisms responsible for the abnormal pulmonary vascular phenotype may differ between Eng+/- and Alk1+/- mice, perhaps explaining some of the disease heterogeneity. Our data also indicate that anti-VEGF can reverse the angiogenic/angiostatic imbalance present in lungs of Eng and Alk1 heterozygous mice.

C-051
ANTI-ANGIOGENIC THERAPY IN HHT: EFFECTS ON HEPATIC VASCULATURE IN MOUSE MODELS

DS Ardelean[1], M Jerkic[1], M Yin[2], RS Kerbe[2], FS Foster[2], M Letarte[1]

[1]*Molecular Structure and Function Program, Hospital for Sick Children and Department of Immunology, University of Toronto;* [2]*Biological Sciences, Sunnybrook Health Sciences Center, and Department of Medical Biophysics, University of Toronto, Toronto, ON, Canada.*

Non-commercial use only

Mice expressing a single copy of endoglin or ALK1 (Eng+/- or Alk1 +/-) serve as models of HHT1 and HHT2 respectively. We analyzed the hepatic vasculature of mutant and wild type (WT) mice and assessed the effects of anti-VEGF treatment with the G6-31 monoclonal antibody (from Genentech). Fifteen week-old mice received 4 i.p. injections (5 mg/kg; 7 days apart) of antibody or vehicle. Five to six days after the last injection, high circulating levels of antibody-bound VEGF were observed and hepatic hemodynamic parameters were assessed using contrast-enhanced micro-ultrasound (CE-US) imaging prior to sacrifice. Tissues were collected and microvascular density was measured on histological slides by quantifying CD31+ microvessels (<20 microns in diameter) using an automated computerized method. Liver microvascular density was similar in mutant and WT samples, but showed a significant decrease following anti-VEGF treatment in Eng+/-, Alk1 +/- and WT mice, suggesting a non-specific effect of this antibody on hepatic microvessel density. To assess hepatic microvascular hemodynamics in vivo, blood flow rate and tissue blood volume were evaluated using CE-US. Mutant and WT mice showed similar hepatic microvascular perfusion, suggesting no apparent defect in the liver of mutant mice. The anti-VEGF treatment significantly reduced hepatic blood flow and blood volume in Eng+/- mice, when compared to vehicle treatment or to WT mice; it had no significant effect in Alk1+/- mice, indicating that the liver vasculature of Eng+/- mice might be more affected by anti-VEGF treatment. The expression of angiogenic factors was also tested by Western blot in total liver extracts of WT and mutant mice and after anti-VEGF treatment. No difference was found between control and mutant mice (for CD31, VEGFR2, VEGF and Angiopoietin 2) but a significant reduction in CD31 and VEGFR2 was observed only in Eng+/- mice after anti-VEGF treatment. Our findings indicate that G6-31 antibody has a strong hepatic anti-microvascular effect in Eng+/- mice, beyond that observed in Alk1+/- and WT mice. This suggests that HHT and particularly HHT1 patients treated with anti-angiogenic drugs should be monitored by ultrasound to assess the non-specific effects of therapy on hepatic microvasculature.

C-052
VEGF ANTIBODY CAN PREVENT AND NORMALIZE ARTERIOVENOUS MALFORMATIONS IN AN ANIMAL MODEL FOR HEREDITARY HEMORRHAGIC TELANGIECTASIA 2

C Han[1], S Choe[1], YH Kim[1], YJ Lee[2], SP Oh[2]

[1]*Department of Physiology and Functional Genomics, College of Medicine, University of Florida, Gainesville, FL 32610;* [2]*World Class University program, Lee Gil Ya Cancer and Diabetes Institute, Gachon University of Medicine and Science, Incheon, Republic of Korea*

Arteriovenous malformation (AVM) refers to a vascular anomaly where arteries and veins are directly connected through a complex, tangled web of abnormal AV fistulae without a normal capillary network. Hereditary hemorrhagic telangiectasia (HHT) types 1 and 2 arise from heterozygous mutations in endoglin (ENG) and activin receptor-like kinase 1 (ALK1), respectively. Epistaxis is the most common symptom of HHT, mostly due to rupture of telangiectases formed in the nasal mucosa. Recently, a growing number of case reports demonstrated Bevacizumab (VEGF-neutralizing antibody) is effective as a therapy for epistaxis. In these studies, the final output was epistaxis index, i.e., frequency, duration, and amount of nose bleeding. There has been no direct demonstration how the VEGF blockade can reduce the epistaxis index. Previously, we have shown that secondary factors such as wounding in addition to the genetic ablation are required for Alk1-deficient vessels to develop skin AVMs. Here we present evidence that AVMs establish from nascent arteries and veins rather than from remodeling of a preexistent capillary network in the wound-induced skin AVM model. We also show that VEGF can mimic the wound effect on skin AVM formation, and VEGF neutralizing antibody can prevent skin AVM formation and ameliorate internal bleeding in Alk1-deficient adult mice. Based on the window chamber images, we can roughly divide the processes of AVM formation in three phases; initiation, maturation, and matenance. With topical applications at different phases during AVM development, we demonstrate that the VEGF blockade not only prevents the formation of AVM but also normalizes established AVM lesions.

C-053
TOPICAL TIMOLOL FOR TREATMENT OF EPISTAXIS IN HEREDITARY HEMORRHAGIC TELANGIECTASIA ASSOCIATED WITH BRADYCARDIA - A LOOK AT CYP2D6

N Epperla, MH Brilliant, HJ Vidaillet

Marshfield Clinic; Marshfield Clinic Research Foundation, Marshfield, WI, USA

Introduction. 1. Topical timolol can be used to treat epistaxis in hereditary hemorrhagic telangiectasia (HHT) with a rapid and persistent response. 2. Pharmacogenetic variants of CYP2D6 may increase the possibility of adverse effects. *Case Presentation*. A 59 y/o male with a history of HHT was hospitalized for symptomatic bradycardia (low heart rate/lightheadedness). He had started 0.5% Timoptic maleate drops (intranasal) three weeks prior for prevention of epistaxis with excellent response. His family history is significant for pacemaker in his father at age 59, sudden death in paternal grandfather in his 30's and paternal aunt at age 66. Timoptic drops were suspended. Extensive work up including CBC, CMP and TSH; CT scan head; 2D-Echo and tilt table test were all normal. In view of symptomatic bradycardia and significant cardiac history in the family he was referred for genetic studies to evaluate cardiac risk factors and CYP2D6 activity. Genetic testing revealed that he is an intermediate metabolizer of CYP2D6 (*1/*4) explaining the reason for bradycardia after beta blocker usage. He did not have further episodes of bradycardia after discontinuation of topical timolol. *Discussion*. Timolol is a non-

non-commercial use only

selective b-blocker, which is largely eliminated by the liver and it is primarily metabolized by CYP2D6, with a minor contribution from CYP2C19. Ocular administration of timolol has been associated with systemic adverse effects (e.g. bradycardia), since beta blockade is observed even at low plasma concentrations of timolol. The change in the heart rate is the most striking effect of the systematically absorbed fraction of ophthalmic timolol, with 0.5% aqueous formulations presenting larger effects than 0.1% hydrogel formulations. In addition, application of timolol eye drops intranasally gave rise to higher plasma concentrations and greater b-blockade in poor metabolizers than in extensive metabolizers. *Conclusion*. Topical timolol is effective in treatment of epistaxis in HHT. Pharmacogenetic variants of CYP2D6 as well as drug–drug interactions involving CYP2D6 may increase the possibility of adverse effects and should be kept in mind when prescribing pharmacotherapy to HHT patients for treatment of epistaxis with timolol products.

C-054
PROPRANOLOL AS ANTIANGIOGENIC CANDIDATE FOR THE THERAPY OF HEREDITARY HEMORRHAGIC TELANGIECTASIA

V Albiñana[1], L Recio-Poveda[1], R Zarrabeitia[2], C Bernabeu[1], LM Botella[1]

[1]*Centro de Investigaciones Biológicas (CIB), Consejo Superior de Investigaciones Científicas (CSIC) and Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), Madrid, Spain;* [2]*Hospital Sierrallana, Centro de Referencia HHT, Torrelavega, Cantabria, Spain*

The β-blocker Propranolol, originally designed for cardiological indications (angina, cardiac arrhythmias and high blood pressure), is nowadays, considered the most efficient drug for the treatment in Infantile Haemangiomas (IH), a vascular tumour that affects 5-10% of all infants. However, its potential therapeutic benefits in other vascular anomalies remain to be explored. In the present work we have assessed the impact of Propranolol in endothelial cell cultures to test if this drug could be used in the vascular disease Hereditary Hemorrhagic Telangiectasia (HHT). This rare disease is the result of abnormal angiogenesis with epistaxis, mucocutaneous and gastrointestinal telangiectases, as well as arteriovenous malformations in several organs, as clinical manifestations. Mutations in Endoglin (ENG) and ACVLR1 (ALK1) genes, lead to HHT1 and HHT2, respectively. Endoglin and ALK1 are involved in the TGF-β1 signalling pathway and play a critical role for theproper development of the blood vessels. As HHT is due to a deregulation of key angiogenic factors, inhibitors of angiogenesis have been used to normalize the nasal vasculature eliminating epistaxis derived from telangiectases. Thus, the antiangiogenic properties of Propranolol were tested in endothelial cells. The drug was able to decrease cellular migration and tube formation, concomitantly with reduced RNA and protein levels of ENG and ALK1. Moreover, the drug showed apoptotic effects which could explain cell death in IH. Interestingly, Propranolol showed some profibrinolytic activity, decreasing PAI-1 levels. These results suggest that local administration of Propranolol in the nose mucosa to control epistaxis might be a potential therapeutic approach in HHT.

non commercial use only

Session VIII
Anemia, and venothrombous complications in HHT

C-055
DEVELOPING A TOOL TO ASSESS DIETARY IRON INTAKE IN A UK POPULATION WITH HHT

HE Finnamore[1,3,4], J Le Couteur[5], M Hickson[2], K Whelan[3], CL Shovlin[1,6]

[1]*NHLI Cardiovascular Sciences, and* [2]*Investigative Medicine, Imperial College London, UK;* [3]*Diabetes and Nutritional Sciences Division, King's College London, School of Medicine, UK;* [4]*University of Liverpool Medical School, UK;* [5]*Nutrition and Dietetics, and* [6]*Respiratory Medicine, Imperial College Healthcare NHS Trust, London UK*

Background. Individuals with hereditary haemorrhagic telangiectasia (HHT) are at greater risk of iron deficiency anaemia, due to blood loss through epistaxis and gastrointestinal bleeding. Manipulation of diet is a non-pharmacological method for optimising iron intake and absorption. In our pilot study (Finnamore et al, submitted) we demonstrated that even in well-informed British HHT patients with moderate to severe epistaxis, dietary iron intake was still not sufficiently optimised. *Objective*: To devise a screening tool to assess iron intake, for use in cohorts with HHT. *Methods:* 26 British HHT sufferers completed 7 day weighed food diaries which were analysed using the dietary analysis software Diet Plan. The top 20 foods contributing to dietary iron intake in this UK population were established using Microsoft Excel, and in preliminary analyses, the 5 items contributing the highest daily iron intake per individual (in grams), scored on a 5 to 1 scale which was summed for statistical analyses. *Results:* Contrary to expectations, the highest mean daily intake of iron was recorded not from meats, fish or vegetables, but from fortified breakfast cereals and breads. The highest ranked iron-containing items across all participants were breads (86 points), followed by breakfast cereals (80), meat (51), vegetables (16), and pastries/biscuits (15 points). Within breads, white bread scores (42 points) were similar to those for wholemeal, granary, and brown bread combined (44 points). Within cereals, shredded wheat (22 points) ranked highest, followed by weetabix (13 points), then muesli (9 points). Amongst meat and fish, beef was ranked most highly (28 points), and potatoes (18 points) exceeded all other vegetables and soups combined. Further analyses compiling absolute rankings spanning all food items ingested by patients is in progress. *Conclusions:* Assessment of dietary iron intake can provide an opportunity to direct nutritional education in order to aid dietary replacement of iron lost through epistaxis. HHT sufferers may be unaware that fortified staple foods provide such opportunities to increase dietary iron ingestion. This is important because optimising iron intake through diet should reduce symptoms of iron deficiency and anaemia, and for many individuals, reduce the need for often poorly tolerated oral iron supplementation.

C-056
LEFT ATRIAL APPENDAGE CLOSURE FOR STROKE PREVENTION IN PATIENTS WITH HEREDITARY HEMORRHAGIC TELANGIECTASIA AND ATRIAL FIBRILLATION

V MM Vorselaars, S Velthuis, MJ Swaans, JJ Mager, R Snijder, B JW M Rensing, L VA Boersma, MC Post

Department of cardiology, Department of pulmonology, St. Antonius Hospital, Nieuwegein, the Netherlands

Purpose. Oral anticoagulation (OAC) is contraindicated in patients with hereditary hemorrhagic telangiectasia (HHT), because of the associated severe bleedings. In atrial fibrillation (AF) most thromboembolic complications arise from the left atrial appendage (LAA). Therefore percutaneous transcatheter LAA closure might be a good strategy for patients with HHT. We report our experience with LAA closure in HHT. *Methods*. Patients were eligible for the procedure if they had HHT and AF with an indication for OAC (CHA2DS2-VASc score ≥ 2). The Watchman LAA Occlusion Device was placed under general anaesthesia, using biplane fluoroscopy and (3D) transoesophageal echocardiography guidance. If LAA occlusion was achieved, oral anticoagulation was discontinued and aspirin was started. *Results*. Percutaneous LAA closure was performed in six HHT patients (50% male, mean age 70.4 ± 5.1 years) without any major complication. The median CHA2DS2-VASc score was 4 (range 2-5). At six months follow-up, no OAC was used and aspirin was discontinued in three patients. No thromboembolic event occurred. After 12 months a transient ischemic attack occurred in one patient (without a pulmonary shunt, but with an incomplete LAA closure and no aspirin). *Conclusions*. Percutaneous closure of the LAA provides an alternative strategy to chronic oral anticoagulation therapy for stroke prevention in HHT patients with high thromboembolic risk AF.

C-057
LOW SERUM IRON LEVELS ARE ASSOCIATED WITH PULMONARY EMBOLI/DEEP VENOUS THROMBOSES (VENOUS THROMBOEMBOLI) IN HEREDITARY HAEMORRHAGIC TELANGIECTASIA

JA Livesey, RA Manning, JH Meek, JE Jackson, E Kulinskaya, MA Laffan, CL Shovlin

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

Background. Venous thromboemboli (VTE) represent particular hazards for individuals with hereditary hemorrhagic telangiectasia, because paradoxical emboli through pulmonary arteriovenous malformations can cause stroke, and anticoagulant treatment regimes may exacerbate HHT-related haemorrhage. Previously, we demonstrated that, as in the general population, long term VTE risk was predicted by elevated plasma levels of coagulation Factor VIII at least 6 months from any acute illness, infection or thrombosis.[1] *Methods*. Associations between log-transformed factor VIII and patient-specific variables were assessed in stepwise multiple regression

non commercial use only

analyses on data from 609 patients with hereditary haemorrhagic telangiectasia, recruited prospectively in two separate series at a single centre. Age-specific incidence rates of radiologically-proven VTE were calculated, and logistic regression analyses performed to identify factors associated with clinical VTE in HHT patients. *Results*. The overall VTE incidence rate was 138.3 per 100,000 patient years. Many occurred in patients currently or recently hospitalised with long term inflammatory/immobility states, particularly following a pulmonary AVM-induced brain abscess, but age-standardised incidence rates for community-restricted VTEs (87.5 per 100,000) were also high compared to rates for hospitalised patients from the general population. In each series, there was an inverse association between factor VIII and serum iron that persisted after adjustment for age, inflammation and/or von Willebrand Factor. Iron response elements within untranslated regions of factor VIII transcripts provide potential mechanisms for the association. Low serum iron levels were also associated with VTE: The age-adjusted odds ratio of 0.91 (95% confidence interval 0.86, 0.97) per 1ᵘmol/L increase in serum iron implied a 2.5-fold increase in VTE risk for a serum iron of 6ᵘmol/L compared to mid-normal range (17ᵘmol/L). The association appeared to depend upon factor VIII, as once adjusted for factor VIII, the association between VTE and iron was no longer evident. *Conclusions*. In HHT, low serum iron levels attributed to inadequate replacement of haemorrhagic iron losses are associated with elevated plasma levels of coagulation factor VIII and venous thromboemboli.

References:
1. Shovlin, Sulaiman, Govani, Jackson, Begbie. Thromb Haemost. 2007;98:1031-9.
2. Livesey, Manning, Meek, Jackson, Kulinskaya, Laffan, Shovlin. Thorax. 2012;67:328-33.

C-058
IRON DEFICIENCY IS EXPLAINED BY UNDER-REPLACEMENT OF IRON LOSSES IN HEREDITARY HAEMORRHAGIC TELANGIECTASIA

HE Finnamore, J Le Couteur, M Hickson, B Busbridge, K Whelan, CL Shovlin

Imperial College Healthcare NHS Trust, London UK; Imperial College London, UK, Diabetes and Nutritional Sciences Division, King's College London, UK; University of Liverpool Medical School, UK

Background: Iron deficiency is a global health burden that carries additional risks in the setting of hereditary haemorrhagic telangiectasia (HHT), when it is usually attributed to iron losses from nasal and gastrointestinal bleeding. Nevertheless, it was important to formally establish whether inappropriately high hepcidin levels were likely to limit iron absorption from the gastrointestinal tract, as in patients with a related condition, pulmonary arterial hypertension. *Methods:* A formal comparison of dietary intake and haemorrhagic losses was performed in 50 individuals with HHT. Power calculations indicated that 48 recruits would provide 90% power to detect clinically significant differences in haemoglobin and iron between participants stratified into two iron intake groups, using a two group t test with a 0.05 two sided significance level. Blood tests performed for validation therefore included haemoglobin, iron and other haematinic values, supplemented by measurements of bioactive hepcidin peptide by competitive radioimmunoassay. *Results:* Forty-three of the 50 (86%) study participants met their recommended dietary intake (UK, recommended nutrient intake (RNI); US, recommended dietary allowance (RDA). There was no relationship between RDA, RNI, age, or gender with haematinic or iron indices. Median haemorrhagic losses were 277 (IQR 21, 1398) mls/month, allowing calculation of the extra iron increment required by each individual to compensate. Only ten of the 50 (20%) met this adjusted iron requirement. The adjusted requirement was a powerful predictor of lower haemoglobin (p=0.009), mean corpuscular haemoglobin concentration (p<0.001), log-transformed serum iron (p=0.009) and higher log-transformed red cell distribution width (p<0.001). Iron tablet use blunted associations with haematinic indices, but once adjusted for iron tablet use, reciprocal relationships with haemoglobin and serum iron persisted. Under-replacement of iron losses was confirmed as the cause of iron deficiency in HHT, because hepcidin levels were appropriate for iron stores: Hepcidin levels were lower in patients with serum iron and ferritin levels in the lowest tertile, and as in the general population, ferritin explained 60% of the hepcidin variance (p<0.001). *Conclusions*. Iron handling is normal in HHT, and iron deficiency explained by under-replacement of haemorrhagic losses, particularly nosebleeds.

C-059
IRON TABLET PROFILING

C Gilson, M Busbridge, CL Shovlin

Imperial College Healthcare NHS Trust, London UK; Imperial College London, UK

Background: Iron tablets are are commonly prescribed for individuals with hereditary haemorrhagic telangiectasia (HHT), to prevent or treat iron deficiency anaemia. Potential variability in absorption, and side effect profiles are under-explored in current HHT practice. *Methods:* Pharmacokinetics of iron tablet absorption was examined at six time points over 48 hs in 12 healthy volunteers, randomly assigned to receive ferrous sulphate 200mg od for 48hs, or no agent. Unbiased questions on iron tablet tolerance were included in a wider survey of health and treatments for people with and without HHT. *Results:* All twelve healthy volunteers had normal iron indices at baseline. For the control group, all serum iron values remained in the normal ranges (8.1-27.5[median 16.0] ᵘmol/L). Serum iron levels were higher in the six healthy volunteers taking ferrous sulphate (range 11.2-49.3 [median 24.3] ᵘmol/L). By two-way ANOVA, correcting for matching, iron treatment explained 23% of the variance in iron levels over 24hs (p<0.0001), and by linear regression, higher increments in serum iron were associated with higher increments in serum ferritin after 48hs (coefficient 0.21 (0.002, 0.41), p=0.048). In the online survey, barely half of the 568 users of iron tablets repor-

non-commercial use only

ted that iron tablets were always or sometimes fine to take (280/521 HHT patients (53.7% [95% confidence intervals 50.0, 58%]), 28/47 healthy controls (59.6% [95%CI 45.0, 74.1]), p=0.44). Very high proportions reported constipation (218/568, 38.3% [34.3, 42.4%]); nausea (131/568, 23.1% [19.6, 26.6%]) and diarrhea (60/568, 10.6% [8.0, 13.1%]), with no difference between the healthy controls and HHT patients. Once adjusted for indices of HHT hemorrhage, persistent anemia was reported three times as frequently by HHT patients reporting diarrhoea, and almost four times more frequently if iron tablets needed to be stopped. *Conclusions:* As little as two ferrous sulphate tablets are sufficient to modify iron stores in healthy volunteers, but responses are highly variable. Poor tolerance of iron tablets is associated with persistent anemia in patients with HHT.

The authors thank the Wellcome Trust-McMichael Clinical Research Facility, and the HHT Survey Research Team.

C-060
THE TOLERANCE OF ANTIPLATELET AND ANTICOAGULANT AGENTS IN HEREDITARY HAEMORRHAGIC TELANGIECTASIA

HL Devlin, AE Hosman, CL Shovlin

Imperial College London UK; Imperial College Healthcare NHS Trust, London, UK; Medical Schools of Imperial College London UK (HLD), Barts and the London SMD, UK (HLD),and the Academic Medical Center, University of Amsterdam, the Netherlands

Background: Hereditary haemorrhagic telangiectasia (HHT) leads to haemorrhage because of vascular telangiectasia and arteriovenous malformations (AVMs). HHT patients also have thrombotic pathologies including venous thromboemboli and ischaemic stroke, that would normally be treated with anticoagulant or antiplatelet agents. There has been little evidence to guide clinicians and patients in the use of these agents in HHT. *Methods:* To capture experiences in an unbiased manner, relevant questions were incorporated into a wider ethically-approved survey. Participants with and without HHT were recruited from a specialist UK service, and online following advertisement by the HHT Foundation International. At the time of data download, 1302 individuals had responded, including 973 with a diagnosis of HHT supported by sufficient diagnostic criteria elsewhere in the questionnaire. *Results:* Three-quarters of HHT participants (700/973, 71.9%) stated they had never used antiplatelets or anticoagulants. For 381/973 (54.4%), this was because they had been advised by a doctor not to use, due to their diagnosis of HHT, AVMs, or existing haemorrhagic state. For deceased relatives with myocardial infarctions, equal numbers of respondents reported that the HHT diagnosis led to withholding of treatment, contributing to their relative's death, as reported the use of treatments leading to haemorrhages that worsened outcome. High proportions of the 273 participants using antiplatelets/anticoagulants reported worsening of nosebleeds. Surprisingly, however nearly half of all HHT-affected individuals who used antiplatelet or anticoagulant therapy reported no change (40.4%, 153/379) in their nosebleeds. More non-nosebleed hemorrhagic events were reported by anticoagulant users (29/147; 19.7%) than by antiplatelet users (20/228; 8.8%), p= 0.0027, Fisher's exact test). Nevertheless, no change in nosebleeds was reported by 46.2% (43/93) of heparin users, or 38.2% (21/55) of warfarin users. *Conclusions:* These data indicate unexplained and wide variation in tolerance of anticoagulants and anti-platelet therapies in HHT patients. We suggest that this supports their use, with caution, in HHT patients where there is a strong indication for use.

We thank the HHT Foundation International for advertising, and many survey respondents.
Devlin, Hosman, and Shovlin. N Engl J Med 2013

C-061
ANEMIA IS AN IMPORTANT CLINICAL PROBLEM IN HHT

M Montifar[1], RS Kasthuri[2], H Kim[3], WL Young[4], ME Faughnan[1] and the HHT BVMC Investigator Group

[1]*Division of Respirology, St. Michael's Hospital, University of Toronto, Cananda;* [2]*Department of Medicine, University of North Carolina at Chapel Hill, USA;* [3]*Department of Epidemiology and Biostatistics, University of California at San Francisco, USA;* [4]*Department of Neurology, University of California at San Francisco, USA*

Chronic bleeding is frequently reported in HHT and resultant anemia is a recognized clinical problem, though this has not been rigorously studied. Our aim was to describe the prevalence, severity and determinants of anemia in HHT. *Methods:* We collected data from the first 525 HHT patients recruited to the BVMC HHT Project including age, sex, HHT gene mutation, history of epistaxis, GI bleeding, anemia and transfusion. We performed univariate analyses and logistic regression to identify independent predictors of anemia. *Results:* Of 525 patients, 334 (64%) were female. Mean age at recruitment was 47 years. Of these, 242 (46%) reported history of anemia. On univariate analysis, history of anemia was associated with older age at recruitment (54 vs. 40 years, p<0.01), female sex (p=0.046), history of epistaxis (p<0.01), history of GI bleeding (p<0.01) and negatively correlated with endoglin mutation. On multivariate analysis, history of anemia remained significantly associated with age at recruitment (OR 1.05, p<0.001), history of epistaxis (OR 3.60, p0.01), history of GI bleeding (OR 13.69, p<0.001) and endoglin mutation (OR 0.55, p0.02). Mean age of onset of GI bleeding was not different between the groups. Onset of epistaxis was later in patients with history of anemia (15 vs. 11 years, p<0.01). Anemia was more frequent in women (49% vs 40%), where it was diagnosed at an earlier age (34 vs 43 years, p0.001). Age of onset of epistaxis and age of onset of GI bleeding were not significantly different between genders. In the anemia group, 121/242 (50%) received blood transfusion. *Conclusions:* Anemia is a frequent complication of HHT, often requiring treatment with blood transfusions. History of anemia in HHT is associated with history of epistaxis

Non-commercial use only

and GI bleeding, and was negatively associated with the presence of endoglin mutation. Anemia was associated with older age at recruitment and more prevalent in women, where it was diagnosed at earlier age. There was no significant gender difference in the age of onset of epistaxis or GI bleeding, suggesting that the earlier age at anemia diagnosis in women represents non-HHT related causes.

Session IX
Pulmonary involvement: PAVMs and pulmonary hypertension in HHT

C-062
PULMONARY SHUNT GRADING ON TRANSTHORACIC CONTRAST ECHOCARDIOGRAPHY PREDICTS THE INDICATION FOR TRANSCATHETER EMBOLOTHERAPY OF PULMONARY ARTERIOVENOUS MALFORMATIONS

S Velthuis[1], E Buscarini[1], MWF Van Gent[1], P Gazzaniga[3], G Manfredi[2], C Danesino[4], CJJ Westermann[5], R Snijder[5], JJ Mager[5], MC Post[1]

[1]*St Antonius Hospital, Department of Cardiology, Nieuwegein, Netherlands,* [2]*Maggiore Hospital of Crema, Crema, Italy,* [3]*Maggiore Hospital of Crema, Department of Cardiovascular, Crema, Italy,* [4]*University of Pavia, Department of Genetics and Microbiology, Pavia, Italy,* [5]*St Antonius Hospital, Department of Pulmonology, Nieuwegein, the Netherlands*

Background: Pulmonary arteriovenous malformations (PAVMs) are associated with severe neurological complications in patients with hereditary haemorrhagic telangiectasia (HHT). Screening for PAVMs is performed with transthoracic contrast echocardiography (TTCE) and confirmed with chest high-resolution computed tomography (HRCT) to evaluate the opportunity for transcatheter embolotherapy. *Purpose:* We determined whether pulmonary shunt grading on TTCE predicts the indication for transcatheter embolotherapy of PAVMs. *Methods:* A total of 1020 consecutive persons (mean age 44.4±15.5 years, 58% female), referred for HHT screening between 2004 and 2011 at two specialized HHT clinics, were prospectively included and underwent both TTCE and chest HRCT. A quantitative three-point grading scale was used to classify the pulmonary shunt on TTCE (grade 0, no microbubbles; 1, <30 microbubbles; 2, 30-100 microbubbles; 3, >100 microbubbles). Transcatheter embolotherapy was performed in all PAVMs judged large enough for endovascular closure based on chest HRCT. *Results:* TTCE documented a pulmonary shunt in 547 persons (53.6%). The positive predictive value of a pulmonary shunt grade 1, 2 or 3 on TTCE for the presence of PAVMs on chest HRCT was 12%, 45% and 93% respectively. Based on chest HRCT, transcatheter embolotherapy was performed in 39 (26%) and 127 (78%) patients with a pulmonary shunt grade 2 or 3 on TTCE respectively, while none of the 473 and 231 patients with respectively a pulmonary shunt grade 0 or 1 had PAVMs large enough for transcatheter embolotherapy. *Conclusions*: Pulmonary shunt grading on TTCE predicts the indication for transcatheter embolotherapy of PAVMs. Additional chest HRCT should be withheld in patients with a pulmonary shunt grade 1, since these shunts are too small for transcatheter embolotherapy.

non commercial use only

C-063
GRADE OF PULMONARY RIGHT-TO-LEFT SHUNT ON CONTRAST ECHOCARDIOGRAPHY AND CEREBRAL COMPLICATIONS; A STRIKING ASSOCIATION

S Velthuis[1], E Buscarini[2], M WF van Gent[1], P Gazzaniga[3], G Manfredi[2], C Danesino[4], WJ Schonewille[5], CJJ Westermann[6], R Snijder[6], JJ Mager[6], MC Post[1]

Department of Cardiology[1], Neurology[5] and Pulmonology[6], St. Antonius Hospital, Nieuwegein, The Netherlands. Department of Gastroenterology[2], Cardiology[3], Maggiore Hospital, Crema, Italy. Genetic Institute[4], University of Pavia, Pavia, Italy

Background: A pulmonary right-to-left shunt (RLS) carries the risk of cerebral paradoxical embolization and severe neurological complications. Recognising patients at risk is important to facilitate appropriate management strategies, but a direct relation between pulmonary shunt size and risk of complications remains controversial. *Purpose:* This study evaluated the potential relation between pulmonary shunt size on transthoracic contrast echocardiography (TTCE) and prevalence of cerebral manifestations in persons screened for hereditary haemorrhagic telangiectasia (HHT). *Methods:* We conducted a two-center, cross-sectional study of all consecutive persons screened for HHT between 2004 and 2011. Pulmonary shunt grading was performed according to contrast opacification of the left ventricle on TTCE (grade 0, no microbubbles; 1, <30 microbubbles; 2, 30-100 microbubbles; 3, >100 microbubbles). Cerebral manifestations were defined as ischemic stroke, transient ischemic attack or brain abscess, diagnosed by a neurologist and confirmed by appropriate imaging techniques. *Results:* A pulmonary RLS was present in 530 out of 1038 patients (51.1%, mean age 44.3±15.6 years, 58.6% women). The presence of a cerebral manifestation (n=51) differed significantly between pulmonary shunt grades on TTCE; 1.4%, 0.4%, 6.5% and 20.9% for grade 0, 1, 2 and 3 respectively. Pulmonary shunt grade 1 was not associated with an increased prevalence of cerebral manifestations (OR 0.44, 95%CI 0.05-4.13, p=0.47), while pulmonary shunt grade 2 (OR 4.78, 95%CI 1.14-20.0, p=0.03) and grade 3 (OR 10.4, 95%CI 2.4-45.3, p=0.002) were both independent predictors for the prevalence of a cerebral ischemic event or brain abscess. *Conclusion:* Pulmonary RLS grade on TTCE is strongly associated with the prevalence of cerebral complications in patients screened for HHT.

C-064
DIAGNOSIS AND TREATMENT OF THORACIC COMPLICATIONS OF PULMONARY ARTERIOVENOUS MALFORMATIONS: RUPTURE OR THROMBOSIS. 22 CASES.

M El Hajjam, S Binsse, J Sellier, T Chinet, J Roume, A Ozanne, I Bourgault, G Lesur, J-H Blondel, A Cordier, S Blivet, C Fagnou, M Bonay, C Karam, A Nicod-Tran, S Chagnon, M Eyries, L Gouya, P Lacombe

Consultation Pluridisciplinaire Maladie de Rendu-Osler, Hôpital Ambroise Paré, Boulogne. Hôpital du Kremlin-Bicêtre. HHT Center, Paris, France

Purpose: To describe clinical presentation, imaging findings and therapeutic options in patients with rupture or thrombosis of pulmonary arteriovenous malformations (PAVMs). *Materials and methods:* During a 12-year period, all consecutive patients with rupture or thrombosis of PAVMs were recorded from our database and reviewed retrospectively. The following criteria were analyzed: age at presentation, clinical presentation, imaging findings using multidetector computed tomography (MDCT), and type of mutation. The clinical follow-up and technique of embolization were also analyzed. *Results:* A total of 970 patients were evaluated at our HHT center. 425 patients had PAVMs. From our database, 11 (5 men and 6 women) were identified to have a spontaneous rupture of PAVM, eight adults and 3 children (mean age 51 years). Ten of them were already diagnosed with HHT. In 5 patients, Endogline mutation was identified. In 3 patients ALK1 mutation was identified. 6 patients presented hemoptysis related to pulmonary hemorrhage and 5 had hemothorax. Ten patients were successfully treated by prompt embolization. During the same period, 11 cases (8 women, 3 men) of PAVMs thrombosis were encountered with a mean age of 35 years. Eight of them were already diagnosed with HHT. 6 neurological complications were found: 5 cases of cerebral ischemic events and 1 case of cerebral abscess. Two patients had pulmonary hypertension, and two had polycythaemia. Ten patients were treated by transcatheter embolization and 1 by surgery. *Conclusion:* Rupture and thrombosis of PAVM are rare events (5%), which must be suspected in case of hemoptysis or hemothorax. Prompt embolization is safe and effective. Thrombosis of PAVMs is associated with high rate of neurological complications. It represents a local source of systemic embolisms which detection is improved by enhanced MDCT performed in case of systemic embolism. *Keywords:* HHT, hemoptysis, hemothorax, PAVM, thrombosis.

C-065
OXYGEN DELIVERY AND CONSUMPTION IS PRESERVED IN HYPOXAEMIC PATIENTS WITH PULMONARY ARTERIOVENOUS MALFORMATIONS AND HEREDITARY HAEMORRHAGIC TELANGIECTASIA

V Santhirapala, LSGE Howard, K Murphy, B Mukherjee, M Busbridge, HC Tighe, JMB Hughes, JE Jackson, CL Shovlin

Imperial College London School of Medicine (VS, Imperial College London, UK and Imperial College Healthcare NHS Trust, London, UK

Background: Low blood oxygen concentrations (hypoxaemia), are assumed to cause dyspnea (breathlessness). Hypoxaemia usually results from alveolar hypoxia due to reduced inspired oxygen concentrations or respiratory pathologies including asthma, chronic obstructive pulmonary disease (COPD) and pulmonary fibrosis. Alveolar

Non-commercial use only

hypoxia stimulates hypoxic pulmonary vasoconstriction, thereby increasing right ventricular work. In contrast, anatomic right-to-left shunts including pulmonary arteriovenous malformations (PAVMs), cause hypoxaemia without alveolar hypoxia. *Methods:* To test whether isolated arterial hypoxaemia, as occurs in patients with PAVMs, is associated with dyspnea or impaired exercise capacity, two prospective studies were performed, correlating patient variables with self-reported dyspnea (2006-11), or measurements made during maximal cardiopulmonary exercise tests on air (2011-12). *Results:* In 165 consecutive and previously unreported patients with PAVMs and hereditary hemorrhagic telangiectasia, SaO2 ranged from 78.5-99% (median 92%) but displayed no relationship with dyspnea grade: Five patients were athletes, despite severe resting hypoxemia (SaO2<85%). Many patients were iron deficient, which prevented compensatory polycythaemia, but there was no relationship between iron deficiency and dyspnea grade. On cardiopulmonary exercise testing, the 21 patients with PAVMs (SaO2 80-96%) were no more dyspneic than 12 age-matched healthy volunteers (SaO2 96-99%). Five PAVM patients acted as their own controls, through tests pre and post embolization when resting SaO2 had risen from 88-94% to 94-96% (p=0.009), and chest x-rays confirmed PAVM sac obliteration. All exercised to similar maximum heart rates before and after embolization, but with no difference in perceived dyspnea, maximum workload (medians 119W/113W) or oxygen consumption at peak exercise (peak VO2 medians 1.69/1.72Lmin-1). Patients and controls had comparable relationships between peak VO2 and oxygen pulse (oxygen consumed per heart beat). Treated patients reset to virtually identical points on the oxygen pulse/peak VO2 line. Polycythaemia only partially explained the compensation, suggesting stroke volume is increased. Compensation was less successful in patients with concurrent COPD or sleep apnea. *Conclusions:* Despite severe hypoxaemia, PAVM patients can maintain normal oxygen delivery during peak exercise by harnessing integrated adaptive responses that maintain oxygen delivery and uptake with each heart beat (the "O2 pulse"). Significant dyspnea should prompt a search for alternate conditions.

C-066
THE ROLE OF TRANSTHORACIC CONTRAST ECHOCARDIOGRAPHY IN THE CLINICAL DIAGNOSIS OF HEREDITARY HAEMORRHAGIC TELANGIECTASIA

S Velthuis[1], VMM Vorselaars[1], MWF Van Gent[1], CJJ Westermann[2], R Snijder[2], JJ Mager[2], MC Post[1]

[1]*St Antonius Hospital, Department of Cardiology, Nieuwegein, Netherlands,* [2]*St Antonius Hospital, Department of Pulmonology, Nieuwegein, the Netherlands*

Background: Hereditary haemorrhagic telangiectasia (HHT) can be diagnosed according to the four clinical Curaçao criteria, including presence of pulmonary arteriovenous malformations (PAVMs). In the last few years, transthoracic contrast echocardiography (TTCE) replaced chest high-resolution tomography (HRCT) for the screening of PAVMs. *Purpose:* We evaluated the added value of TTCE to the current clinical Curaçao criteria in diagnosing HHT. *Methods:* Between 2004 and 2012, a total of 487 first-degree relatives of HHT-causing mutation carriers were included, who underwent both TTCE and chest HRCT. Genetic testing was performed in all persons and considered as gold standard for the presence or absence of HHT. A quantitative three-point grading scale was used to classify the pulmonary shunt on TTCE (grade 0, no microbubbles; 1, <30 microbubbles; 2, 30-100 microbubbles; 3, >100 microbubbles). *Results:* Genetic testing demonstrated the presence of HHT in 334 patients (68.6%, mean age 43.9±14.8, 57.2% female). Chest HRCT confirmed PAVMs in 114 out of 218 patients with a pulmonary shunt on TTCE (52.3%). Addition of any pulmonary shunt grade on TTCE to the current criteria changed the number of positive criteria in 92 persons (18.9%), which increased the sensitivity from 88% (95%CI 0.84-0.91) to 94% (95%CI 0.91-0.96), but decreased the specificity from 74% (95%CI 0.66-0.80) to 70% (95%CI 0.62-0.77). The contribution of only pulmonary shunt grades ≥ 2 on TTCE to the current criteria altered the number of positive criteria in 30 persons (6.2%) and resulted in a sensitivity of 90% (95%CI 0.86-0.93), with a specificity of 74% (95%CI 0.66-0.80). *Conclusion:* The addition of only pulmonary shunt grades ≥2 on TTCE increases the sensitivity without affecting specificity of the current clinical Curaçao criteria in diagnosing HHT.

C-067
PERI-PROCEDURAL COMPLICATIONS ASSOCIATED WITH TRANSCUTANEOUS EMBOLISATION FOR PULMONARY ARTERIOVENOUS MALFORMATIONS: A SYSTEMATIC REVIEW AND META-ANALYSIS

JW Donaldson[1], IP Hall[2], RB Hubbard[1], AW Fogarty[1], TM McKeever[1]

[1]*Division of Epidemiology and Public Health, University of Nottingham, UK,* [2]*Division of Therapeutics and Molecular Medicine, University of Nottingham, UK*

Objective: The evidence for the safety and efficacy of transcutaneous embolisation (TCE) for pulmonary arteriovenous malformations (PAVMs) is derived from interpretation of small retrospective case series which may be subject to bias. We sought to summarise the safety data for TCE from the last 25 years by conducting a meta-analysis of the literature. *Methods:* Eligible studies were identified through the Embase and Medline search databases using predefined criteria. Study inclusion was agreed after appraisal of the abstracts or full text carried out by two independent reviewers. Where multiple papers published from similar specialist centres with overlapping recruitment time periods or populations were identified, the largest study only was included. Peri-procedural complications were defined as those occurring within 30 days of TCE, or after, if clearly attributable to the proce-

non-commercial use only

dure itself. A proportions meta-analysis using a random effects model was undertaken to estimate the overall prevalence of the commoner peri-procedural complications. *Results:* We identified 18 studies most of which were retrospective case series published between 1988 and 2011. A total of 999 patients underwent embolisation, 89% of whom had HHT. The mean age at procedure was 40 years with a male:female ratio of 1:1.3. Significant complications included; one procedure-related death (occurring late due to pyogenic infection secondary to pulmonary infarction), 5 strokes, 2 venous thromboembolic events and 20 episodes of ischaemic chest pain. Estimates from meta-analyses for the most common complications included; pleurisy/pleuritic chest pain (9.8%, CI 5.8-14.6%, I^2=81.5%), ischaemic chest pain (2.2%, CI 1.4-3.2%, I^2=0%), pulmonary infarct (1.7%, CI 0.6-3.3%, I^2=56.2%) and haemoptysis (1.7%, CI 0.7-3.0%, I^2=47.2%). *Conclusion:* Our meta-analysis supports the generally held view that embolisation for patients with PAVMs is a safe procedure, though some 3% of procedures are associated with a significant complication. Our study provides more detailed information on the frequency of complications which should guide clinicians and radiologists when explaining or consenting for the procedure.

C-068
CONTRAST-ENHANCED MAGNETIC RESONANCE ANGIOGRAPHY FOR MANAGEMENT OF PAVMS IN PATIENTS WITH HHT

GK Schneider, U Geisthoff, A Buecker, A Massmann

Saarland University Medical Center, Homburg/Saar, Germany, Clinics of City Cologne, Germany

Purpose: To evaluate CE-MRA in patients with HHT as a screening procedure for detection of PAVMs and for follow-up after embolization-therapy for detection of reperfused PAVMs. *Methods and Materials:* Between 1999 and 2012 a total of 334 patients (mean age 42,5y, age range 4–78 years, male 128, female 206) with confirmed HHT or first degree relatives underwent screening pulmonary CE-MRA (MultiHance 0.1 mmol/kg bodyweight) for detection of PAVMs. CE-MRA was performed on 1.5 T MR-scanners. Technique includes time-resolved 3D-imaging using TWIST and high-resolution pulmonary CE-MRA. Patients with at least one PAVM with a feeding artery diameter >3 mm were referred for catheter angiography for embolization. Follow-up CE-MRA for detection of reperfused, respectively newly developed PAVMs 3 month, 12 month and thereafter in case of no reperfusion in 2-year intervals. *Results:* CE-MRA detected 348 PAVM in 118 of 334 patients (35%). 158 PAVMs in 48 men, 190 PAVMs in 59 women (94 PAVMs in 34 women of childbearing age). 91 of 118 patients with 289 PAVMs detected on CE-MRA underwent catheter-embolization . Significantly (p<0.001) fewer PAVMs (228/289 [79%]) were demonstrated on global DSA, the remaining PAVMs could only be demonstrated after selective catheterization of the feeding arteries. 214 PAVMs were embolized in 91 patients using platinum coils or vascular plugs. CE-MRA was rated as very useful when used as a roadmap to selectively catheterize feeding arteries of PAVMs. Follow-up CE-MRA showed 57 newly developed PAVMs in 16 patients (interval 1-6 years), and 43 reperfused PAVMs in 27 patients (interval 3 months-7 years) of which 7 patients where embolized elsewhere. All reperfused PAVMs were confirmed by DSA. *Conclusion:* CE-MRA should be the method of choice for management of PAVMs in HHT due to the lack of ionizing radiation and high sensitivity in detection of clinically relevant PAVM/reperfused PAVM. CE-MRA can replace CT in management of PAVMs and thus reduce accumulated radiation dose significantly, since regular follow-up studies are mandatory.

C-069
FEMALE SEX AND ENG MUTATION ARE ASSOCIATED WITH AN INCREASED RISK OF PAVM IN PATIENTS WITH DEFINITE HHT

JR Gossage[1], H Kim[2], ME Faughnan[3], WL Young[2], and the BVMC Investigators.

[1]*Georgia Regents University, Augusta, GA, USA;* [2]*University of California-San Francisco, San Francisco, CA, USA; and* [3]*St. Michael's Hospital & Li Ka Shing Knowledge Institute, University of Toronto, Toronto, Canada*

Introduction: Patients with HHT commonly have arteriovenous malformations (AVM) involving lung, liver, brain, and GI tract. We hypothesized that the presence of brain AVM (BAVM) would increase the likelihood of having pulmonary AVM (PAVM). *Methods:* The Brain Vascular Malformation Consortium (BVMC) is a consortium of 14 North American HHT Centers that is building a database of HHT patients to study the risk factors for bleeding from BAVM. All patients in the database have definite HHT by strict Curacao criteria. We queried the database to examine the predictors of PAVM. For this study, patients were considered to have PAVM if PAVM were visualized on radiographic imaging. Univariate analysis of demographic and HHT features was performed followed by multivariable logistic regression of variables with P<0.1 in univariate analysis. *Results:* The database includes 524 patients, 130 of whom have BAVM. The high prevalence of BAVM reflects the enrollment strategy which prioritizes enrollment of patients with BAVM followed by patients without BAVM in a 1:3 ratio. Amongst all patients, the mean age was 46 years, 63.6% were female, 85.5% had a family history of HHT, 94.5% had nosebleeds, 89.7% had mucocutaneous telangiectasias, 48.9% had PAVM, 15.5% had HHT related GI bleeding, and 18.9% had liver AVM. PAVM patients had a mean age of 46.8 years compared to 45.2 in patients without PAVM (P=0.33). PAVM were more commonly seen in patients with BAVM than without BAVM (53.8 versus 47.2%) but this difference was not statistically significant (P=0.225). Multivariable analysis showed that female sex (OR=1.6, 95% CI=1.1-2.3, P=0.016) and ENG mutation (OR=1.8, 95% CI=1.2-2.8, P=0.006) were associated with a greater risk of having PAVM whereas

Non commercial use only

HHT patients with ACVRL1 mutation were less likely to have PAVM (OR=0.21, 95% CI=0.11-0.39, P<0.001). None of the other characteristics were significantly associated with PAVM. *Conclusions:* In patients with definite HHT, female sex and ENG mutation were associated with a greater risk of having PAVM whereas patients with ACVRL1 mutation were less likely to have PAVM. There was no significant association between BAVM and PAVM.

Session X
Epistaxis and gastrointestinal bleeding in HHT

C-070
LIFESTYLE AND DIETARY INFLUENCES ON NOSEBLEED SEVERITY IN HEREDITARY HAEMORRHAGIC TELANGIECTASIA

BM Silva, AE Hosman, HL Devlin, CL Shovlin

Imperial College London, Imperial College Healthcare NHS Trust London, and the Medical Schools of Imperial College London, UK; the Academic Medical Center, University of Amsterdam, the Netherlands and Barts and the London SMD, UK

Background: Epistaxis (nosebleeds) is the most common clinical feature of hereditary haemorrhagic telangiectasia (HHT) affecting more than 90% of individuals. Severity and frequency varies widely. Reasons for the varying patterns of nosebleeds are not well understood. *Methods:* To capture experiences in an unbiased manner, relevant questions were incorporated into a wider ethically-approved survey. Participants with and without HHT were recruited from a specialist UK service, and by online advertisement. Reported effects of specific treatments or lifestyle factors on epistaxis were assigned positive values if beneficial, negative values if detrimental, zero if "no difference," and summed to enable statistical analysis. *Results:* Epistaxis affected 649/666 (97%) participants with HHT and was significantly more frequent than in control participants. 326 participants reported the use of specialist invasive treatments for HHT epistaxis, and reported effects on epistaxis evaluated to test the methodology. Commonly used interventional and medical treatments (including cauterisation, laser treatment, septal dermoplasty, Young's procedure, arterial ligation, arterial embolization, female hormones, anti-oestrogens, tranexamic acid, aminocaproic acid, nasal creams and bevacizumab) all had significantly positive (beneficial) scores. Laser therapy was more frequently reported as beneficial than cauterisation (Mann Whitney p<0.0001). In contrast, lifestyle and dietary factors were generally reported as detrimental, but room humidification, nasal lubrication and saline treatments were all reported as beneficial (95% confidence intervals greater than zero). Multiple food items were volunteered as being detrimental to epistaxis. The most frequently reported items were alcohol (n=45; 6.8% of participants) and spices (n=26, 3.9% of participants). Remaining foods reported to exacerbate epistaxis were also found to be high in salicylates (including red wine, spices, chocolate, coffee and certain fruits), natural antiplatelet activity (garlic, ginger, ginseng, gingko biloba and vitamin E15) or in omega-3 acids (oily fish, salmon). *Conclusion:* This study supports existing treatments, and suggests lifestyle and dietary manoeuvres that may also improve nosebleeds in hereditary haemorrhagic telangiectasia.

The authors thank the HHT Foundation International for advertising the study, and the many individuals with and

non commercial use only

without HHT who completed the questionnaire. Silva, Hosman, Devlin, Shovlin. Laryngoscope 2013(Feb 12).doi:10.1002/lary.23893.

C-071
THE MINIMALLY IMPORTANT DIFFERENCE IN THE EPISTAXIS SEVERITY SCORE AMONG PATIENTS WITH HEREDITARY HEMORRHAGIC TELANGIECTASIA

CA Merlo[1,2], JB Hoag[3], S Mitchell[1], G Robinson[1], S Mathai[1], PB Terry[1], DD Reh[1]

[1]*The Johns Hopkins University School of Medicine,* [2]*The Johns Hopkins Bloomberg School of Public Health,* [3]*Drexel University School of Medicine, Baltimore, MD, USA*

Introduction: Epistaxis is the most common manifestation of HHT affecting more than 96% of patients with this disease. However, little is known about the relationship between differences in the severity of epistaxis and quality of life. The purpose of this study, therefore, was to determine the minimally important difference (MID) of the HHT epistaxis severity score (HHT-ESS) in a diverse population of individuals with HHT and to correlate this with quality of life measures. *Methods:* The HHT-ESS questionnaire and the Medical Outcomes Study 36-item short form (SF-36), both well-validated questionnaires, were administered to subjects with HHT through the use of an internet-based survey program. Demographic information, location of visceral AVMs, information related to treatments for epistaxis, and aspects of life affected by disease were also collected. Descriptive analyses were performed with calculations of means and medians for continuous and proportions for categorical variables. An anchor-based method using the Physical Component Summary Score (PCS) was used to estimate the MID. *Results:* Six hundred and ninety subjects were included in the study. All domains of the SF-36 except role physical and social functioning were weakly associated with change in HHT-ESS. The physical functioning domain ($r=0.45$, $p<0.0001$) and the PCS ($r=0.44$, $p<0.0001$) of the SF-36 were most strongly associated with HHT-ESS. Anchor-based analyses using a change in PCS of 5 units demonstrated an MID estimate of 0.41 for the HHT-ESS. *Conclusion:* Using an anchor-based method, MID in the HHT-ESS is estimated to be 0.41. These results have important clinical implications in both evaluating the response to treatments for patients with epistaxis and HHT as well as to aid in calculating power and sample size for clinical trials.

C-072
A MANAGEMENT ALGORITHM FOR EPISTAXIS IN HHT – A COHORT OF 363 PATIENTS

J Rimmer[1], VJ Lund[1,2]

[1]*Royal National Throat Nose & Ear Hospital, London,* [2]*University College London, UK*

Introduction: Epistaxis is well-recognised as one of the life-threatening sequelae of hereditary haemorrhagic telangiectasia (HHT). Epistaxis is the predominant symptom in patients with HHT and may have a profoundly negative effect on quality of life. There is great variation in the medical and surgical management of this chronic health condition, in part due to patient choice, severity of bleeding and comorbidities. *Methods:* A prospective cohort study of all patients attending our tertiary referral service at The Royal National Throat Nose & Ear Hospital from 1987 to 2013. *Results:* Three hundred and sixty-three patients with HHT were included, 181 male and 182 female. Of these, 206 patients (57.1%) underwent at least one laser treatment for nasal telangiectasia. Eighty-four septodermoplasties were performed in 61 patients (16.8%). Sixty-two patients (17.1%) underwent nasal closure, of which 54 were bilateral and 9 required revision. Thirty-seven patients (10.2%) have been treated with tamoxifen in the last 3 years. *Discussion:* We present one of the largest series of patients with symptomatic epistaxis secondary to HHT. In our experience, repeated laser coagulation was an effective and safe treatment for mild to moderate epistaxis, or as an adjunctive treatment after septodermoplasty. Septodermoplasty was performed if the telangiectasia were larger than 2-3mm in diameter, when laser coagulation was less effective and in patients with moderate to severe bleeding. Successful nasal closure was the only definitive treatment leading to complete cessation of epistaxis. In our series, tamoxifen reduced the frequency and severity of bleeding in some patients. We propose a step-wise algorithm for the treatment of epistaxis in HHT based on our experience.

C-073
DEVELOPMENT AND VALIDATION OF AN ENDOSCOPIC STAGING SYSTEM FOR HEREDITARY HEMORRHAGIC TELANGIECTASIA

DD Reh, LX Yin, K Laeeq, CA Merlo

Johns Hopkins Medicine, Baltimore, MD, USA

Background: Hereditary hemorrhagic telangiectasia (HHT) is an inherited autosomal dominant disease that is characterized by the presence of nasal mucosal telangiectases causing severe, recurrent epistaxis necessitating medical and surgical treatment. Recently, a validated questionnaire, the Epistaxis Severity Score (ESS), was developed as a standardized measure of epistaxis severity that provides physicians with a means to evaluate treatment efficacy. Although prior endoscopic staging systems have been proposed to evaluate nasal findings in HHT patients, none have been correlated to the ESS. *Objectives/Hypothesis:* Nasal endoscopy can be used to identify specific intranasal findings in HHT patients that correlates with a patient's ESS. *Methods:* Individuals with HHT confirmed by Curaçao criteria were recruited consecutively at the Johns Hopkins HHT Center for Excellence. Study subjects were evaluated by a single otolaryngologist with nasal endoscopy between August 2010 through November 2012. Endoscopic findings were noted including patterns of telangiectases, density and location of telangiectases, degree of nasal crusting, and presence of

non-commercial use only

septal perforation and an endoscopic composite score was calculated for each subject. Multiple linear regression models were used to correlate endoscopic findings to the ESS. *Results:* A total of 32 subjects completed the study. Mean (SD) age was 50.1 (13.4), and 20 (62.5%) were female. In the cohort, mean (SD) ESS was 3.99 (2.14) and ranged from 0.5 to 8.22. Most subjects (51.6%) had more than 4 nasal sites involved, the majority (58.1%) had punctate telangiectases, and most (53.1%) had telangiectases that were <0.5mm in proximity to each other. One-half of the cohort had no crusting, while 28.1% had mild crusting and 21.9% had moderate/severe crusting. Telangiectases were most commonly located in the middle nasal septum and inferior turbinate (81.3%) and in the anterior nasal septum (75%), while telangiectases were less commonly seen in the middle turbinate (43.8%). After adjusting for age and sex, the endoscopic composite score was strongly associated with the ESS (r=0.69, p=0.01). *Conclusion:* This newly developed objective endoscopic scoring system correlates highly with patient reported ESS and may provide valuable information in evaluating response to treatment and may be a useful outcome measure in future clinical trials.

C-074
EPISTAXIS SEVERITY DOES NOT PREDICT LIKELIHOOD OF BRAIN OR LUNG AVM IN HHT

KJ Whitehead[1], J McDonald[2], PD Ward[3], K Wilson[3]

[1]*University of Utah, Dept. of Medicine, SLC, UT,*
[2]*University of Utah, Dept. of Pathology, SLC, UT,*
[3]*University of Utah, Dept. of Surgery, SLC, UT, USA*

Patients with hereditary hemorrhagic telangiectasia (HHT) develop telangiectasias or arteriovenous malformations (AVMs) in many vascular beds with clinical consequences. Even severe AVM manifestations of HHT may be asymptomatic before catastrophic complications. Many patients assume that epistaxis severity is an indicator of AVM severity and the need for screening. Since January 2010 we have routinely applied the Hoag epistaxis severity score (ESS) to all patients and have systematically screened all patients for brain and lung AVM. We sought to compare the severity of epistaxis with other severe manifestations of HHT. The medical records of all patients 18 and older with definite HHT (meeting Curaçao criteria, or with a positive genetic test) were reviewed for severe involvement of epistaxis, brain or lung AVM, or complicated liver AVM. Severe epistaxis was defined as ESS > 7.0, or Young's nasal closure, or previous septal dermoplasty. Mild epistaxis was defined as ESS < 3.0 with no history of interventions. Severe brain AVM was defined as one or more macro AVM (>1.0 cm), or 5 or more micro AVM (<1.0 cm). Severe lung AVM was defined as AVM seen by CT amenable to coil embolization. Groups were compared by Chi Square or Fisher's exact tests. Of a total of 134 patients with definite HHT, 29 patients had severe epistaxis, 68 patients had moderate epistaxis and 37 patients had mild epistaxis, most had adequate screening for brain or lung AVM for interpretation. The severity of epistaxis was not predictive of the likelihood of severe brain AVM (3/36 mild, 3/67 moderate, 2/28 severe epistaxis, p=0.7140) or lung AVM requiring embolization (12/36 mild, 22/67 moderate, 5/29 severe, p=0.2585). The likelihood of severe AVM manifestations of HHT is not significantly different among groups with differing severity of epistaxis. There is no level of epistaxis that predicts absence of severe involvement with arteriovenous malformations.

C-075
LONG-TERM RESULTS OF EXTENSIVE ENDOSCOPIC TREATMENT OF GI TELEANGIECTASES IN PATIENTS WITH HEREDITARY HEMORRHAGIC TELANGIECTASIA AND GASTROINTESTINAL BLEEDING

S Crinò[1], E Buscarini[1], F De Grazia[1], G Lupinacci[1], G Manfredi[1], S Alicante[1], A Zambelli[1], P Gazzaniga[2], S Gandolfi[3], PA Forner[4], C Danesino[5], C Olivieri[5], C Canzonieri[5], F Ornati[5], F Pagella[6], M Grosso[7], G Pongiglione[8], E Boccardi[9], on behalf of HHT-NET

[1]*Gastroenterology Dept,* [2]*Cardiology Dept,* [3]*Radiology Dept, Maggiore Hospital,* [4]*ENT Dept, Crema,* [5]*Dipartimento di Medicina Molecolare, Genetica medica, University of Pavia,* [6]*ENT Institute, University of Pavia,* [7]*Radiology Dept, Ospedale S Croce, Cuneo,* [8]*Paediatric Cardiology Dept, Ospedale Bambin Gesù, Roma,* [9]*Interventional Neuroradiology Unit, Niguarda Hospital, Milan, Italy*

Background and study aims: This prospective study aimed to evaluate the immediate and long term outcome of extensive endoscopic treatment of bleeding GI teleangiectases in Hereditary Hemorrhagic Telangiectasia (HHT), its safety, and to identify predictors of treatment outcome. *Patients and methods:* 30 consecutive Italian patients with HHT were admitted at the Crema HHT referral center with anemia and occult or overt GI bleeding and having failed to respond to a first line treatment with iron administration possibly associated to endoscopic treatment of bleeding GI teleangiectases, and/or blood transfusion and/or medical treatment. Patients with no or partial response to first line treatment were addressed to an extensive endoscopic treatment of GI teleangiectases (1-3 endoscopic sessions), with argon plasma coagulation by push enteroscopy possibly associated to colonoscopy. Hemoglobin and transfusion requirements were evaluated before and after endoscopic treatment, and every 1-3 months during follow-up. Treatment outcome was judged, on an intention to treat basis, upon NCCN classification of anemia severity (grades 1 to 4), and blood transfusion requirement in PRBC units/year. Complete response to treatment was defined as a mean Hb > 10 g/dl with no blood transfusion requirement. Partial response to treatment was defined as grade shift of anemia severity from 4 to 3 or 2 and/or a >50% reduction of blood transfusion requirement. Complications of endoscopic treatment were classified as mild, moderate, severe or fatal and their onset as immediate, early, or late. We evaluated correlations between outcome of endoscopic treatment and: 1) demographic/genetic features, 2) number, size and location of teleangiectases and, 3) hepatic artero-venous mal-

Non-commercial use only

formations (HAVM) degree. Statistical analysis included Kolmogorov Smirnov test, Pearson correlation test, Partial correlation, Logistic Regression Models, Paired T-Test. *Results:* 29/30 patients could complete the endoscopic treatment and underwent a total of 91 endoscopic procedures. Immediate outcome of endoscopic treatment was : complete response in 24 , 80%, non response in 5, 17.% of patients. Long term outcome, on a mean follow-up of 45,8 months, was complete response in 18, 60% of patients; 6, 20 % had a recurrence of anemia after 30.1 months and received a second session of treatment. Altogether complication rate was 2.2%. A statistically significant inverse correlation was found with HAVM degree (p=0.048). *Conclusions:* Extensive endoscopic treatment of GI teleangiectases for GI bleeding in HHT patients is effective and safe.

C-076
DETECTION OF ENDONASAL TELANGIECTASES WITH NARROW BAND IMAGING (NBI) IN PATIENTS SUFFERING FROM HHT

BJ Folz, CG Konnerth

Dept. of ORL, HNS; Karl Hansen Medical Center, Bad Lippspringe, Germany

Background: The primary source of recurrent Epistaxis in HHT patients are endonasal telangiectases. Nasal endoscopy can depict these telangiectses in patients with fully developed disease. In cases that are unclear or in young children telangiectases may be hard to find, despite the presence of Epistaxis. The aim of the present study was to analyze, whether NBI could be useful in the depiction of nasal telangiectases and to compare the performance of NBI with the diagnostic performance of white light (WL) imaging. Compared to WL imaging NB imaging uses two light frequency bands with a wave length maximum of 415 nm and 540 nm, respectively. Visible is a higher proportion of blue light. The absorption features of haemoglobin are supposed to reveal an exact depiction of capillary mucosal vessels and venous vessels of the submucosa. *Methods:* A prospective case study of 13 patients (female: 9 p., male: 4 p.; age: 70.2/44.8 years) with HHT was initiated. All subjects were diagnosed using WL imaging with a 30° angled rod lense endoscope and NB imaging prior to laser therapy of nasal telangiectases. Images were stored digitally and were evaluated by two independent investigators with regard to overall visibility, contrast and diagnostic accuracy. *Results:* NBI-mode showed a more pronounced contrast of telangiectases and allowed an assignment of telangiectases to superficial and deeper layers of the mucous membranes. Smaller vessels which could not be seen on WL imaging were detectable by NBI. This was of diagnostic value in the profound parts of the nasal cavity, where density of telangiectases was low. *Conclusion:* NBI renders optimized contrast imaging of telangiectatic vessels as compared WL imaging. This feature may be useful in HHT patients with occult sources of bleeding or in the screening of children from HHT families.

Session XI
Endoglin, ALK1 and Smad4 in TGF-beta and BMP pathways

C-077
ENDOTHELIAL ENDOGLIN IS INVOLVED IN LEUKOCYTE ADHESION AND TRANSMIGRATION. IS THIS A NOVEL PATHOGENIC MECHANISM IN HHT?

E Rossi[1], F Sanz-Rodriguez[2], N Eleno[3], A Düwell[3], FJ Blanco[1], C Langa[1], LM Botella[1], C Cabañas[4], JM Lopez-Novoa[3], C Bernabeu[1]

[1]*Centro de Investigaciones Biológicas, Consejo Superior de Investigaciones Científicas (CSIC), and Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), Madrid, Spain,* [2]*Departamento de Biología, Facultad de Ciencias, Universidad Autónoma de Madrid, Madrid, Spain,* [3]*Departamento de Fisiología y Farmacología, Unidad de Fisiopatología Renal y Cardiovascular, Universidad de Salamanca, Salamanca, Spain,* [4]*Centro de Biología Molecular Severo Ochoa, CSIC and Universidad Autónoma de Madrid, Madrid, Spain*

Human endoglin is an RGD-containing transmembrane glycoprotein identified in vascular endothelial cells. Although endoglin is essential for angiogenesis and its expression is up-regulated in inflammation and at sites of leukocyte extravasation, its role in leukocyte trafficking is unknown. This function was tested in endoglin heterozygous mice (Eng+/-) and their wild-type siblings Eng+/+ treated with carrageenan or LPS, as inflammatory agents. Both stimuli showed that inflammation-induced leukocyte transendothelial migration to peritoneum or lungs was significantly lower in Eng+/- than in Eng+/+ mice. Leukocyte transmigration through cell monolayers of endoglin transfectants was clearly enhanced in the presence of endoglin. Coating transwells with the RGD-containing extracellular domain of endoglin, enhanced leukocyte transmigration, and this increased motility was inhibited by soluble endoglin. Leukocytes stimulated with CXCL12, a chemokine involved in inflammation, strongly adhered to endoglin coated plates and to endoglin-expressing endothelial cells. This endoglin-dependent adhesion was abolished by soluble endoglin, RGD peptides, the anti-integrin 5 1 inhibitory antibody LIA1/2 and the chemokine receptor inhibitor AMD3100. These results demonstrate for the first time that endothelial endoglin interacts with leukocyte integrin 5 1 via its RGD motif, and this adhesion process is stimulated by the inflammatory chemokine CXCL12, suggesting a regulatory role for endoglin in transendothelial leukocyte trafficking. Mutations in ENG give rise to Hereditary Hemorrhagic Telangiectasia type 1 (HHT1), a disorder associated with abnormal angiogenesis. Because infiltrating leukocytes can modulate the angiogenic response and there is a decreased leukocyte transmigration through HHT endothelial cells or on inflammation in an animal model of HHT1, it can be postulated that endoglin

Non-commercial use only

haploinsufficiency in HHT1 patients may lead to an impaired leukocyte trafficking as the basis of an abnormal angiogenesis.

C-078
BMP9 AND BMP10, THE TWO SPECIFIC LIGANDS FOR ALK1 ARE CRITICAL FOR POSTNATAL RETINAL VASCULAR REMODELLING

N Ricard, S Levet, D Ciais, M Subileau, C Mallet, M Bidart, J-J Feige, S Bailly

Inserm U1036, University Joseph Fourier, CEA-Grenoble, France

ALK1 is an endothelial-specific type 1 receptor of the TGFß receptor family whose mutations are responsible of HHT2. In 2007, we reported that BMP9 and BMP10 are specific ligands for ALK1. However, we focused on BMP9, as only circulating BMP9 was able to bind to ALK1. We demonstrated that addition of BMP9, both in vitro and in vivo, inhibited angiogenesis. The aim of this work was to further evaluate the role of BMP9 on angiogenesis in vivo by blocking its expression. To do this, we chose to study postnatal retinal vascularisation. We first injected a neutralizing anti-BMP9 antibody or the extracellular domain of ALK1 (ALK1ECD) in newborn pups at P1 (postnatal day 1) and P3 and analyzed their retinal vascularization at P5. We found a significant increase in retinal vascular density. In contrast, in Bmp9-KO mice (given by Dr SJ Lee, USA) we did not observe any defect in retinal vascularization. Still, injection of ALK1ECD impaired retinal vascularization in Bmp9-KO mice, suggesting the presence of another ligand for ALK1. Interestingly, as for BMP9, we found that BMP10 was also present in blood with a peak around birth although this circulating BMP10 is not able to bind to ALK1. To test a possible role of BMP10, we injected neutralizing anti-BMP10 antibody to Bmp9-KO pups. In these pups, we observed a dramatic reduction of retinal vascular expansion and an increase in vascular density, whereas injection of this antibody to WT pups had no effect. Notably, vessels in anti-BMP10 treated Bmp9-KO pups were larger in diameter, similar to the dilated vessels found in HHT. Finally, we found that in vitro stimulation of endothelial cells by BMP9 and BMP10 increased the expression of genes involved in the Notch signaling pathway (Jagged1, Dll4, Hey1, Hey2, Hes1) and decreased apelin expression suggesting a possible cross talk between these pathways in vascular remodeling. This work demonstrates for the first time that both BMP9 and BMP10 are critical in angiogenesis, one being able to substitute for the other. It will be important in the future to study their respective roles in regard to HHT.

C-079
CIRCULATING BMP10 ACTS THROUGH ENDOTHELIAL ALK1 TO MEDIATE FLOW-DEPENDENT ARTERIAL QUIESCENCE

DW Laux, S Young, JP Donovan, CJ Mansfield, PD Upton, BL Roman

Department of Biological Sciences, University of Pittsburgh, Pittsburgh, PA USA, Department of Medicine, University of Cambridge, Cambridge, UK

Blood flow plays critical roles in vascular development, remodeling, and homeostasis, but the molecular pathways required for transducing flow signals are not well understood. In zebrafish embryos, arterial expression of activin receptor-like kinase 1 (alk1), which encodes a TGF-β family type 1 receptor, is dependent on blood flow, and loss of alk1 mimics lack of blood flow in terms of dysregulation of a subset of flow-responsive arterial genes and increased arterial endothelial cell number. These data suggest that blood flow activates Alk1 signaling to promote a flow-responsive gene expression program that limits nascent arterial caliber. Here, we demonstrate that restoration of endothelial alk1 expression to flow-deprived arteries fails to rescue Alk1 activity or normalize arterial endothelial cell gene expression or number, implying that blood flow may play an additional role in Alk1 signaling independent of alk1 induction. To this end, we define cardiac-derived Bmp10 as the critical ligand for endothelial Alk1 in embryonic vascular development, and provide evidence that circulating Bmp10 acts through endothelial Alk1 to limit endothelial cell number in and thereby stabilize caliber of nascent arteries. Thus, blood flow promotes Alk1 activity by concomitantly inducing alk1 expression and distributing Bmp10, thereby reinforcing this signaling pathway that functions to limit arterial caliber at the onset of flow. Because mutations in ALK1 cause arteriovenous malformations (AVMs), our findings suggest that an impaired flow response initiates AVM development.

C-080
ALK5 AND ALK1 PLAY ANTAGONISTIC ROLES IN TGFβ-INDUCED PODOSOME FORMATION IN AORTIC ENDOTHELIAL CELLS

F Curado, P Rottiers, I Egana, E Genot

IECB and INSERM 1045, Pessac, IECB, INSERM1045, France,

Background: Our team has discovered a novel role for TGFβ in the vascular system. In vitro, TGFβ induces the formation of podosomes in aortic endothelial cells (BAEc)1. Podosomes are transient actin-based punctate adhesion microdomains localized at the ventral plasma membrane. They contain cytoskeletal and signalling components but their prominent feature is their ability to recruit metalloproteases allowing them to degrade the extracellular matrix. Using murine aortic vessel segments, we demonstrated that podosomes form in the living endothelium exposed to TGFβ. Under these conditions, the structures degrade the underlying basement membrane suggesting a role in breaching anatomical barriers2. We are studying the signalling pathways underlying podosome formation in response to TGFβ in BAEc. *Results:* In association with TβRII, ALK5 and ALK1 TβRI, regulate TGFβ responses in BAEc. ALK5 and ALK1 control the activation of distinct Smad protein families, Smad 2/3 and Smad 1/5, respectively, each regu-

Non-commercial use only

lating a subset of TGFβ responsive genes. Both Smad families are activated in BAEc upon TGFβ stimulation. Through a siRNA-based approach, we first established that knock down of either ALK1 or ALK5 inhibits TGFβ-induced podosome formation and extracellular matrix degradation. However, transfection of constitutively active TβRI showed that CA-ALK5 expression bypassed the need of TGFβ for podosome induction whereas CA-ALK1 expression was ineffective. In addition, expression of CA-ALK1 prevented TGFβ-induced podosome assembly. Downstream of TβRI, Smad2 depletion reduced TGFβ -induced podosome formation whereas Smad3 depletion completely abolished it. In sharp contrast, depletion of Smad1 or Smad5 proteins enhanced the TGFβ -induced podosome response. Consistent with these results, BMP9, a bona fide ALK1 ligand, produced a dose-dependent inhibition on TGFβ-induced podosome formation. When overexpressed, Smad2 or Smad3, to some extent, bypassed TGFβ signals, whereas Smad1 overexpression diminished the TGFβ-induced podosome response. Alltogether, this study establishes that although TGFβstimulates both ALK5 and ALK1, ALK5 triggers podosome formation and ALK1 mitigates this signal. Depletion of ALK1 perturbs BAEc responses including TGFβ-induced ALK5 signaling and thereby, indirectly, prevents podosome assembly. Thus ALK5 and ALK1 play antagonistic roles in TGFβ-induced podosome formation in BAEc.

1-Varon et al., Mol Cell Biol. 2006;26:3582
2- Rottiers et al., J Cell Sci. 2009;122:4311

C-081
TARGETING ENDOGLIN ACTIVITY IMPROVES SURVIVAL AND LIMITS ADVERSE RIGHT VENTRICULAR REMODELING IN A MURINE MODEL OF PULMONARY HYPERTENSION

NK Kapur, X Qiao, V Paruchuri, EE Mackey, GH Daly, P Nepali, MJ Aronovitz, M Letarte, RH Karas

Molecular Cardiology Research Institute; Tufts Medical Center, Boston, MA, Hospital for Sick Children; Univ of Toronto, Toronto, Ontario, USA

Right ventricular (RV) function is a major determinant of clinical outcomes in pulmonary hypertension. The role of the TGFβ1 auxiliary receptor, endoglin (Eng) in RV remodeling remains unknown. We tested the hypothesis that RV pressure overload (RVPO) induces Eng expression, which promotes TGFβ1-mediated fibrosis and further that blocking Eng activity limits adverse RV remodeling. *Methods and Results:* To explore the functional role of Eng in RV remodeling, RVPO was induced by pulmonary artery constriction (PAC) in male, wild-type (WT) and Eng heterozygous (Eng+/-) mice. Compared to sham controls, PAC increased RV systolic pressure equally in both WT (21+6 vs 50+4, p<0.01) and Eng+/-(24+3 vs 46+9, p<0.01) mice. In WT mice, Eng mRNA and protein expression increased in the RV after 7 days of RVPO accompanied by RV fibrosis and hypertrophy. In contrast to WT, Eng+/- mice had preserved RV cardiac output, less RV fibrosis, reduced RV mass, and reduced cardiomyocyte hypertrophy after PAC. Despite similarly increased levels of active TGFb1 in the RV of WT and Eng+/- mice, levels of phosphorylated Smad-2/3 (pSmad-2/3) and pERK-1/2 were increased in WT, but unchanged in Eng+/- mice after PAC. RV expression and activity of the protein phosphatase, calcineurin, were also increased in WT, but not Eng+/- mice after RVPO. In isolated RV fibroblasts, reduced Eng activity limited TGFβ1-induced collagen expression, fibroblast to myofibroblast conversion, and expression of the transient receptor potential cation channel 6 (TRPC6). The dependence of TGFβ1 signaling on Eng expression was further tested using a neutralizing anti-endoglin antibody (TRC105). Compared to IgG-treated controls, treatment with TRC105 limited RV fibrosis, pSmad-2/3 expression, and Type 1 Collagen expression in WT mice after PAC. Compared to WT, both Eng+/- and TRC105 treated mice had improved survival after PAC (60%; n=7/12 vs 100%; n=8/8 vs 88%; n=7/8, respectively, p<0.01 for Eng+/- or TRC105-treated mice vs WT). *Conclusion:* These data identify endoglin as a critical component of TGFβ1 signaling in the RV and further identify endoglin as a potentially novel therapeutic target to improve survival in pulmonary hypertension. These findings may also have important implications for HHT patients with pulmonary hypertension.

C-082
ATORVASTATIN PREVENTS ENDOGLIN AND ENOS DECREASED EXPRESSION IN TNF-ALPHA INDUCED INFLAMMATION IN HUVECS

P Nachtigal, L Zemankova, M Varejckova, J Pfeiferová, K Jezkova, I Nemeckova

Department of Biological and Medical Sciences, Faculty of Pharmacy in Hradec Kralove, Charles University in Prague, Czech Republic

Endoglin affects the expression of eNOS and seems to play important role in endothelial dysfunction and atherosclerosis. In our previous papers, we demonstrated that atorvastatin treatment increases endothelial expression of endoglin and eNOS in atherosclerotic mouse aorta, together with reduced atherosclerosis, suggesting its interesting role in atherogenesis. In this study, we wanted to elucidate whether atorvastatin treatment can prevent TNFβ reduced endoglin expression and whether statin induced eNOS expression depends on endoglin in vitro in human endothelial cells HUVEC. HUVEC cells were exposed to TNFβ (10ng/ml) for 2, 4, 6 and 24h to mimic inflammatory conditions. Atorvastatin was added 24h before TNF exposure, at a concentration of 3 μM and 5 μM, DMSO 0.1% (v/v) was used as control. Cells with siRNA of endoglin were prepared by using Amaxa HUVEC Nucleofector kit. The protein expression was determined by flow cytometry and Western blot analysis. Levels of soluble endoglin were detected by means of ELISA. We showed that TNFβ treatment for 24h significantly decreased endoglin and eNOS expression in HUVEC, together with significant increase of soluble endoglin in medium. 24 hours pretreatment of atorvastatin at a concentration of 5 μM, followed by 24h TNFβ

Non-commercial use only

exposure significantly prevented decrease of endoglin, eNOS and phosphorylated Smad2 expression, when compared to cells treated by TNFβ only. Endoglin silencing reduced the expression of endoglin and eNOS with no effect of atorvastatin treatment on both endoglin and eNOS in silenced HUVECs.

In conclusion, TNFβ induced inflammation in endothelial cells results in reduced expression of endoglin and eNOS in HUVECs, which could be prevented by atorvastatin treatment with possible involvement of Smad2 signaling. Moreover, siRNA analysis proofed that atorvastatin induced eNOS expression depends on endoglin expression. Since endoglin and eNOS play important role in various cardiovascular pathologies including endothelial dysfunction, atherosclerosis, hypertension, preeclampsia and hereditary hemorrhagic telangiectasia, we propose that statin effects on tissue and soluble endoglin in these diseases should be evaluated in clinical studies.

The study was supported by grant from The Grant Agency of Charles University in Prague number 300811/C and grant SVV/2013/267003.

Session XII
Paediatrics and natural history of HHT

C-083
DIAGNOSTIC YIELD OF RESCREENING FOR ARTERIOVENOUS MALFORMATIONS IN CHILDREN WITH HEREDITARY HEMORRHAGIC TELANGIECTASIA

GA Latino, ME Faughnan, S Carpenter, SA Al-Saleh, F Ratjen

[1]*University of Toronto, Toronto, Canada,* [2]*Division of Respiratory Medicine, Hospital for Sick Children, Toronto, Canada,* [3]*Physiology and Experimental Medicine, Research Institute, Hospital for Sick Children, Toronto, Canada,* [4]*Division of Respiratory Medicine, St Michael's Hospital, Toronto, Canada,* [5]*Li Ka Shing Knowledge Institute, St Michael's Hospital, Toronto, Canada,* [6]*King Saud bin Abdulaziz University for health sciences, Riyadh, Saudi Arabia*

Introduction: Patients with HHT and untreated AVMs are at risk of serious sequelae. As such, screening for pulmonary and brain AVMs is recommended in HHT and is standard practice in North America. Although customary to rescreen children every five years, the diagnostic yield of rescreening in children negative at initial screening is unclear. *Methods:* A retrospective chart review of all children (0 to 18 years) assessed for HHT at The Hospital for Sick Children from 1997-2011 was conducted. Patients were categorized as having: 1) a genetic diagnosis of HHT; 2) a clinical diagnosis of HHT (≥3 Curacao criteria); 3) a likely diagnosis of HHT (2 Curacao criteria); or 4) an unlikely diagnosis of HHT (≤1 Curacao criteria). All imaging reports (bubble echocardiography, CT thorax, MRI head) were reviewed for the initial assessment of included patients and for the subsequent rescreening of children with an initial negative screen. The incidence of AVMs was then established. Patients with an unlikely diagnosis of HHT were excluded. All children with positive contrast enhanced echocardiography had a CT thorax, which was the gold standard for the diagnosis of pulmonary AVMs in this study. *Results:* 183 patients assessed for HHT were identified, approximately half of whom were female (81 or 44 %). 91 patients (50%) had a genetic diagnosis of HHT, 16 (9 %) fulfilled clinical diagnostic criteria but were negative for HHT gene mutations, and 36 (20%) had a likely diagnosis of HHT. 40 children were unlikely to have HHT and were excluded. Of the included patients, 110/143 (76.9%) had been screened using both CT and echocardiography. To date, all patients with initial negative screening for visceral AVMs were also negative at rescreening (Tables 1 and 2). *Conclusions*: The diagnostic yield of rescreening at 5 years for AVMs in children with confirmed or suspected HHT and initial negative screening is essentially zero. While the analysis presented to date is limited by a small sample size, our data suggests that the interval for rescreening may be extended beyond 5 years in children. Similar studies following children and adults with HHT longitudinally over a longer time period are currently in progress.

non commercial use only

Table 1: Incidence of AVMs in children with a definite (genetic or clinical) diagnosis of HHT

Screening modality		Initial Screening	Re-screening (for children with an initial negative screen)
Contrast enhanced	N	89	14
Echocardiography	Mean age (years)	8.0	13.6
	Negative result (%)	61 (69%)	12 (86%)
	N	91	13
CT Thorax	Mean age (years)	8.1	13.6
	Negative for PAVMs (%)	52 (57%)	13 (100%)
MRI Head	N	87	21
	Mean age (years)	8.0	12.46
	Negative for CAVMs (%)	75 (86%)	21 (100%)

Table 2: Incidence of AVMs in children with a likely diagnosis of HHT

Screening modality		Initial Screening	Re-screening (for children with an initial negative screen)
Contrast enhanced	N	34	5
Echocardiography	Mean age (years)	10.2	14
	Negative result (%)	27 (79%)	5 (100%)
	N	33	10
CT Thorax	Mean age (years)	9.4	14.1
	Negative for PAVMs (%)	33 (100%)	10 (100%)
	N	34	7
MRI Head	Mean age (years)	9.1	15.7
	Negative CAVMs (%)	33 (97%)	7 (100%)

C-084
DETECTION OF PULMONARY ARTERIOVENOUS MALFORMATION BY CONTRAST ECHOCARDIOGRAPHY IN PEDIATRIC HEREDITARY HEMORRHAGIC TELANGIECTASIA

P Balagny, C Karam, J Sellier, M El Hajjam, S Binsse, T Chinet, J Roume, A Ozanne, I Bourgault, G Lesur, J-H Blondel, A Cordier, S Blivet, C Fagnou, M Bonay, P Lacombe, O Dubourg, N Mansencal

Consultation Pluridisciplinaire Maladie de Rendu-Osler, Hôpital Ambroise Paré Boulogne, HHT Center, Paris, France

Background: In hereditary hemorrhagic telangiectasia (HHT), assessment of pulmonary arteriovenous malformations (PAVMs) may be difficult in pediatric patients. The aim of this study was to assess the reliability of contrast echocardiography in a pediatric population presenting with HHT. *Methods:* We prospectively studied 22 pediatric patients presenting with HHT. All these patients underwent transthoracic contrast echocardiography (TTCE) and low-dose thoracic computed tomography (CT). Each TTCE examination was performed using second harmonic imaging, allowing to improve the quality of 2-dimensional imaging. The contrast protocol consisted of the injection of agitated 5% glucose solution through an upper extremity vein. We used the classification proposed by Barzilai et al.: grade 0 means no opacification of the left ventricle after the first 3 cardiac cycles following contrast appearance in the right atrium, grade 1 means minimal opacification; grade 2, moderate; grade 3, extensive opacification without outlining the endocardium; and grade 4, extensive opacification with clear endocardial definition. We considered CT as normal when no PAVMs or only one microscopic PAVMs was detected. *Results:* Mean age of the population was 11 ± 5 years (12 male). A PAVM was detected in 10 patients (45%) by CT. TTCE was feasible in all pediatric patients. Using TTCE, a grade 0 was found in 4 patients, a grade 1 in 7 patients, a grade 2 in 5 patients, a grade 3 in 6 patients and no patient had a grade 4. In case of grade 0 or 1, no patient had a significant PAVMs, whereas for grade 2 and 3, all patients excepted one had PAVMs. The sensibility and specificity of TTCE for the detection of PAVMs was respectively 100% and 92%. *Conclusion:* Detection of PAVMs by TTCE is feasible in pediatric patients presenting with HHT. The reliability of TTCE is high in this specific population. A low grade classification could presumably allow to avoid CT irradiation in pediatric patients.

C-085
CHILDREN SCREENING FOR PAVM: 15 YEARS FOLLOW-UP IN THE NETHERLANDS

A. Gauthier, AL Diederik, CJJ Westermann, R Snijder, JJ Mager

St Antonius Hospital, Nieuwegein, The Netherlands

Purpose: There is still controversy on the best screening protocol for children of an HHT patient for pulmonary arteriovenous malformations (PAVMs). At St. Antonius Hospital in The Netherlands, children of HHT patients are screened conform the same protocol since 1998. Our protocol includes clinical evaluation, supine and upright pulse oxymetry and chest radiography. If a low saturation or the chest XR is suggestive of a PAVM, we perform a CT scan. We do not perform transthoracic contrast echocardiography in children. We are well aware that we miss small PAVMs but think we detect the PAVMs that we would treat in childhood. *Method:* Patients' files were reviewed via database, hospital files and communication from other hospitals in The Netherland. We looked for complications of undiagnosed PAVM (brain abscess, stroke or hemoptysis). *Result:* 359 children were screened since 1998; most of them had positive family history of HHT (92.7%). The mean follow-up is 7,0 years (0,1-15,0 years). We found a definite clinical diagnostic (3 or 4 Curacao criteria) in 101 children (28,1%) while 99 children (27.5%) met 2 criteria and 134 children (37,2%) 1 criterion. Genetic testing has been done in 122 children (33,9%). It was positive in 81 of those children (66.4%). PAVM were found in 40 patients and embolisation was performed in 31 children. There was no case of brain abscess, stroke or hemoptysis in the screened children during the follow-up. PAVMs were diagnosed in 3 additional patients during follow-up in adulthood. *Conclusion:* In our 15 years experience, screening children of HHT patients for PAVMs was done in a simple, non-invasive manner, with chest-XR and measurement of saturation only. Although small PAVMs are missed, no

non-commercial use only

complications were encountered during follow-up. This might also be related to the fact that children with possible or definite HHT were advised prophylactic use of antibiotics, even when no important PAVMs were found on the basis of normal saturation and normal chest XR.

C-086
EPIDEMIOLOGICAL SURVEY ON CANCER RATES IN PATIENTS WITH HEREDITARY HAEMORRHAGIC TELANGIECTASIA AND CONTROLS

AE Hosman, HL Devlin, BM Silva, CL Shovlin

Imperial College London, Imperial College Healthcare NHS Trust, London, UK; and the Medical Schools of The Academic Medical Center, University of Amsterdam, the Netherlands; Imperial College London, and Barts and the London SMD, UK

Introduction: HHT patients have multi-systemic vascular lesions, that lead to major morbidity and mortality: Despite the well known risks, life expectancy is surprisingly good, particularly for patients over 60ys[1]. We hypothesised that HHT patients may be protected against life-threatening cancers compared to the general population. *Methods:* To capture cancer-histories in an unbiased manner, relevant questions were incorporated into a wider ethically-approved survey. Power calculations indicated that to distinguish incidence rates of specific cancer subtypes would require unrealistic response rates, so the study was designed to capture data on multiple relatives per respondent. Participants were recruited from HHTIC London and following advertisement by the HHT Foundation International. Following data download, all HHT-related questions were reviewed independently by two members of the study team, to allow blinded assignment of status based on the Curaçao criteria (HHT-subject, unknown, or control). For HHT respondents, where it was known which side of the family HHT came from, HHT relatives could also be assigned as HHT-affected, unknown or control. *Results:* In total, 1154 participants completed the study. Following designation of participants and relatives, cancer data were available on 2166 people with HHT and 2817 controls. In total 398/2166 (18.4%) HHT subjects and 668/2817 (23.7%) controls had experienced a cancer. Age of onset data were available for 307 (77%) HHT and 532 (80%) control cancer cases. Age-adjusted quadratic regression was used to determine whether cancers occurred more of less frequently in HHT than controls. As expected, cancer rates were strongly age-related ($p<0.0001$, all cancers) and after age-adjustment, there was no significant difference in the overall rates of all cancers, colon, prostate, or haematological cancers between HHT subjects and controls. However, there were significant differences in the rates of both breast ($p=0.019$) and lung ($p=0.0012$) cancer between the groups. *Conclusions*: The findings suggest that there may be differences in cancer incidence in HHT patients and the general population, and that this may depend upon specific underlying pathologies of different cancers.

1. Kjeldsen et al, J Intern Med 1999;245:31–39

C-087
CLINICAL MANIFESTATION IN LARGE COHORT OF PEDIATRIC PATIENTS WITH HHT1 AND HHT2: A CROSS-SECTIONAL STUDY

GM Lenato[1], P Giordano[2], P Suppressa[1], M Sangerardi[2], P Piccarreta[2], P Lastella[1], F Dicuonzo[3], A Scardapane[4], ML Fiorella[5], C Sabbà[1]

[1]*Clinica Medica "Frugoni" and Rare Disease Center, University Hospital of Bari,* [2]*Pediatric Unit, University Hospital of Bari, Bari,* [3]*Neuroradiology Unit, University Hospital of Bari,* [4]*Radiodiagnostic Unit, University Hospital of Bari,* [5]*Otolaryngology Unit, University Hospital of Bari, Italy*

Background: Hereditary Haemorrhagic Telangiectasia (HHT) entails a marked clinical relevance, due to sudden vascular complications, secondary to visceral arteriovenous malformations (AVMs). Such AVMs and their complications can also occur in childhood. However, the risk associated to AVMs can be considerably reduced by means of an early preventive screening. To date, there are still insufficient data regarding the clinical features of pediatric HHT patients, in terms of prevalence, symptoms, onset, and morbidity of AVMs. *Objective:* The goal of the present study consists in an evaluation of the clinical features in a large cohort of pediatric patients with genetically confirmed HHT. *Methods:* The children were enrolled in this study by genetic testing, through confirmation/exclusion of the disease-causing mutation previously identified in the family. Carriers of ENG mutations and of ACVRL1 mutations were defined as HHT1 and HHT2 patients, respectively. Screening for brain AVM was carried out by MRI and MRA, pulmonary AVMs were detected by Multi-Slice CT, liver involvement was investigated through Eco-Color-Doppler and Abdominal Dynamic MRA. Endonasal and cutaneous telangiectases were visualized by rhinoscopy and capillaroscopy, respectively. *Results:* Fourty-four children (mean age: 9.65; range 1–18 years) were subjected to instrumental screening, of which 22/44 were HHT1 and 22/44 were HHT2. Cerebral screening disclosed large AVMs in 4/44 cases, all HHT1, and micro-AVMs in three cases. Pulmonary AVMs were detected in 20/44 patients (14 of which being HHT1) and nine of them had lung AVMs amenable to treatment. Three children had cerebral lesions secondary to lung AVMs. Hepatic screening showed signs of liver involvement in 23/44 children (17 of which being HHT2), without association to clinical risk in any case. At least one endonasal telangiectasis wase found in 30/44 patients. Fifteen children had cutaneous telangiectases at capillaroscopy. *Conclusions*: Children with HHT have a high prevalence of AVMs, so an appropriate clinical and instrumental screening is advisable.

Non-commercial use only

C-088
EPISTAXIS SEVERITY SCORE IN PEDIATRIC PATIENTS WITH HEREDITARY HEMORRHAGIC TELANGIECTASIA

DA Stevenson[1], J McDonald[2,3], P Bayrak-Toydemir[2,3], PD Ward[4], K Wilson[4], K Whitehead[5]

[1]*University of Utah, Dept. of Pediatrics, SLC, UT,* [2]*ARUP Laboratories, SLC, UT,* [3]*University of Utah, Dept. of Radiology, SLC, UT,* [4]*University of Utah, Dept. of Surgery, SLC, UT,* [5]*University of Utah, Dept. of Medicine, SLC, UT, USA*

Although the manifestations of hereditary hemorrhagic telangiectasia (HHT) increase with age, presentation of symptoms begins in the pediatric period. Data on the pediatric natural history of HHT are lacking. An epistaxis severity score (ESS) for HHT (www2.dexelmed.edu/hht-ess/) is available and a 3-month recall ESS has been applied to all patients at our center since January 2010. Our objective was to assess epistaxis severity in a pediatric cohort. The medical records of individuals ages 0-18 years evaluated at the University of Utah for known or suspected HHT (N=73) were reviewed over 3 years (January 2010-2013). Forty-three individuals had a molecular diagnosis of HHT [ACVRL1(N=27); ENG(N=14); SMAD4(N=2)]. In this group, mean age=9.9 years (range 0.2-18); mean ESS =1.32 (range 0-4.22), with variance mostly driven by epistaxis frequency and duration; only one individual was anemic, one patient underwent laser photocoagulation, and one described gushing or pouring intensity epistaxis. The mean age of epistaxis onset was 5 years (range 0.1-13), with 6 individuals never having epistaxis. Among patients likely to already have epistaxis onset (age ≥7), epistaxis was more severe in ENG (ESS=2.52, N=7) than ACVRL1 (ESS=1.40, N=19, p=0.046). For both genotypes, epistaxis severity worsened with age. No individuals that were mutation- negative fulfilled Curacao criteria (score ≥3), but 20 of the remaining 31 children were highly suspicious for HHT based on Curacao criteria score of 2 ("possible HHT") with 2 or more family members with scores of 2. This group had mean age=7.8 years (range 1.5-16) and did not differ significantly from the mutation positive cohort [mean ESS =1.8 (range 0-4.45); mean age of epistaxis onset 4.2 years (range 1-13)]. The remaining 11 children had telangiectases and/or epistaxis but did not have a significant family history. Our data suggest that epistaxis in the pediatric population for confirmed HHT is mild with average onset of 5 years. Medical attention for epistaxis was rarely required and anemia exceedingly rare. Epistaxis patterns were similar in the mutation-negative group highly suspicious for HHT. There was a trend for increased ESS in ENG vs. ACVRL1 but larger cohorts are needed.

C-089
LONGITUDINAL STUDY OF NATURAL HISTORY OF ARTERIOVENOUS MALFORMATIONS IN EVOLUTIONARY AGE OF HEREDITARY HAEMORRHAGIC TELANGIECTASIA

P Suppressa[1], P Giordano[2], GM Lenato[1], M Sangerardi[2], P Lastella[1], D Quaranta[3], L Chiumarulo[4], R Valerio[1], P Buonamico[5], B Covella[2], D De Mattia[2], C Sabbà[1]

[1]*Clinica Medica "Frugoni" and Rare Disease Center, University Hospital of Bari,* [2]*Pediatric Unit, University Hospital of Bari,* [3]*Dermatology Unit, University Hospital of Bari,* [4]*Neuroradiology Unit, University Hospital of Bari,* [5]*Internal Medicine Unit, University Hospital of Bari, Bari, Italy*

Background: Hereditary Haemorrhagic Telangiectasia (HHT) has a clinical spectrum showing a considerable variability. Although HHT is generally characterized by a higher penetrance with increasing age, HHT-related manifestations can also arise in paediatric age. Since complications secondary to otherwise occult visceral arteriovenous malformations (AVMs) involve a marked clinical risk, HHT International Guidelines recommend HHT patients to be enrolled in a periodic radiological survey, and preventive treatment whenever necessary. However, the most appropriate timing of the radiological surveillance of AVM is still a matter of debate, especially in children and young adults. To this purpose, it would be crucial to know the natural history of already existing AVMs over time and the eventual occurrence of de novo AVMs. Yet, addressing such target requires a prospective longitudinal observation, which has never been carried out in paediatric HHT patient thus far. *Objective:* The objective of the present study is to perform a longitudinal observation of HHT-related visceral AVMs during evolutionary age. *Methods:* Patients in pediatric age, initially subjected to AVM screening, were fully instrumentally monitored after some years, they, independent of their AVM status at the first screening. *Results:* Among the children enrolled in the first screening, 12 patients accepted the instrumental monitoring. The mean time of follow-up after the first screening was 6.6 years. In the 12 patients subjected to the longitudinal observation, a de novo small pulmonary AVM was detected in one case and regression of a small pulmonary AVM occurred in one case. In one patient, we observed very slight enlargement of a lung AVM, already detected upon first screening. In two patients, cerebral ischemic lesions secondary to pulmonary AVM were observed at first screening, which evolved towards lacunar and cyst-like regions inside the brain parenchyma. Onset of de novo brain AVM did not occur in any of the 12 patients, including the two patients with cerebral ischemic lesions upon first screening. *Conclusions:* Our study shows that a follow-up of 6 years after the first screening represents an adequate timing for monitoring natural history and de novo formation of AVMs in HHT during evolutionary age.

non-commercial use only

C-090
A HEREDITARY HEMORRHAGIC TELANGIECTASIA SEVERITY SCORE

GA Latino, ME Faughnan, H Kim, W Young, The Brain Vascular Malformation Consortium

[1]*St. Michael's Hospital and the Li Ka Shing Knowledge Institute, University of Toronto, Toronto, Canada,* [2]*Center for Cerebrovascular Research, Department of Anesthesia and Perioperative Care, University of California, San Francisco, CA,* [3]*The Brain Vascular Malformation Consortium, Rare Diseases Clinical Research Network, National Institutes of Health, USA*

Introduction: To date, there are no known methods to categorize disease severity in HHT. Here, we present the first known attempt at developing an HHT severity score, which incorporates organ involvement and chronic bleeding, and correlating scores to a composite adverse outcome. *Methods:* We collected data from the first 525 HHT patients recruited to the HHT Project of the BVMC, including age, sex, HHT mutation type, and the prevalence of epistaxis, mucocutaneous telangiectasia and visceral AVMs. An HHT severity score was calculated for all patients, which ranged from 0 to 7, and included: 1 point for each organ affected by AVMs (maximum of 3 points); a maximum of 2 points for chronic bleeding (1 point each for epistaxis and GI bleeding); and 2 points for severe organ involvement (i.e. diffuse PAVMs OR symptomatic liver involvement). Patients with incomplete information were excluded. Based on the calculated score, patients were categorized as having mild (0-2), moderate (3-4) or severe (5-7) disease. The occurrence of any one adverse outcome, which included stroke, ICH, seizure, anemia, transfusions, hemoptysis, hemothorax, brain abscess, and death, was then identified in all patients. The frequency of any adverse outcome was correlated with severity score categories using Fisher's exact test. *Results:* The frequency of any adverse outcome was significantly different across the three severity groups (46.4% in the mild group, 65.0% in the moderate group and 95.0% in the severe group, p<0.001). Modeling the severity groups as categorical variables, the moderate group was significantly more likely to have an adverse outcome (OR =2.14, 95%CI 1.37-3.33, p=0.001) than the mild group, and the severe group was significantly more likely to experience an adverse outcome (OR =10.4, 95%CI 2.37-45.64, p=.002) than the mild group. *Conclusions:* We present the first HHT Severity Score and have correlated this with severe outcomes. Though the score requires further validation, this represents the first step in developing an HHT severity score to help predict disease outcomes and guide clinical management.

Table 1: Description of study population (N=525)

Female	269/428 (63%)
Mean age ± SD (years)	45.9 ±17.6
Epistaxis	411/428 (96%)
Mucocutaneous telangiectasia	393/428 (92%)
Pulmonary AVMs	219/428 (51%)
Brain AVMs	103/428 (24%)
Hepatic AVMs	341/428 (80%)

C-091
AGE OF PRESENTATION IN HHT: BRAIN AVM DIAGNOSIS VS. EPISTAXIS

D Lin[1], A Zessler[2], W Young[3], ME Faughnan[4] and the Brain Vascular Malformation Consortium (BVMC)

[1]*Johns Hopkins University School of Medicine,Division of Neuroradiology, Baltimore, MD,* [2]*Johns Hopkins University,Baltimore, MD,* [3]*Center for Cerebrovascular Research, Department of Anesthesia and Perioperative Care, University of California, San Francisco, CA,* [4]*St. Michael's Hospital and the Li Ka Shing Knowledge Institute, University of Toronto, Toronto, Canada*

Purpose: Compare age at diagnosis and first complication of brain arteriovenous malformation (BAVM) with that at diagnosis of epistaxis. *Methods:* Data collected for 524 participants of the Brain Vascular Malformation Consortium (BVMC) study was extracted and reviewed. In the subset of participants who had BAVM and epistaxis, the mean age of onset was compared using t-test. *Results:* Participant characteristics are summarized in Table 1. At least 79% (414 of 524) subjects had epistaxis, which occurred at a mean age of 13 years (range 0-61). BAVM was present in 127 (24%) of the 524 subjects, with a mean age of BAVM diagnosis of 29 years (range 0-71), and mean age of onset of symptoms (hemorrhagic or nonhemorrhagic) at 25 years (range 0-58), both significantly higher compared to the age of epistaxis onset (P<0.000, 2-tailed unpaired t-test). In 9 out of 127 cases (7.1%) BAVM diagnosis predated epistaxis, at a mean age of 1.5 years. In 5 of 127 cases (3.9%) brain symptoms predated epistaxis, all 5 cases occurring during the first year of life. Among those with epistaxis, 118 subjects had a diagnosis of BAVM and 95% of them reported epistaxis prior to or at the time of BAVM diagnosis. Forty-eight of the 118 subjects with both BAVM and epistaxis had neurological symptoms, among which intracranial hemorrhage was the most common neurological complication (in 19 of 48 subjects). *Conclusion:* In HHT, epistaxis often pre-dates the diagnosis of, and clinical complications of, BAVM. In other words, it is reasonable to triage children and young adults with epistaxis (in an HHT family) for immediate BAVM screening. However, children and young adults (from an HHT family) who do not have epistaxis are still at risk of BAVM and complications. Given the lower frequency of BAVM and complications in this group, the current practice of diagnosis via genetic testing before brain screening appears reasonable. These results need to be verified in a prospective cohort as they are limited by survival bias and therefore risk of early BAVM complication (before epistaxis) is likely underestimated.

Table 1.

Characteristics	N=524 (%)
female gender	333 (63.5)
age at enrollment (years)	46.4
children (age < 18 years)	39 (7.4)
epistaxis	414 (79)
brain AVM	127 (24)

Non-commercial use only

POSTERS

GENETICS AND GENOTYPE/PHENOTYPE IN HHT

P-093
GENOTYPE-PHENOTYPE CORRELATION IN A NATIONAL MUTATION STUDY OF DANISH PATIENTS WITH HEREDITARY HEMORRHAGIC TELANGIECTASIA

PM Tørring[1,2], K Brusgaard[1], LB Ousager[1], PE Andersen[3], AD Kjeldsen[2]

HHT-Centre OUH. Departments of [1]Clinical Genetics, [2]Otorhinolaryngology, [3]Interventional Radiology, Odense University Hospital and Institute of Clinical Research, University of Southern Denmark, Odense, Denmark

Conflict of interest: None. The full manuscript has been submitted for publication. Abstract *Purpose:* Hereditary Hemorrhagic Telangiectasia (HHT) is an autosomal dominantly inherited vascular disease characterized by the presence of mucocutaneous telangiectasia and visceral arteriovenous malformations (AVMs). About 85% of HHT patients carry mutations in ENG, ACVRL1 or SMAD4 genes. We report here on the genetic heterogeneity in the Danish national HHT population and address the prevalence of pulmonary AVM (PAVM). *Methods:* Probands of 107 apparently unrelated families received genetic testing, including sequencing and multiplex ligation-dependent probe amplification (MLPA) analyses of ENG, ACVRL1 and SMAD4. *Results:* In 88% of the probands (n=94), a mutation was identified in one of the three genes. In total we identified 66 unique mutations, primarily in ENG and ACVRL1, of which 27 (41%) were novel. Large deletions were identified in both ENG and ACVRL1. The prevalence of PAVM was 52.0% in the patients with ENG mutations and 13.1% in the ACVRL1 mutation carriers. Eighty percent of the patients were diagnosed clinically, fulfilling the Curaçao criteria, and the remaining were diagnosed by genetic testing. *Conclusions:* The majority of the mutations found in Danish patients with HHT are private. The observed mutation detection rate was similar to that in other series with strict ascertainment criteria.

P-094
CONSAGUINITY IN HHT – SCREENING A FAMILY WITH HHT IN BOTH PARENTS

M Mei-Zahav, H Blau, E Bruckheimer

HHT center, Schneider Children's Medical Center of Israel, Sackler Faculty of Medicine, Tel Aviv University, Israel

Background: HHT is an autosomal dominant inherited disease. The marriage of two related HHT patients poses the offspring to the inheritance of one or two mutations. We describe the clinical presentation of an Arab family with both parents, 1st degree cousins carrying the same Endoglin mutation. *Methods:* The children of two HHT patients were assessed at the HHT center at Schneider's CMCI in Israel. Bubble echocardiography followed by chest CT when indicated was performed to detect pulmonary AVMs. Cerebral AVMs were detected by head MRI. *Results:* The mother carried seven pregnancies. Two pregnancies (twin; single) were terminated in 1st trimester due to spontaneous abortions. It is hypothesized that the abortions represent inheritance of both HHT mutations and are incompatible with life. All five children were assessed at the HHT center. Four children, all males, were diagnosed with clinical and genetic HHT. One daughter does not have HHT. All four children were diagnose with pulmonary AVMs. Three were diagnosed with an isolated PAVM which was embolized in all three with good results. One child was diagnosed with diffuse PAVMs. He had repeated embolotherapies with closure of segmental arteries to lower lobes with no significant improvement. Two children were diagnosed with cerebral AVMs, One required cerebral embolotherapy. *Conclusions:* A wide clinical variability was demonstrated in children of 2 parents with HHT. As described earlier homozygosity is probably incompatible with life.

P-095
GENETIC EPIDEMIOLOGY OF HEREDITARY HEMORRHAGIC TELANGIECTASIA ASSOCIATED WITH PULMONARY ARTERIOVENOUS MALFORMATIONS IN JAPAN

T Shioya, M Satake, A Kawagoshi, K Sato, M Sano, H Ito

Akita University Graduate School of Health Sciences Department of Physical Therapy, Akita University Graduate School of Medicine Department of Pulmonary Medicine, Japan

Method and Subjects: We report a genetic epidemiologic study in a county, A, in the Akita prefecture (population 1.1 million) located in northern Japan. A total of 137 pedigree members were traced of which 81 were alive and 42 were affected by HHT in a county A. National survey for PAVMs associated with HHT was carried out among the 4,409 pulmonary specialists those who belong to Japanese Respiratory Society in 2011. Results: Linkage analysis complicated with PAVM revealed a linkage to the HHT1 locus (encoding endoglin; ENG). Three novel mutations were found in four families, all of which led to a frame shift: a G to C transversion at the splicing donor site of intron 3 (Inv3+1 G>C) in one family, one base pair insertion (A) at nucleotide 828 (exon 7) of the erdoglin cDNA in two large families (a828-29 ins A), and a four base pair deletion (AAAG) beginning with nucleotide 1120 (exon 8) of the endoglin cDNA (c.1120-1123 delAAAG) in one family. The insertion of A in exon11 (c.147O-1471 insA) mutation was found in one family. PAVMs were associated in 18 out of 42 HHT patients (42.8%) in this county. In the national epidemiologic survey in Japan, HHT was proven in 50 out of 202 PAVMs (24.7%). The percentage of female patients of PAVMs not

Non-commercial use only

associated with HHT was 82%, whereas that of PAVMs associated with HHT was 56 Summary and Conclusion: The population prevalence of HHT in the county was estimated to be 1:8,000-1:5,000, roughly comparable with those reported in European and U.S. populations, which is contradictory to the traditional view that HHT is rare among Asians. There was a gender difference in PAVMs associated with HHT and non- HHT. We recommend that families with HHT be screened for gene mutations in order that high-risk individuals complicated with PAVMs receive early diagnosis and treatment initiation that will substantially alter their clinical course and prognosis.

P-096
HEREDITARY HAEMORHAGIC TELANGIECTASIA, AN AUSTRALIAN COHORT: CLINICAL AND INVESTIGATIVE FEATURES

M Salaria[2], J Taylor[1], M Bogwitz[1], A McLauchlin[1], I Winship[1,3]

[1]*Department of Genetics, Royal Melbourne Hospital, Grattan Street Parkville,* [2]*Department of Genetics, Southern Health, Clayton,* [3]*Department of Medicine, MDHS, University of Melbourne, Parkville, Australia*

This retrospective study describes the phenotypic features of families with hereditary haemorrhagic telangiectasia (HHT) seen at The Royal Melbourne Hospital. This is a large tertiary/quaternary academic hospital in Victoria, Australia, a state with a population of some 6 million people. We wished to assess the experience of HHT in the state of Victoria, and to customize a protocol for surveillance of patients with HHT. Data was abstracted from clinical records of all patients referred to the Clinical Genetics Service between 2007 and 2011 with a suspected diagnosis of HHT.

	%O2 sat-stand/lying	PAVMs	Embolotherapy	%O2 sat, post 1st emboloth.	CAVM/emboloth.
S.13y	73/67	diffuse	X3	75	Small/no
S.11y	95/89	isolated	yes	98	No
S.10y	99/96	Isolated	Yes	99	No
S.5y	100/100	Isolated	Yes	100	Large/yes

These data were analysed for clinical features, types of HHT and genetic testing results where available. Our cohort comprising 40 females and 23 males, was assessed using the Curacao criteria. Twenty-two patients fulfilled the criteria for a definite diagnosis, 30 had a possible diagnosis, and 11 were assessed as unlikely to have HHT at the time of data analysis. Seventeen patients had pulmonary arterio-venous malformations (PAVMs), five had cerebral AVMs (CAVMs), five had hepatic AVMs (HAVMs), three had confirmed bowel telangiectasia, and one patient had a pancreatic AVM. Two female patients with HHT had complicated pregnancies during their follow-up with us. Timely access to specialist care is a recurrent challenge to the people in our cohort, with epistaxis the most frequent and troublesome complication of HHT. Three families had mutations in the ENG gene, three had mutations in the ACVRL1 gene and two families had mutations in the SMAD4 gene. Our clinic has become a referral centre for the country, with requests from throughout Australia for co-ordination of management at the Royal Melbourne Hospital. The optimal management of patients with HHT is provided by a multidisciplinary team approach, including a clinical geneticist, genetic counsellor, otorhinolaryngologist, respiratory physician, neurologist, interventional radiologist, gastroenterologist, haematologist, and an obstetric team with experience in managing pregnancy in women with HHT.

P-097
IDENTIFICATION OF NOVEL VARIANTS IN ARGENTINEAN PATIENTS WICH SUFFERS FROM HEREDITARY HEMORRHAGIC TELANGIECTASIA

AR Cajal[1-4], CV Ramirez[1], NC Bravo[1], LD Costa[2], M Serra[3-4]

[1]*Genomic and Molecular Medicine Unit. Institute of Basic Sciences and Experimental Medicine (ICBME). Italian Hospital of Buenos Aires,* [2]*LBAL. Institute of Basic Sciences and Experimental Medicine (ICBME). Italian Hospital of Buenos Aires,* [3]*HHT Unit Director. Internal Medicine. Italian Hospital of Buenos Aires,* [4]*HHT Unit and ARG (Argentinian Rendu Study Group). Italian Hospital of Buenos Aires, Argentina*

Hereditary Hemorrhagic Telangiectasia (HHT) is an autosomal dominant disorder characterized by telangiectasia and arteriovenous malformations. Genetic diagnosis of HHT type 1 or 2 is made if a mutation is identified in ENG or ACVRL1 genes. Our sample consisted of 10 unrelated HHT cases (three or four HHT clinical diagnostic criteria). Coding región of ENG and ACVRL1 genes were analysed through DNA-sequencing. For the analysis of not reported missense variants (NCBI dbSNP nor HHT mutation databases), an in silico analysis (PolyPhen-2 and SIFT softwares) and family segregation study were done. *ACVRL1 gene:* Mutations asociated with HHT2 were identified in exons 8 and 10 (c.1126A>G;p.Met376Val and c.1451G>A;p.Arg484Gln) in 2/10 patients. Four SNP's previously described were identified in seven patients. *ENG gene:* Two out of ten patients showed mutations asociated with HHT1 in exons 9a and 10 (c.1199delG; p.Gly400fsX420 and c.1346_1347delCT,p.Ser449fsX499). Six SNP's previously described and three novel missense heterozygous variants were identified. In silico analysis does not support pathogenicity of 2/3 variants (c.176A>G;p.Asn59Ser and c.1672A>G;p.Gly558Arg) while the other variant (c.1109T>A;p.Leu370Gln) is potentially damaging (PolyPhen: score=0.977, SIFT: score=0). In order to evaluate if this predicted damaging variant tracked with the disease, family segregation study was perform with seven probands' family members (Table 1). The variant is carried by all studied family members affected, but not by a proband´s sister (unknown clinical status) whose daughter (HHT clinical diagnosis) carries the variant. Although the in silico analysis supports pathogenicity, the co-segregation study of this variant is negative. The use of segregation studies and softwares which predict impact of amino acid substitutions on the structure and function of human proteins, are useful tools for evaluation of novel sequence variants.

non-commercial use only

However, it is not only needed to examine a healthy control group (novel variants could be rare alleles) but also functional studies to confirm the pathogenicity of findings. In our sample of Argentinean patients, we achieved to identified four patients with HHT (rate of success in molecular diagnosis: 40%, 2/4 with HHT1 -50%- and 2/4 with HHT2 -50%-). In order to increase this rate, additional approaches like MLPA and sequencing SMAD4 should be used.

Table 1: Molecular result and clinical findings

Individual	Molecular Result	Telangiectasia	Epistaxis	Solid Organ Involvement
Proband	c.1109 T>A	yes	yes	yes
Sister	Negative for c.1109 T>A	Unknown	unknown	unknown
Daugther	c.1109 T>A	yes	yes	yes
Son	c.1109 T>A	yes	yes	yes
Grandson	Negative for c.1109 T>A	Unknown	Unknown	Unknown
Aunt	c.1109 T>A	yes	yes	yes
Cousin	c.1109 T>A	yes	yes	yes

P-098
HEREDITARY HAEMORRHAGIC TELANGIECTASIA IN NORTH AFRICAN AND SUB-SAHARAN PATIENTS

C Canzonieri[1], F Ornati[2], E Matti[3], F Chu[3], G Manfredi[4], C Olivieri[1], E Buscarini[4], F Pagella[3], C Danesino[1] on behalf of HHT-NET

[1]*General Biology and Medical Genetics, Department of Molecular Medicine, University of Pavia, Pavia, Italy.* [2]*Department of Cardiology, Foundation I.R.C.C.S. Policlinico "S. Matteo", Pavia, Italy,* [3]*Department of Otorhinolaryngology, Foundation I.R.C.C.S. Policlinico "S. Matteo", Pavia, Italy,* [4]*Department of Gastroenterology, Maggiore Hospital, Crema, Italy*

As is know, Hereditary Haemorrhagic Telangiectasia in black African descent is a rarity. To date, only one paper reports a mutation in a HHT black adult patient born in Kenya. The other cases in literature were published before the identification of the two disease related gene. Regular immigrants from North African and sub-Saharan countries, for whom the Italian public health service is fully available, were recorded to be (December 2011) about 760.500 and 350.000 respectively, but a high number of non-registered immigrants are certainly present. We report two single cases among the about 500 index cases, collected by the centres caring for HHT in northern Italy, in Pavia and Crema. The HHT diagnosis on the patients was performed according to Curaçao criteria. The first is a female patient born in Morocco (regular immigrant: about 501.600) with a history of nosebleeds and pulmonary arteriovenous malformations. The second one is a male patient born in Senegal (regular immigrant: about 81.000). He showed recurrent and spontaneous nosebleeds, telangiectasia and a clearly positive family history (his father, three sibs and two children were reported to suffer from nosebleeds). Molecular analysis of ENG and ACVRL1 gene was performed to identify the disease-causing mutation. We found a mutation in intron 2 of ENG [c. 220-1 G>C (Splice Defect)] and a mutation in exon 8 of ACVRL1 [c. 1232 G>A (p. R411Q)], respectively. In our lab, analysis of exon 3, including intron-exon boundaries, reveals 20% of the mutations identified in ENG gene. The mutation observed is yet not published. The exon 8 carries 24% of the mutations identified in ACVRL1 gene. Among them, the mutation observed was found in 5/38 index cases from unrelated families and more over has also been reported several times in the HHT mutation database (http://arup.utah.edu/ database/hht/), in patients from different ethnic origin. Overall these data support the observation about the rarity of HHT in Black Africans.

P-099
CAPILLARY MICROSCOPY IN HEREDITARY HEMORRHAGIC TELANGIECTASIA: A PROSPECTIVE STUDY OF 44 PATIENTS

S Riviere[1], E Marnas[2], AK Van Kien[2], JP Laroche[2], B Lorcerie[3], I Quere[2]

[1]*Service de Medecine interne et maladies multiorganiques, centre de compétence pour la maladie de Rendu Osler, CHU Montpellier, France,* [2]*Service de Medecine interne et maladies vasculaires, CHU Montpellier, France,* [3]*Service de Medecine interne, CHU Dijon, France*

Telangiectasia and epistaxis are the clinical hallmarks of hereditary hemorrhagic telangiectasia (HHT). The physiopathology of this condition is poorly understood but seems to involve a proangiogenic inhibitor deficiency. Telangiectasis involves arteriovenous microshunts with collapse of the capillary bed. Nailfold capillary microscopy is a non invasive imaging technique allowing direct observation of the microvasculature, which has been little studied in HHT. Our aim was to describe capillary nailfolds in HHT patients. Methods: From October 1 2012 to January 30 2013, 44 consecutive HHT patients were prospectively included on referral to our regional center for HHT. All capillaroscopic examinations were performed by a single investigator. A megacapillary was defined as a symmetric, enlarged loop >50 m in diameter. Telangiectasia was defined a bunch or tangle of megacapillaries. *Results:* Population: 44 HHT patients (18 men and 26 women), with a mean age of 51.8(±19.5) years. Epistaxis, telangiectasia, pulmonary arteriovenous malformations (PAVM) and hepatic arteriovenous malformation (HAVM) were present in 97.7, 85.4, 44.2 and 39.5% of patients, respectively. Mutations had been identified in 31 of the 44 (70%) patients: 61% for the endoglin gene, 39% for the ALK1 gene. *Nailfold examination:* Capillaroscopy results were abnormal in all HHT patients. Megacapillaries were observed in 43% and at least one telangiectasia in 70.5 % of patients. Avascular areas were found close to these telangiectases in 54 % of cases. Small and non traumatic microhemorrhages were seen in 40% of the patients. Loop enlargement, such as a draining limb with tortuous configuration in particular, were noted in 52% of patients. Telangiectasia was more frequent in patients with than without PAVM (p=0.002). *Conclusion:* Capillary nailfold microscopy results were systematically abnormal in HHT patients. HHT should be

non-commercial use only

considered as a diagnosis in patients with megacapillaries or telangiectases, together with recurrent epistaxis.

P-100
SEARCH FOR GENETIC MODIFYING FACTORS FOR HEPATIC VASCULAR MALFORMATIONS IN HHT

S Giraud[1], S Dupuis-Girod[2], C Bardel-Danjean[3], MF Carette[4], B Gilbert-Dussardier[5], S Riviere[6], JC Saurin[7], M Eyries[8], A Kitzis[9], E Decullier[10], G Lesca[1], A Calender[1]

[1]*Hospices Civils de Lyon, Service de Génétique, Hôpital E. Herriot, Lyon, France,* [2]*Hospices Civils de Lyon, Service de Génétique, Hôpital Louis Pradel, Bron, Centre de Référence National pour la maladie de Rendu-Osler, France,* [3]*CNRS, UMR5558, Laboratoire de Biométrie et Biologie Evolutive, Université Claude Bernard-Lyon 1, Villeurbanne, France,* [4]*Assistance Publique-Hôpitaux de Paris, Service de Radiologie, Hôpital Tenon, Paris, France,* [5]*CHU la Milétrie, Service Génétique, Poitiers, France,* [6]*CHU de Montpellier, Service de Médecine Interne, Hôpital St Eloi, Montpellier, France,* [7]*Hospices Civils de Lyon, Service de Gastro-Entérologie, Hôpital E. Herriot, Lyon, France,* [8]*Assistance Publique-Hôpitaux de Paris, Département de Génétique, GH Pitié-Salpêtrière, Paris, France,* [9]*CHU la Milétrie, Laboratoire de Génétique, Poitiers, France,* [10]*Hospices Civils de Lyon, pôle IMER, Lyon, France*

HHT is an autosomal dominant disorder characterized by angiodysplasia and caused by mutations in the ENG, ACVRL1 and SMAD4 genes coding proteins involved in the TGF-β/BMP9 signalling pathway. Most common visceral complications are caused by pulmonary (PAVM), cerebral or hepatic arteriovenous malformations (HAVM). Prevalence of HAVM is higher in ACVRL1 mutation carriers but there is a large inter and intrafamilial variability in visceral disease severity, suggesting a role for modifier genes, in addition to the ENG or ACVRL1 mutation. This hypothesis was recently supported by Benzinou et al., (2012) who showed that single nucleotide polymorphisms within the PTPN14 locus may influence the development of PAVM. DNA from 353 patients in which genetic diagnosis was confirmed and who had underwent hepatic evaluation by sonography or by CT-scan were collected in 3 laboratories. Genetic and clinical data have been collected in CIROCO, French HHT patient database. Patients were classified in 3 groups according to their hepatic evaluation as proposed by Gincul et al., (2008): stage 1 for patients without clinical, biological or radiological signs of hepatic disease, stage 2 for patients with a mild disease and stage 3 for patients with a severe phenotype (liver transplantation, heart failure, or abnormal diameters of hepatic artery and vein). A toal of 50 HapMap SNPs located in 8 genes encoding proteins involved in the TGF-β signalling pathway were genotyped. Association with the presence of HAVM is tested by a logistic mixed effect model, allowing us to take into account familial relationships between patients. Univariate and haplotype analyses will be performed. These statistical analyses are in progress. Detailed results will be presented at the meeting.

P-101
ASSOCIATION OF VARIANTS IN INFLAMMATORY GENES WITH LESION BURDEN IN FAMILIAL CCM1

H Choquet[1], L Pawlikowska[1], J Nelson[1], A Akers[2], B Baca[3], B Hart[4], L Morrison[3], H Kim[1] for the Brain Vascular Malformation Consortium (BVMC) Study

[1]*Center for Cerebrovascular Research, Department of Anesthesia and Perioperative Care, University of California, San Francisco, CA,* [2]*Angioma Alliance, Durham, NC,* [3]*Departments of Neurology and Pediatrics, and* [4]*Radiology, University of New Mexico, Albuquerque, NM, USA*

Objective: Evidence is emerging that inflammation plays a key role in the pathogenesis of Cerebral Cavernous Malformations (CCM). We hypothesized that inflammation influences disease severity, as manifested by greater lesion burden in familial CCM type 1 (CCM1). The purpose of this study was to investigate whether genetic variants in inflammatory genes are associated with increased lesion burden in familial CCM1. *Methods:* Lesion burden was assessed on susceptibility-weighted MR imaging for 176 CCM1 patients who all carry the same founder mutation termed the common Hispanic mutation (CCM1-CHM) and were recruited as part of the Brain Vascular Malformation Consortium (BVMC) Project 6201 study. We selected three candidate genes involved in inflammatory pathways and containing variants previously reported to modify risk in other vascular disease settings: IL-1 , IL-6 and its receptor IL-6R. We used Affymetrix Axiom genome-wide genotype data to conduct association analyses between genetic variants in inflammatory genes and lesion burden. *Results:* Lesion burden (range: 0-713; mean ± SD: 60.5 ± 116.3) was highly variable among CCM1-CHM patients and positively correlated with increasing age (P<0.001). Linear regression analysis, adjusting for age and gender, showed that four variants in IL-1 were associated with lesion burden (P<0.05), but only rs13010814 remained significant after Bonferroni correction for multiple testing (=0.39; 95%C.I. 0.16-0.62; P=0.001). None of the 15 variants tested at the entire IL-6 locus was associated with lesion burden. However, 9 variants out of 17 tested at the entire IL-6R locus, were associated with lesion burden (P<0.05) and two remained significant after Bonferroni correction (=0.36; 95%C.I. 0.13-0.59; P=0.003 and =0.37; 95%C.I. 0.14-0.61; P=0.002 for rs12754243 and rs34844505, respectively). *Conclusions:* This study suggests that common variants in inflammatory genes such as IL-1 and IL-6R are associated with CCM lesion burden. Further work is needed to confirm our findings and elucidate how these genetic variants influence CCM1 disease severity.

Non-commercial use only

P-102
HEREDITARY HAEMORRHAGIC TELANGIECTASIA IN LAS PALMAS (CANARY ISLANDS) SPAIN

C Vázquez[1], A Santana[1,4], L Recio[2], C Bernabeu[2,3], LM Botella[2,3]

[1]*Unidad de Genética, Hospital Universitario Insular-Materno Infantil de Canarias,* [2]*Centro de Investigaciones Biológicas. CSIC (Consejo Superior de Investigaciones Científicas) Madrid,* [3]*CIBERER (Centro de Investigación en Red de Enfermedades Raras),* [4]*Research Unit, Hospital de Gran Canaria Dr. Negrin, Spain*

Hereditary Haemorrhagic telangiectasia (HHT) (OMIM 187300/ ORPHA774) is a vascular autosomic dominant disease leading to epistaxis, telangiectasias, gastrointestinal haemorrhages and arteriovenous malformations in lung, liver and brain. Prevalence is around 1-5,000/10,000 worldwide. Insulation and founder effects lead to a higher prevalence in some geographic regions such as the Caribbean Dutch Antilles, the French Jura region, and the Danish Fyn island. HHT is transmitted in 90% due to mutations in either Endoglin (ENG), or in Activin receptor-like kinase 1 (ACVRL1/ALK1) genes (HHT type 1 or 2, respectively). A North-South geographical variation seems involved in the HHT1 or 2 predominant type. HHT1is more frequent in the North countries of America and Europe, while HHT2 is more abundant in the Mediterranean countries. In the present communication we show for the first time a study of HHT in Las Palmas (Canary Islands, Spain). Seven independent cohorts with clinical criteria of HHT have been identified so far. Among them, two different mutations in ALK1 have been found. One is a missense mutation, located in exon 8 of ALK, c.1234 G>A; p.R411Q in a large family with 16 affected members identified. Other 4 families with a total of 40 affected members share the same mutation, in exon 4 of ALK1, c.353_360dupAGCTGGCC, p.L121fs. Moreover, four additional families, recently identified by clinical criteria, are still awaiting for the genetic determination. An estimation of the HHT patients belonging to the families identified so far, would yield around 200 HHT affected among the 600,000 inhabitants of this island, a ratio of 1 HHT case, every 3.000 inhabitants. Mutation c.353_360dupAGCTGGCC, p.L121fs, seems to be the founder mutation. However, the origin of the founder mutation, and its evolution due to insularity, are currently under investigation. The results of the present work add the HHT prevalence in Las Palmas (Canary islands) to the list of HHT higher prevalences, found in the Caribbean and Fyn islands.

P-103
A WHOLE EXOME SEARCH FOR ADDITIONAL HHT GENES

CJ Gallione[1], ET Cirulli[1], K Shianna[1], JK Ploos van Amstel[2], TGW Letteboer[2], N Prigoda-Lee[3], D Rushlow[3], R Klatt[4], M Letarte[4,5], CJJ Westermann[6], DA Marchuk[1]

[1]*Duke University Medical Center, Durham, NC, USA,* [2]*University Medical Center, Utrecht, the Netherlands,* [3]*Impact Genetics, Toronto, Canada,* [4]*The Hospital for Sick Children, Toronto, Canada,* [5]*University of Toronto, Toronto, Canada,* [6]*St. Antonius Hospital, Nieuwegein, the Netherlands*

Although linkage analyses have documented the existence of additional HHT genes, the HHT3 and HHT4 genes have not yet been identified. Neither have any additional families mapping to these regions been published. From this absence of data, we surmise that these loci might represent rare mutations, at least in most populations. In lieu of a family-based approach to identify novel HHT genes, we are employing genome-wide exome sequencing in "mutation-negative" HHT cases. Our cases were ascertained from two HHT DNA diagnostic centers and are generally represented by a single proband, or in a few cases, a nuclear family. In total, 19 samples were subjected to whole exome sequence analysis and analyzed for sequence variations. We will report the results of our search thus far, that has yielded a number of candidate genes harboring unique sequence variations in at least two different families. One might have hypothesized that our approach would enrich for HHT3 or HHT4 cases. Intriguingly, by searching genome-wide, we found that many of the best candidate genes did not fall within the limits of the HHT3 and HHT4 loci. This suggests that either HHT3 and 4 are extremely rare, or that these forms of HHT are primarily or exclusively caused by non-coding sequence changes in known genes, or finally, that the relevant transcripts are not yet annotated in the genome databases. We will continue to add samples to our dataset and we especially welcome data sharing from other groups using similar approaches towards the identification of additional HHT genes.

non-commercial use only

CELLULAR AND MOLECULAR INVOLVEMENT IN HHT AND RELATED PATHOLOGIES

P-104
EVIDENCE FOR A COMPROMISED IMMUNE SYSTEM IN A SPANISH COHORT WITH HEREDITARY HEMORRHAGIC TELANGIECTASIA

ML Ojeda-Fernandez[1,2], R Zarrabeitia[2,3], M Serra[4], L Recio-Poveda[1], C Bernabeu[1,2], LM Botella[1,2]

[1]*Centro de Investigaciones Biológicas, Consejo Superior de Investigaciones Científicas (CSIC),* [2]*Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), Madrid, Spain,* [3]*HHT Unit, Hospital Sierrallana, IFIMAV, Torrelavega, Santander, Spain,* [4]*Hospital Italiano, Buenos Aires, Argentina*

Hereditary hemorrhagic telangiectasia (HHT) is an autosomal vascular dominant disorder characterized by recurrent epistaxis, cutaneous telangiectases and visceral arteriovenous malformations (AVMs) that may affect various organs. Although several case reports suggest that HHT patients have a higher susceptibility to infectious complications such as cerebral abscesses, septicemia or osteo-

myelitis, their immune function has been poorly studied. To throw light on the putative involvement of the immune system in HHT, the relationship between infectious diseases and HHT has been studied retrospectively, in a cohort of HHT patients referred to the Spanish HHT Reference Center. The HHT syndrome was confirmed by clinical and genetic analysis. Among 195 patients analyzed during the period 2005-2010, thirteen cases of severe uncommon infections were identified such as endocarditis, osteomyelitis, meningitis and cerebral abscesses. Extracerebral infections accounted for 69% in HHT1 and 95% in HHT2; the pathogens were identified in some cases, including *Staphylococcus aureus, Streptococcus viridans* and *Helicobacter pylori*. Cerebral infections accounted for 31% in HHT1 and 5% in HHT2, mainly due to multiple anaerobic bacteria like Bacteroides fragilis and Peptostreptococcus. HHT1 patients tend to present more infections in the central nervous system than HHT2. The most common infections in HHT2 patients are located in the digestive system, usually Ulcus (*Helicobacter pylori*) and peritonitis. These data suggest that HHT is associated with a significant frequency of infectious diseases uncommon in the non-HHT general population. Accordingly, the HHT condition should be considered a risk factor for severe infections, as cerebral abscesses and endocarditis. Factors associated with a compromised immune system may explain the high rate of infection. A greater knowledge about the immune factors contributing to the development of life-threatening and mild infections in HHT, would improve patient information, diagnosis and prevention.

P-105
CHARACTERIZATION OF CIRCULATING ENDOTHELIAL CELLS IN HEREDITARY HAEMORRHAGIC TELANGIECTASIA

P Suppressa[1], GM Lenato[1], P Lastella[1], V Liso[2], A Mestice[2], C Margiotta[1], E Dani[1], L Scagliusi[1], A Mazzocca[1], C Sabbà[1]

[1]*Clinica Medica "Frugoni" and Rare Disease Center, Bari, Italy,* [2]*Haematology, Unit, University Hospital of Bari, Bari, Italy*

Background: Patients with Hereditary Haemorrhagic Telangiectasia (HHT) suffer from multiple arterio-venous shunts. HHT-typical shunts seem to be associated to an angiogenic imbalance mainly affecting endothelial cells, consisting in increased mobilization and loss of arterio-venous identity. Similarly to what happens to several other cardiovascular diseases, circulating endothelial cells (CECs) might play a relevant role in the pathogenic mechanism(s) and/or disease severity of HHT. CECs can have two different sources, deriving from either bone-marrow stem cells or mobilization of mature endothelial cells of pre-existing vessels. CEC levels have been associated to a different effectiveness of vascular repair, as well as to various degree of vascular damage, and were reported to represent a biomarker of different vascular disorders. *Aims:* To characterize the number of CECs in HHT patients, based on immunophenotypical properties, compared to two age-matched control populations (healthy volunteers and patients affected by non-HHT vascular diseases). *Methods:* Forty-four consecutive HHT patients were recruited bythe HHT Interdepartmental Center of Bari. Two control groups were enrolled: 20 healthy volunteers and 90 patients with non-HHT vascular disorders. CECs were defined as CD31+/VEGFR2+/CD34+/CD45-. Circulating hematopoietic cells (HSCs) were defined as CD34+/CD45low cells. CEC and HSC levels in peripheral blood was assessed by flow-cytometry analysis. *Results:* HHT patients had a significantly higher number of CECs (50.1 ± 80.5) when compared to both healthy controls (10.9 ± 14.5) and non-HHT vascular-disease controls (5.3 ± 11.9) (p\0.0005). Conversely, the number of HSCs did not differ significantly in the three groups (652 ± 1053 in HHT, 510 ± 355 in healthy controls, 665 ± 1137 in non-HHT vascular-disease controls). The number of CECs and the number of HSCs did not correlate with age, sex, and affected gene (Endoglin vs. ALK1/ACVRL1). *Conclusions:* Circulating Endothelial Cells are significantly elevated in HHT. These interesting observations might be explained by either an activated proliferation of bone-marrow-derived CECs or a stronger mobilization from pre-existing vessels. Since CECs are not increased in non-HHT vascular diseases, our observations suggest in fact that high levels of CECs are not associated to mere vessel damage secondary to haemorrhage.

P-106
EXPRESSION OF ENDOGLIN ISOFORMS IN THE MYELOID LINEAGE AND THEIR ROLE DURING AGEING AND MACROPHAGE POLARIZATION

M Aristorena[1,2], FJ Blanco[1,2], ML Ojeda-Fernandez[1,2], M de las Casas-Engel[1], E Gallardo-Vara[1], A Corbi[1], LM Botella[1,2], C Bernabeu[1,2]

[1]*Centro de Investigaciones Biologicas (CSIC),* [2]*CIBER de Enfermedades Raras (ISCIII), Madrid, Spain*

Endoglin (CD-105, TGF-β receptor III) is a homodimeric transmembrane glycoprotein that plays a crucial role in vascular remodeling and angiogenesis and is involved in important physiopathological processes such as Hereditary Hemorrhagic Telangiectasia (HHT), preeclampsia or cancer. Two different alternatively spliced isoforms of endoglin have been reported, L-endoglin and S-endoglin. Endoglin expression is up-regulated during the monocyte-to-macrophage transition, but little is known about its role in the immune system. Interestingly, an increased expression of the S-endoglin isoform during senescence of the monocyte-macrophage lineage, in both human and murine models, was observed. To assess the individual effect of endoglin isoforms on the monocytic lineage, we performed a stable isotope labeling of amino acids in cell culture (SILAC) analysis of both L-endoglin and S-endoglin transfectants in the human promonocytic cell line U937. By differentiating the monocytic endoglin transfectants into macrophages, we have also analyzed the gene expression, focusing on the typical pro-inflammatory (M1) and anti-inflammatory (M2) expression pat-

non commercial use only

terns in order to study macrophage polarization and the role of endoglin in the immune system during aging. Our functional validation studies suggest a non-redundant role for each endoglin isoform on the monocyte biology. In addition, we find that S-endoglin is a marker of senescence in the myeloid lineage and appears to impair the monocytic differentiation into a pro-inflammatory M1 phenotype.

CENTRAL NERVOUS SYSTEM INVOLVEMENT AND TREATMENT IN HHT

P-107
CLINICO-RADIOLOGICAL CHARACTERISTICS OF PRIMARY AND SECONDARY NEUROLOGICAL MANIFESTATIONS IN A LARGE COHORT OF HHT PATIENTS

M Gallea[1], P Favrole[1], B Marro[2], M Hermier[3], E Decullier[4,6], MF Carette[2,7], J Dupuis-Girod[5,6], S Alamowitch[1,7]

[1]*Department of Neurology, Tenon Hospital, Assistance Publique-Hôpitaux de Paris, Paris, France,* [2]*Department of Radiology, Tenon Hospital, Assistance Publique-Hôpitaux de Paris, Paris, France,* [3]*Department of Radiology, Hospices Civils de Lyon, Hôpital louis Pradel, Lyon, France,* [4]*Pôle IMER, Hospices Civils de Lyon, Lyon, France,* [5]*Department of Clinical Genetics and National Reference of Rendu-Osler Disease, Hospices Civils de Lyon, Hôpital Louis Pradel, Lyon, France,* [6]*Université de Lyon 1, Lyon, France,* [7]*Université Pierre et Marie Curie, Paris VI, Paris, France*

Background: Hereditary hemorrhagic telangiectasie (HHT) is an autosomal dominant genetic disease with a wide spectrum of vascular malformations, including pulmonary arteriovenous malformations (PAVMs), cerebral vascular malformations (CVMs) and hepatic arteriovenous malformations. Main neurological complications are cerebral abcess, cerebral ischemic event and cerebral hemorrhage. PAVMs are associated with cerebral ischemic event and cerebral abcess (identified as secondary neurological complications). CVMs (identified as primary neurological manifestations) may be asymptomatic or can lead to neurologic deficits mainly when they hemorrhage. Details on clinical and radiological aspects of these neurological manifestations were rarely reported in the literature, especially for ischemic events, and mainly as case reports or small series, or often restricted to one of the potential complications. Moreover, genotype-phenotype correlations need to be confirmed for primary or secondary neurological manifestations in HHT. *Objective:* To precisely describe primary and secondary neurological manifestations (symptomatic or not) in a large cohort of consecutive patients with HHT and to evaluate gentype-phenotype correlations. *Methods:* We performed a retrospective study of consecutive patients from 2 french HHT specialized centers (Lyon; reference center, 2140 patients) and (Tenon, Paris, 361 patients). Inclusion criteria were: 1) a clinically definite diagnosis (Curacao criteria) and/or a genetically established diagnosis of HHT, and 2) a cerebral (+- medullary) MRI and/or CT scan and with a MR and/or CT angiography. In these patients, we identified "neurological patients" if a neurological manifestation was reported in the past history and/or during the follow-up after HHT diagnosis, and/or if a parenchymal and/or vascular lesion was reported on cerebral or medullary radiological explorations. General HHT patient's data were collected using the french HHT CIROCO database. For identified neurological patients, all additional medical files were exhaustively reviewed. All the available radiological exams were reviewed. *Results:* A total of 488 patients were included for the study: 130 patients from Tenon (36%), and 358 patients from Lyon (17%). Clinico-radiological phenotypes and statistical analysis will be presented. HHT patients with and without neurological manifestations will be compared. Genotype-phenotype correlations will be analysed.

MOLECULAR DIAGNOSTICS, MARKERS AND EPIDEMIOLOGY FOR HHT

P-108
MOLECULAR AND GENETIC HETEROGENEITY IN HHT: THE RESULTS OF 12 YEARS OF DNA DIAGNOSTICS IN THE NETHERLANDS.

TGW Letteboer, JJ Mager, R Snijder, AJM van Erkel, CJJ Westermann, JK Ploos van Amstel

[1]*Department of Medical Genetics, University Medical Center Utrecht,* [2]*St.Antonius Hospital, Nieuwegein, The Netherlands*

Hereditary Hemorrhagic Telangiectasia (HHT) or Rendu-Osler-Weber disease is an autosomal dominant, heterogeneous disorder caused by mutations in the ENG gene (HHT1), the ACVRL1 gene (HHT2) or SMAD4 gene (JP-HHT). The estimated prevalence in the Netherlands is 1:5000. The molecular heterogeneity has been extensively studied, also in the Dutch population. In the Dutch population, ENG mutations are more frequent than ACVRL1 mutations, SMAD4 mutations are rare. Here we present the results of 12 years of DNA analysis performed in the Netherlands, in probands, referred for DNA analysis, irrespective of the clinical diagnosis and fulfillment of the clinic to the Curacao criteria. In 12 years, DNA analysis has been performed in 754 apparently unrelated probands. The majority of patients were from the Netherlands. DNA analysis involves the sequence analysis of the coding region (including flanking intronic regions) of ENG and ACVRL1 and subsequent Multiplex Ligation dependent Probe Amplification (MLPA) to search forge large deletions or duplications. When normal and on request, in addition SMAD4 analysis was performed. In 211 probands (28%) a pathogenic ENG mutation was detected; 158 probands (21%) had a pathogenic ACVRL1 mutation. In only 6 probands (0.8%) a SMAD4 mutation was detected. No mutation was detected in the

non-commercial use only

majority of the probands (51%). These results confirm, that ENG mutations are more frequent than ACVRL1 mutations, also in an unselected patient population. Whether other genes are involved or other regions of the ENG and ACVRL1 gene to explain the mutation negative probands, has still to be solved. In DNA-diagnostic, the significance of unclassified variants found in probands, remains a challenge. In 12 years of DNA analysis 8 probands were found in whom unclassified variants occurred in combination with a (known) pathogenic mutation. In 2 of the 8 probands the unclassified variant and the mutation occurred in the same gene. These results attribute to the classification of these mutations.

ANTIANGIOGENIC THERAPIES IN HHT AND OUTCOMES

P-109
BEVACIZUMAB PHARMACOKINETICS INFLUENCES CARDIAC OUTPUT AND EPISTAXIS IN HEREDITARY HEMORRHAGIC TELANGIECTASIA (HHT)

N Azzopardi[1], S Dupuis-Girod[2], D Ternant[1,3], AE Fargeton[2], I Ginon[4], F Faure[5], E Decullier[6], MF Carette[7], B Gilbert-Dussardier[8], PY Hatron[9], P Lacombe[10], B Lorcerie[11], S Riviere[12], R Corre[13], S Bailly[4], G Paintaud[1,3]

[1]*CNRS, UMR 7292 (GICC), Tours,* [2]*Hospices Civils de Lyon, Genetic Department and National Reference Center for Rendu-Osler Disease, Lyon,* [3]*CHRU Tours, Laboratory of Pharmacology-Toxicology, Tours,* [4]*Hospices Civils de Lyon, Centre Hospitalier Lyon Sud, Service de Cardiologie, Pierre-Bénite,* [5]*Hospices Civils de Lyon, Hôpital E. Herriot, Service d'ORL, Lyon,* [6]*Hospices Civils de Lyon, pôle IMER, Lyon, Université de Lyon, Faculté de médecine, Université Lyon 1,* [7]*Service de Radiologie, Hôpital Tenon, Paris Cedex 20, Assistance Publique – Hôpitaux de Paris, Université Pierre et Marie Curie (Paris VI),* [8]*Service de génétique médicale, CHU La Milétrie, Poitiers, France,* [9]*Service de médecine interne, Université Lille2, CHRU de Lille, Lille, France,* [10]*Hôpital Ambroise Paré, Service de Radiologie, Assistance Publique-Hôpitaux de Paris, Université Paris Ile-de-France Ouest, Boulogne, France,* [11]*Hôpital de Dijon, Service de Médecine Interne,* [12]*Service de Médecine Interne A, Centre Hospitalier Universitaire, Montpellier, France,* [13]*Hôpital Pontchaillou, Rennes, France,* [4]*INSERM U1036, CEA Grenoble, France*

Hereditary Haemorrhagic Telangiectasia (HHT) is a genetic disorder of angiogenesis. Anti-vascular endothelial growth factor (VEGF) drugs, such as bevacizumab, were previously shown to be effective in HHT. *Objectives:* To describe the relationship between bevacizumab serum concentration, and both reduction of cardiac output and epistaxis duration in HHT. *Methods:* A single-center, phase II study included HHT patients who were treated with 6 infusions of 5 mg/kg bevacizumab every 14 days. Patients were followed up over 12 months after the beginning of bevacizumab treatment. Cardiac output (CO) measurements were performed before the first bevacizumab injection and 3 and 6 months after the first injection. Duration of epistaxis episodes were daily recorded by patients. Bevacizumab concentrations were measured by ELISA technique and were described using a two-compartment pharmacokinetic (PK) model with first-order elimination. Pharmacokinetic-pharmacodynamic (PK-PD) modelling was used to describe the relationship between bevacizumab concentration and decrease in both CO and epistaxis duration. The probabilities of daily epistaxis duration categories were described using a Poisson distribution of parameter. Cardiac output and were related to bevacizumab concentrations in an effect compartment. A population approach was applied using Monolix 4.2 software. *Results:* A total of 317 blood samples were available in 25 patients. Bevacizumab concentrations and therapeutic responses were satisfactorily described by the modelling. Mean (relative standard error) estimated PK and PK-PD parameters were: central volume of distribution: V1 = 3.67 L (7%), elimination clearance: CL = 0.13 L/day (14%), peripheral volume of distribution: V2 = 4.32 L (24%), distribution clearance: Q = 0.26 L/day (9%), effect compartment transfer constant: ke0 = 0.0009 day-1 (35%), initial and minimal cardiac index: CO0 = 5.81 L/min (3%) and COmin = 2.12 L/min (10%), respectively, concentration of bevacizumab leading to 50% reductions in both C00+COmin and 0: C50 = 4.5 mg/L (14%), daily epistaxis duration Poisson distribution parameter: 0 = 0.62 (29%). *Conclusions:* In patients with HHT, effects of bevacizumab on cardiac output and epistaxis duration are related to its serum concentrations. The induction treatment used (total duration of 2.5 months) was associated with long-lasting reductions in cardiac output and duration of epistaxis.

P-110
ELECTRICAL STIMULATION OF SINGLE MURAL CELL VISUALIZED BY FLUORESCENT MICROSCOPY AS A VALUABLE TOOL FOR HHT HIGH OUTPUT SCREENING DRUGS

J Thalgott[1], D Dos-Santos-Luis[1], L Venance[1], F Lebrin[1]

[1]*CNRS Unité mixte de recherché 7241/INSERM U1050, Center for Interdisciplinary Research in Biology, Collège de France, Paris, France*

Hereditary Haemorrhagic Telangiectasia (HHT) is a genetic vascular disorder caused by mutations in either ENG or ACVRL1. These genes encode receptors for members of the Transforming Growth factor- family ligands that share functions in signalling in endothelial cells. Clinical manifestations include arteriovenous malformations (AVMs), which range from large AVMs in major organs to small telangiectasic lesions in the nasal septum, oral mucoas and gastrointestinal tract. Current understanding of HHT pathogenesis indicates that these lesions might be partially attributable to impaired recruitment of mural cells. In fact, our recent discovery of thalidomide as a potential therapeutic agent for HHT confir-

Non-commercial use only

med the importance of mural cell dysfunction responsible for the formation of fragile vessels. However, little is known about the identity of these mural cells, their physiological functions in quiescent or immature vessels, and in particular the consequences of endoglin or ALK1 haploinsufficiency to maintain vessel stability. To address this concern, we have used NG2DsRedBAC-transgenic mice, which have the mural cells labelled in red to characterize the contractile properties of the mural cells in the retinal vasculature of the Eng+/- or Acvrl1+/- mice (mouse HHT models). This vascular bed is amenable to testing the mechanisms underlying the bidirectional control of capillary constriction. We stimulated mural cells of adult mice electrically with a pipette pressed on their soma, aiming to raise intracellular calcium concentration. In control mice, low-voltage electrical stimulation was sufficient to constrict most of the mural cells from arterial capillaries (85%) where high-voltage electrical stimulation was required to induce venous capillary to constrict. Mural cells that were stimulated to constrict induced sometimes, distant mural cells to subsequently constrict. However in Eng+/- mice, only few mural cells from the arterial capillaries (20%) responded to low-voltage stimulation compared to control and Acvrl1+/- mice indicating that the endothelial-mural cell-cell interaction is defective in the arterial capillary bed of the Eng+/- retina. Finally, thalidomide was able to rescue the vessel constriction of the Eng+/- mice validating that electrical stimulation of a single mural cell visualized by fluorescent microscopy provides a valuable tool for HHT high output screening drugs.

P-111
EFFICACY OF BAZEDOXIFENE IN THE TREATMENT OF HEREDITARY HEMORRHAGIC TELANGIECTASIA. CLINICAL EFFECTS AND EXPRESSION ANALYSIS.

R Zarrabeitia[1], ML Ojeda-Fernandez[2,3], V Albiñana[2], C Bernabeu[2,3], LM Botella[2,3]

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

Hereditary hemorrhagic telangiectasia is a dominantly inherited genetic vascular disorder in which epistaxis affect severely the quality of life of patients. Development of vascular malformations in HHT patients has been attributed to a dysregulation of the TGF-beta signalling pathway on endothelial cells. This causes vessels to weaken and become prone to bleeding, a major feature of HHT. Hormonal therapy (estrogens and SERMs) is one of therapeutic strategies for the management of bleeding in HHT. In 2010, Raloxifene was designated by EMA and FDA, as the first orphan drug for the treatment of HHT bleeding. The use of this type of SERM due to their safety profile, make it an interesting therapeutic approach to decrease severe nose bleedings. Currently we are starting with a new generation SERM similar to raloxifene, but with advantages of safety and efficacy. To this purpose, Bazedoxifene, in a dose of 20 mg a day, was used in postmenopause HHT women, affected by osteoporosis, without previous thromboembolic episodes, and without hypercoagulability factors. Plasma samples were collected before, and following 1 and 3 months, after the initiation of the treatment. The levels of ENG and ALK1 expression were measured by RT-qPCR in the macrophages derived from blood samples after 24 hours of in vitro culture. Angiogenic factors in the plasma samples derived directly from patients will also be evaluated and correlated with their clinical manifestation during the treatment. Treated patients experienced an improvement in the haemoglobin levels and a decrease in the frequency and amount of epistaxis.

P-112
LOCAL ADMINISTRATION OF BEVACIZUMAB: A THERAPEUTIC OPTION IN HHT?

T Kühnel, C Rohrmeier

Department of Otorhinolaryngology, University of Regensburg, Germany

Bevacizumab is a monoclonal antibody targeting vascular, endothelial growth factor. It proofed to be effective in the treatment of colorectal carcinomas and macular degeneration. Patients suffering from HHT show increased endothelial growths factor (VEGF) in blood samples. Recent literature reports on local administration of Bevacizumab ranging from 1,75mg each side to more than 100mg. We injected Bevacizumab submucosally in the nasal septum in patients who responded poorly to laser treatment in nine patients. Two patients had 1,75mg, the other seven patients received 3,75mg each side. 1,75 mg had no effect on bleeding intensity and frequency. Seven patients reported about significant improvement after having had 3,75mg injected in the mucosa of the nasal septum each side. No side effects particularly no septal perforations were observed. Though there is obvious need for larger trials we feel that local administration of Bevacizumab helps to improve therapy in severe cases of recurrent epistaxis in HHT patients.

Non commercial use only

HEPATIC INVOLVEMENT IN HHT

P-113
ABDOMINAL INVOLVEMENT IN HEREDITARY HEMORRHAGIC TELANGIECTASIA (HHT): A PITORIAL REVIEW.

M El Hajjam, J Sellier, S Binsse, M Bensalah, T Chinet, J Roume, A Ozanne, I Bourgault, G Lesur, J-H Blondel, A Cordier, S Blivet, C Fagnou, M Bonay, C Karam, A Nicod-Tran, S Chagnon, M Eyries, L Gouya, P Lacombe

Consultation Pluridisciplinaire Maladie de Rendu-Osler, Hôpital Ambroise Paré, Boulogne. Hôpital du Kremlin-Bicêtre. HHT Center, Paris, France

Background: HHT is a rare autosomal dominant disease characterized by arteriovenous malformations involving different tissues and organs. If the hepatic involvement is well known (over 70% of HHT patients), other abdominal locations such as splenic, pancreatic and gastro-intestinal malformations are underestimated and insufficiently illustrated. *Aim:* To review the spectrum of abdominal involvement in HHT using usual screening imaging tools (Doppler US, CT and MRI). *Materials and methods:* Retrospective analysis of 530 patients followed by our pluridisciplinary team over an 8-year period. The technique of imaging procedures and visceral features of HHT are described. *Results:* Hepatic lesions consist of telangiectases, confluent vascular masses, perfusion defects, focal nodular hyperplasia or pseudo-focal nodular hyperplasia, different vascular shunts (arterio-portal, arterio-systemic and porto-systemic) and their complications (portal hypertension, pseudo-cirrhosis, biliary ducts ischemia), and hepatic and peri-hepatic (inferior phrenic) artery/ies hypertrophy. The most discriminating sign is the tortuous, hypertrophic or aneurismal hepatic artery (sensitivity 97% and specificity 100%). Pancreatic telangiectases and fistulae are described. They are usually multiple, involving any portion of the pancreas. Splenic involvement has been seldom reported. It includes non specific arterial lesions (aneurisms) and specific parenchymal locations mainly telangiectases and arteriovenous fistulas. Gastro-intestinal tract involvement is also illustrated, and an exceptional huge intestinal tract malformation complicated by portal hypertension is described. Furthermore, we illustrate visceral abdominal sequelae of ischemic or septic systemic emboli in patients with pulmonary arteriovenous malformations (PAVMs), and indirects signs of a systemic supply to embolized PAVMs. *Conclusion:* Radiologists should be familiar with hepatic findings in patients with HHT. The other abdominal locations are unusual, but should be known, as they may bring the missed visceral criteria for HHT diagnosis. *Keywords:* HHT; liver involvement; pancreatic involvement; splenic involvement; gastrointestinal tract involvement; Doppler US ; CT ; MRI.

P-114
DIAGNOSTIC PERFORMANCE OF DOPPLER ULTRASOUND FOR THE DIAGNOSIS OF HEPATIC VASCULAR INVOLVEMENT IN HHT PATIENTS

M Kucharczyk[1,3,4], B Ferreyro[2,4], EL Yeyati[1,3], N Napoli[1], F Angriman[2,4], RG Monaco[1,3], M Serra[2,3,4]

[1]*Radiology Department Hospital Italiano de Buenos Aires. Argentina (HIBA),* [2]*Unit of Internal Medicine HIBA,* [3]*HHT Unit. Hospital Italiano de Buenos Aires,* [4]*ARG (Argentine Rendu Study Group), Argentina*

Background: Hereditary hemorrhagic telangiectasia (HHT) is a genetic disease characterized by cutaneous, mucosal and visceral vascular malformations (VMs). Liver involvement in HHT is mainly characterized by telangiectases and arteriovenous shunts, which are present in 75-80% of patients. Multislice Computed Tomography (MSCT) is considered the gold standard for the diagnosis of hepatic VMs, the diagnostic performance of Ultrasound is still unknown in our setting. *Objective:* This study aimed to assess the diagnostic performance of color and pulsed Doppler ultrasonography (US) by comparing it with MSCT. A secondary objective was to identify the most sensitive US criteria indicating hepatic vascular involvement. *Methods:* 37 HHT patients were systematically screened for VMs by Doppler US and MSCT. MSCT was considered the gold standard and was defined as vascular pathological if there were at least 2 telangiectases and/or VMs (arterio-portal, arterio-venous, porto-venous shunts.We evaluated the diagnostic performance of Doppler US by defining intrahepatic (color spots, subcapsular flow and VMs) and extrahepatic (tortuosity and diameter of hepatic artery, waveform of hepatic vein and of the portal vein) parameters. US was considered pathological if any of these were present. Finally, we estimated sensitivity, specificity, positive and negative predictive values (PPV, NPV) and their respective confidence intervals (95% CI). *Results:* Doppler US was positive in 24/37 (64.8%) patients and MSCT in 28/37 (75.6%) patients. Overall sensitivity, specificity, PPV and NPV of Doppler US were 0.82 (CI 0.71–0.85), 0.89 (CI 0.56–0.99), 0.96 (CI 0.83-0.99) and 0.61 (CI 0.42-0.74) respectively. For intrahepatic parameters, sensitivity and specificity were 0.78 (CI 0.70-0.84), 0.79 (CI 0.44-0.96) respectively, and for extrahepatic parameters were 0.71 (CI 0.60-0.77) and 0.79 (CI 0.44-0.96) respectively. With reference to intrahepatic parameters, the one that individually appeared to be more sensitive was the subcapsular flow. *Conclusion:* Doppler ultrasonography appears to be highly specific and moderately sensitive for diagnosis of hepatic VMs. An abnormal US is highly suggestive of the diagnosis of hepatic VMs. Furthermore, is a non-invasive and relatively low-cost procedure for the screening of liver vascular involvement in HHT patients.

Non-commercial use only

PULMONARY INVOLVEMENT: PAVMS AND PULMONARY HYPERTENSION IN HHT

P-115
DIAGNOSTIC ACCURACY OF THE 100% OXYGEN METHOD IN DETECTING PULMONARY RIGHT-TO-LEFT SHUNTS COMPARED TO TRANSTHORACIC CONTRAST ECHOCARDIOGRAPHY

S Velthuis[1], VMM Vorselaars[1], CJJ Westermann[2], R Snijder[2], JJ Mager[2], MC Post[1]

[1]*St Antonius Hospital, Department of Cardiology, Nieuwegein, Netherlands,* [2]*St Antonius Hospital, Department of Pulmonology, Nieuwegein, Netherlands*

Background: Pulmonary right-to-left shunts are associated with severe neurological complications in patients with hereditary haemorrhagic telangiectasia (HHT). Screening has long been performed with the 100% oxygen method, but transthoracic contrast echocardiography (TTCE) is currently advised as first-line screenings technique. *Purpose:* The present study determined the diagnostic accuracy of the 100% oxygen method in detecting pulmonary shunts, using TTCE as gold standard. *Methods:* We included 189 persons, referred for HHT screening between 2004 and 2010, who underwent pulmonary shunt measurement with both the 100% oxygen method and TTCE. A pulmonary shunt of >5% measured with the 100% oxygen method was considered pathological. A quantitative three-point grading scale was used to classify the pulmonary shunt on TTCE (grade 0, no microbubbles; 1, <30 microbubbles; 2, 30-100 microbubbles; 3, >100 microbubbles). *Results:* A pulmonary shunt on TTCE was present in 95 out of 189 patients (50.3%). The 100% oxygen method demonstrated an abnormal shunt in only 49 (51.6%) of these patients (sensitivity 51.6%, specificity 87.2%, PPV 80.3, NPV 64.0%). Using the 100% oxygen method, a pathological pulmonary shunt was identified in 14.3%, 20% and 72.9% of patients with a pulmonary shunt grade 1, 2 and 3 on TTCE respectively. The 100% oxygen method indicated an abnormal pulmonary shunt in 12.8% of persons without any shunt on TTCE. In 13.3% of patients who underwent endovascular transcatheter embolotherapy of pulmonary shunts, the 100% oxygen method could not detect a pathological shunt. *Conclusions:* Large pulmonary shunts on TTCE may remain undetected using the 100% oxygen method. Our study confirms that the 100% oxygen method is not a useful screenings technique for the detection of pulmonary shunts.

P-116
HEMOPTYSIS IN HHT: A SINGLE SYMPTOM, VARIOUS MECHANISMS. A PICTORIAL REVIEW

J Sellier, M El Hajjam, S Binsse, T Chinet, J Roume, A Ozanne, I Bourgault, G Lesur, J-H Blondel, A Cordier, S Blivet, C Fagnou, M Bonay, C Karam, A Nicod-Tran, M Eyries, L Gouya, S Chagnon, P Lacombe

Consultation Pluridisciplinaire Maladie de Rendu-Osler, Hôpital Ambroise Paré, Boulogne, hôpital du Kremlin-Bicêtre. HHT Center, Paris, France

Background: Hemoptysis is a potential life-threatening condition in HHT, mostly due to rupture of a pulmonary arteriovenous malformation (PAVM) in untreated patient. In previously embolized patients, pathophysiology of hemoptysis is more complex and the therapeutic strategy relays on a careful study of the PAVM vascular supply. We illustrate the different mechanisms of bleeding and the way we treat them. *Materials and Methods:* During a 12-year period, a total of 970 patients with HHT were evaluated at our center. 425 patients had PAVMs. 5% of all patients presented hemoptysis. Patients with hemoptysis were prospectively investigated clinically in association with bronchial endoscopy, computed tomography and/or angiography. All imaging data were collected and reported to a potential cause. Each cause of hemoptysis and its management are illustrated through case reports. *Results:* In patients with PAVM, hemoptysis was mostly due to parenchymal rupture of the malformation, which occurred even during childhood. Immediate embolization of the culprit PAVM was mandatory. In previously embolized patients, bleeding could originate from already embolized malformations. In this case, three different mechanisms of hemoptysis were encountered: - recanalization of a previously embolized artery mainly due to insufficient packing of coils, - reperfusion of the PAVM by growth of pulmonary-to-PAVM anastomoses, - and development of systemic supplies to the embolized area, when previous embolization was too proximal. Recanalization was treated by complementary packing of coils. Symptomatic large pulmonary-to-PAVM anastomoses could be embolized with coils. Hemoptysis due to systemic supply was more difficult to treat because of direct connections between the systemic arteries and the PAVM. Other strategies should prevail to prevent any embolic complication. Moreover, hemoptysis could be related to pulmonary hypertension or its life-threatening complication: rupture of pulmonary artery aneurisms. Benign but recurrent hemoptysis can also originate from tracheo-bronchial telangiectases. *Conclusion:* Hemoptysis in HHT patients is a monomorphic presentation of polymorphic conditions that implies a careful strategy before interventional treatment.

P-117
EMBOLISATION OF PULMONARY ARTERIOVENOUS MALFORMATIONS (PAVMS) IMPROVES QUALITY OF LIFE IN PATIENTS WITH HHT

S Blivet, D Cobarzan, A Beauchet, JH Blondel, M Bonay, I Bourgault, C Fagnou, L Gouya, G Lesur, A Ozanne, J Roume, P Lacombe, Th Chinet

Consultation Pluridisciplinaire Maladie de Rendu-Osler, Hôpital Ambroise Paré Boulogne, HHT Center, Paris, France

Background: the presence of pulmonary arteriovenous malformations (PAVMs) impairs the quality of life in patients with HHT (Blivet S et al. presented at the 9th international HHT Scientific Conference, 2011). The goal of our study was to evaluate the impact of the embolisa-

Non-commercial use only

tion of PAVMs on the respiration-related quality of life in patients with HHT. *Methods:* we prospectively recruited all consecutive patients who underwent embolisation of PAVM in our center between January 2010 and January 2012. The diagnosis of HHT was based on the Curacao criteria and/or the presence of a pathogenic mutation in the ALK-1 gene or the ENG gene. French-speaking patients older than 16 years of age were enrolled. Exclusion criteria included chronic respiratory or cardiac disease unrelated to HHT. The respiration-related quality of life was measured using the Saint George's Respiratory Questionnaire (SGRQ; expressed as percent) before and 6-12 months after embolisation. The SGRQ includes 3 components: the symptoms component is concerned with the effect of respiratory symptoms; the activity component is concerned with activities that cause or are limited by breathlessness; the impacts component is concerned with social functioning and psychological disturbances resulting from the symptoms. *Results:* 27 patients were recruited (age: 41.9±18.5 years, - mean±SD -, 11 males). Seventeen agreed to participate (age: 42.5±19.4 years, 7 males). Thirteen had a mutation in the ENG gene and 2 in the ALK-1 gene. The SGRQ score was 21.5±4.1% before embolisation and 12.5±2.8% after embolisation ($p<0.02$ using Student's paired t test). Of the 3 components, only the activity score decreased significantly ($p<0.01$); there was no significant difference in the symptoms score and the impacts score. *Conclusion:* embolization of PAVMs significantly improves the respiratory-related quality of life in patients with HHT *(Supported by AMRO)*.

P-118
PAVM EMBOLIZATION USING OVERLAY ROADMAP GUIDANCE

AL Diederik, MJL van Strijen, DAF van den Heuvel, M van Leersum, JA Vos

Dept. Interventional Radiology, St. Antonius Ziekenhuis, Nieuwegein, the Netherlands

Introduction: Embolization of PAVM's to reduce the risk of bleeding, hypoxia and paradoxical embolism can be difficult in hard to reach anatomic locations. Traditionally these interventions are performed using combinations of live fluoroscopy and angiographic runs for determining the catheter position and guidance. For difficult PAVM's this can lead to additional treatment time, radiation and use of contrast. *Methods:* With the Philips Allura FD20 system it is possible to obtain a cone beam CT (CBCT) and register this with available high resolution pre-intervention CT scans. With dedicated software the merged images are used to depict the route to the PAVM. This route is visible during fluoroscopy as an navigational overlay and creates a high quality "real-time" roadmap overlay of the lung vasculature. *Results:* We describe the technique of image fusion for navigational purposes in the lung vasculature and specifically for embolization of difficult to reach PAVM's in eligible patients. Practical examples, and figures of dose and procedure time reduction are provided as well as the amount of contrast needed to reach the required catheter position. *Conclusion:* With the help of CBCT roadmap overlay easier navigation to difficult PAVM's is possible. The shorter procedure time leads to reduced radiation and amount of contrast for the individual patient.

P-119
RECANALIZATION AFTER PULMONARY ARTERIOVENOUS MALFORMATION (PAVM) EMBOLIZATION

AL Diederik[1], JJ Mager[2], DAF van den Heuvel[1], R Snijder[2], JA Vos[1]

Dept. of Radiology[1] and Pulmonology[2], St. Antonius Ziekenhuis, Nieuwegein, the Netherlands

Introduction: Recanalization and persistent perfusion after therapeutic embolization is a common and recurring problem. In literature recanalization occurs in 0-25% of embolized pulmonary arteriovenous malformations (PAVMs). Most of the studies with a low recanalization rate have a short follow-up or have small patient groups. Structural long-term follow-up using serial CT may yield a high recanalization rate. In this study we retrospectively analyzed PAVM's treated in a single high volume center. *Material and Methods:* Patients treated with endovascular embolization for PAVM's between November 2004 and November 2011 for whom post-treatment CT's were available were analyzed. All the PAVMs in the study were analyzed and scored for arterial diameter, PAVM type (simple, complex, bronchial artery involvement), location (lobe, central vs. subpleural), HHT-type and age and gender of the patient. Embolization material was noted (coils, plugs). On the angiographic images and the post-treatment CT the distance between the embolization material and the PAVM was measured. On the follow up CT's in the following months and years recanalization and persistent perfusion was scored. *Results:* Until now we found a 20% recanalization rate in a group of 125 PAVM's. This is somewhat high compared to literature and probably caused by long-term follow-up. By the time of the conference we expect to have increased this number to 200 PAVM's and to have finished the subanalysis. *Conclusion:* Long-term follow up after embolization of PAVM's using CT has a high recanalizationrate compared to known literature.

P-120
PRELIMINARY RESULTS OF THE PIRANA TRIAL

AL Diederik[1], JJ Mager[2], DAF van den Heuvel[1], MJL van Strijen[1], R Snijder[2], JA Vos[1]

[1]*Dept. Interventional Radiology,* [2]*Dept. Pulmonology, St. Antonius Ziekenhuis, Nieuwegein, the Netherlands*

Introduction: People suspected of having a pulmonary arteriovenous malformations (PAVM) are currently evaluated by thoracic CT. The sensitivity and specificity of CT are very high, with the inherent disadvantage of ionizing radiation. A single CT scan carries a negligible risk of adverse health effects, however in repeat scans the risk increases, especially in young people. A large proportion

Non commercial use only

of people with PAVMs, usually patients with Rendu-Osler-Weber, is regularly scanned every few years throughout their lives. *Methods:* The PIRANA trial, PAVM Imaging Research and Analysis, is a study that compares MRA to CTA for the detection and follow-up of PAVM's. Enrolment started early 2013 and the first test MRA's have been made. The ultimate goal is to analyze 100 patientssuspected of having a PAVM on cardiac contrast ultra sound or those patients who have been embolized previously and are scheduled for follow up CTA. *Results:* The hypothesis is that MRI has equal sensitivity in the detection of clinically relevant PAVM as CT. In the case of complex PAVM's we expect that MRI (4D dynamic MRA) is even better than standard CTA. *Conclusions:* The study is currently enrolling and we expect to present the preliminary results at this conference in June.

P-121
MORPHOLOGICAL CHANGE OF THE AMPLATZER VASCULAR PLUG II IN PULMONARY ARTERIOVENOUS MALFORMATIONS – DOES SIZE AND SHAPE MATTER?

L Ling, K Patatas, G Robinson

Department of Radiology, Hull Royal Infirmary, UK

Purpose: To assess if demonstrable changes in the size and shape of the Amplatzer Vascular Plug II (AVPII) have any consequence on occluded pulmonary arteriovenous malformations (PAVMs). *Material and Methods:* 28 consecutive patients who underwent PAVM embolisation at our centre using the AVPII between October 2007-November 2012 were identified. There was an equal number of males and females, with a mean age of 53 (range 21-83 years). 27/28 patients had a confirmed diagnosis of hereditary haemorrhagic telangiectasia. Initial appearances of deployed AVPIIs were compared with and measured against subsequent imaging follow-up. Clinical records were also reviewed. *Results:* A total of 41 AVPIIs were deployed in 37 separate PAVMs. The immediate technical success rate for complete occlusion of the PAVMs was 100% with no major early or late complications. Catheter angiographic and/or CT imaging of the treated PAVMs were available in 19/28 patients, equivalent to 24 deployed AVPIIs. 15/24 (63%) of the AVPIIs demonstrated comparable change in configuration on follow-up imaging; from conforming to the luminal diameter of the target vessel on initial deployment, to shortening and expanding to its nominal diameter over time. In our series, this occurred with AVPIIs equal or larger than 8mm in size. Mean radiological follow-up was 21 months (range 5-48). There were no instances of PAVM recanalisation or associated vascular sequelae. *Conclusion:* In our experience, the morphological change of the deployed AMPLATZER Vascular Plug IIs are not associated with untoward vascular sequelae and are effective in the occlusion of PAVMs.

P-122
TREATMENT EFFECTIVENESS OF PULMONARY ARTERIOVENOUS MALFORMATION WITH AMPLATZER VASCULAR PLUG IV IN PATIENTS WITH HEREDITARY HEMORRHAGIC TELANGIECTASIA

JM Rabellino, O Peralta, E Levy Yeyati, E Gentile, M Ulla, RG Monaco, M Serra

Department of Angiography. Hospital Italiano de Buenos Aires. Argentina. (HIBA), Department of Radiology. HIBA, Internal Medicine. HIBA, Hospital Italiano de Buenos Aires, Argentina

Background: Pulmonary arteriovenous malformation (PAVM) are defined as an abnormal communication between pulmonary arteries and veins without interposition of capillaries. 75-90% of PAVM are associated to hereditary hemorrhagic telangiectasia (HHT). Nowadays, it is recommended to treat all PAVM, when it is technically possible. Endovascular treatment through embolization is the first therapeutic option. The most embolic agent used are coils. During the last years, Amplatzer Vascular Plug (AVP) type I and II have been incorporated. AVP type IV has been successfully employed in other vascular territories; nevertheless, there are no reports of its use for the treatment of PAVM. *Objective:* The aim of this study is to present the preliminary results and the recanalization rates for the PAVM treated with AVP IV in malformations with afferent arteries less or equal to 6 mm in diameter. *Methods*: Twelve PAVM in seven HHT patients were treated by Endovascular procedure with AVP type IV and underwent a follow-up multislice chest CT after six months of the intervention. All the CT were compared to a pre-procedure CT scan. The treatment was considered successful when there was a marked reduction or disappearance of the aneurismal sac and/or pulmonary vessels with feeding artery less than 3 mm. Treatment failed when there was an insufficient reduced size of the sac or pulmonary vessels, with feeding artery larger than 3 mm or an interim growth in the aneurismal sac, with unchanged or enlarged pulmonary vessels. *Results:* Ten PAVM were successfully treated with the AVP type IV. In the rest two PAVM, the treatment with the AVP type IV was supplemented with coils because of insufficient occlusion of the malformation seen at the same time of the embolization procedure. The follow-up CT control showed no recanalization of these PAVM. *Conclusion:* Despite the number treated PAVM are still low; the results obtained with AVP IV for the treatment of PAVM with HHT are very promising. This device has interesting characteristics, such as its safety and low rate of recanalization, which might convert it in the first option of treatment PAVMs in the near future.

Non-commercial use only

P-123
TRANSESOPHAGEAL ECHOCARDIOGRAPHY AS PART OF THE SCREENING FOR PULMONARY ARTERIOVENOUS MALFORMATIONS IN HHT

U Geisthoff, S Weise, J Üner, H-W Angenendt, S Maune

Departments of ORL, Internal Medicine, and Radiology, Hospital of the City of Cologne, Cologne, Germany

Background: Transthoracic echocardiography (TTE) eventually followed by thoracic CT is often used as screening procedure for PAVMs in HHT. The value of discrepant findings is still unknown. *Methods:* Patients were offered transesophageal echocardiography (TEE) in cases with discrepant findings or suspicion of cardiac shunting. *Results:* In 208 consecutive patients a total of 130 TTEs were performed. The result showed signs of central shunting in 112 patients. In 2 cases the result was suspicious of a cardiac shunt. CT scan (67) or MRI (9) were performed in 74 cases and revealed visible AVMs in 24 patients. Patients with discrepant findings or suspicion of cardiac shunts were offered TEE. 27 patients accepted the offer and in 23 patients a pulmonary shunt was confirmed while an atrial septal defect was discovered in 4 patients. *Conclusion:* The significance of TTE-positive and imaging-negative findings is still not clear. 23 to 61 out of 130 patients of our cohort (18-47%) may have had so-called microscopic PAVMs or physiologic pulmonary shunts. 4 out of 27 patients (15 %) benefited from TEE by avoidance of long-term follow-up and lacking necessity for antibiotic prophylaxis. However, it has to be discussed with the patient that the incidence perforations of the upper digestive tract due to TEE has been estimated to be between 0.01% and 0.04% with consequent mortalities ranging from 10% to 56%.

P-124
DIRECT HEMODYNAMIC EFFECT OF PULMONARY ARTERIOVENOUS MALFORMATION EMBOLISATION

VMM Vorselaars, S Velthuis, JJ Mager, R Snijder, WJ Bos, JA Vos, MJL van Strije, MC Post

Department of cardiology, Department of pulmonology, Department of internal medicin, Department of (intervention) radiology, St Antonius Hospital, Nieuwegein, the Netherlands

Purpose: Transcatheter embolisation is widely used for pulmonary arteriovenous malformation (PAVM) closure in hereditary hemorrhagic telangiectasia (HHT). At this moment data on the short-term hemodynamic changes induced by closure are scarce. We investigated the haemodynamic effect of transcatheter embolisation of a PAVM, using non-invasive finger pressure measurements. *Methods:* During the procedure blood pressure, heart rate (HR), stroke volume (SV), cardiac output (CO) and total peripheral resistance (TPR) were continuously monitored using a Finometer®. Afterwards changes in these heamodynamic parameters were calculated from the pressure registrations using Modelflow® methodology. *Results:* In total twenty-nine HHT patients (mean age 39±15 years, 11 men) who underwent transcatheter embolisation were included in this study. The total number of embolisations was 72 (mean per patient 2.5). Immediately after transcatheter embolisation the mean arterial blood pressure increased (4.1%, p=0.02). The SV and CO decreased significantly with 11.9% (p=0.01) and 9.5% (p=0.01) respectively, without change in HR (1.8%, p= ns). *Conclusions:* The present study shows that immediately after embolisation of a PAVM, mean arterial blood pressure increased and stroke volume and cardiac output decreased.

P-125
ISCHAEMIC STROKE RISK INCREASES WITH THE SEVERITY OF PULMONARY ARTERIOVENOUS MALFORMATIONS

CL Shovlin, JA Livesey, V Santhirapala, HC Tighe, JE Jackson

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

Background: Ischemic strokes commonly affect individuals with pulmonary arteriovenous malformations (PAVMs) and hereditary hemorrhagic telangiectasia (HHT). Following maximal treatment, PAVMs cannot always be abolished due to persistence of vessels too small for embolization, and/or too diffuse for surgical resection. Surprisingly, our 1999-2005 series did not suggest stroke risk was lower in patients with less severe PAVMs.1 *Methods:* To identify ischemic stroke risk factors, 497 consecutive patients were studied prospectively, representing all HHT patients with CT-proven PAVMs reviewed at our institution from May 1999 to Feb 2013. Relationships between radiologically-confirmed ischaemic stroke and patient-specific variables were determined using logistic regression and receiver operator characteristic (ROC) analyses. *Results:* Sixty-one individuals (12.3%) had at least one non-iatrogenic acute clinical stroke, confirmed as ischemic in etiology, at median age 52ys (IQR 41-63ys). Kaplan Meier curves indicated that approximately 25% of patients would have a clinically evident stroke stroke by 65ys. Ischemic strokes were no more frequent in patients with conventional stroke risk factors (smoking; hypertension, diabetes; hypercholesterolaemia; arrhythmias). Lower oxygen saturations (SaO2) were associated with higher stroke risk (p=0.069). Quadratic regression suggested a near linear inverse relationship between SaO2 and ischemic stroke risk. In the strongest model identified by ROC curve analyses, the adjusted odds ratio for SaO2 was 0.96 [95%CI 0.92, 1.000], implying that the risk of stroke would increase ~1.4 fold with SaO2 90% and ~2.3 fold with SaO2 80%. Lower SaO2 reflected a greater degree of right-to-left shunting, measured on the same day using 99mTc-labelled albumin macroaggregates: in 309 paired same-day values, 73% of the total variance in erect SaO2 was explained by the same-day right-to-left shunt (linear regression coefficient -1.22 [95% confidence intervals -1.31, -1.14], p<0.0001). *Conclusions:* Smaller PAVMs carry lower stroke risks. These data further support the need for therapeutic embolization, while providing a level of reassurance for individuals with less severe right-to-left shunts. The reason

Non commercial use only

why the stroke/SaO2 association was not identified in the earlier analysis1 is explained by more widespread and intensive CT scanning, increasing the denominator of smaller PAVMs.

P-126
PULMONARY ARTERIOVENOUS BRAIN AVM DIAGNOSIS AND EMBOLIC COMPLICATIONS IN ADULT PATIENTS WITH HEREDITARY HEMORRHAGIC TELANGIECTASIA: A CROSS SECTIONAL STUDY

F Angriman[1], B Ferreyro[1], EJ Wainstein[2], M Serra[3]

[1]*Internal Medicine Department, Hospital Italiano de Buenos Aires. Buenos Aires University,* [2]*Internal Medicine Deparment, Respiratory Medicine Section, Hospital Italiano de Buenos Aires,* [3]*Internal Medicine Department. Chief, HHT Center of Excelence, Hospital Italiano de Buenos Aires, Argentina*

Background / Objectives: Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant disorder affecting vascular territories. Its main clinical characteristics are epistaxis, iron deficit anemia, mucocutaneous telangiectasia and systemic arteriovenous malformation (AVM). Patients with pulmonary AVM (PAVM) face higher risk of complications such as cerebral abscesses, stroke and systemic emboli. There is currently no available data on HHT patients in Latin America. We aimed to describe baseline characteristics of HHT patients referred to our Hospital and compare the prevalence of embolic complications in patients with significant PAVM compared to patients without significant PAVM. *Study Design:* Cross sectional study using an existing clinical registry. *Setting:* A tertiary academic teaching hospital in Buenos Aires, Argentina. *Participants:* One hundred and eight consecutive patients between February 2010 and November 2012 were included. We excluded patients without PAVM available data (N=20). *Main Variables:* Significant PAVM was defined as having either one of the following: (1) contrast echocardiography grade 2 or greater, (2) CT scan with bilateral PAVM or feeding artery bigger than 3 mm, (3) or previous PAVM treatment (embolization or surgery). The primary composite outcome (named embolic complications) was: cerebrovascular accident, transient ischemic attack, cerebral abscess or peripheral thrombotic or infectious embolism. *Results:* Patients had a mean age of 46 (+/-16) years and were predominantly female (72%). Thirty five patients had significant PAVM (39.8%). Seventeen participants (19.3%) had embolic complications, the most frequent complication was stroke (14/17, 76%). Patients with significant PAVM were significantly younger, on average by about 10 years ($p = 0.01$); they were more likely to have respiratory symptoms ($p < 0.001$) and less likely to be anemic ($p = 0.01$). Embolic complications were more prevalent in patients with significant PAVM: 34.3% vs. 9.4% ($p = 0.006$). *Conclusions:* we describe the first cross sectional study of HHT patients in Latin America. Significant PAVM and respiratory symptoms may be associated with poor embolic outcomes.

P-127
THE AMPLATZER VASCULAR PLUG II – A SAFE AND EFFECTIVE OCCLUDER OF PULMONARY ARTERIOVENOUS MALFORMATIONS

L Ling, K Patatas, G Robinson

Department of Radiology, Hull Royal Infirmary, UK

Purpose: To assess the long-term efficacy of the AMPLATZER Vascular Plug II in the embolisation of pulmonary arteriovenous malformations (PAVMs). *Material and Methods:* 28 consecutive patients who underwent PAVM embolisation using the AMPLATZER Vascular Plug II device (AVPII) between October 2007-November 2012 (61 months) were identified from a prospectively maintained database. Patients were referred from across the UK for catheter angiography and embolisation to be performed at our centre, with variable geographical follow-up by clinical teams. There was an equal number of males and females, with a mean age of 53 (range 21-83 years). 27/28 patients had a confirmed diagnosis of hereditary haemorrhagic telangiectasia. All available procedural and clinical records and radiological follow-up were reviewed. *Results:* A total of 41 AVPIIs were deployed in 37 separate PAVMs. Of the 41, 17 (41%) were deployed in conjunction with coils to occlude a particular PAVM. The immediate technical success rate for complete occlusion of the PAVMs was 100%. There were no major early or late complications with a 30-day mortality of zero. Angiographic and/or CT imaging of the treated PAVMs were available in 19/28 patients, with a mean radiological follow-up of 21 months (range 5-48). No instances of recanalisation of the PAVMs treated with AVPIIs have been identified in these 19 patients. *Conclusion:* In our experience, the AMPLATZER Vascular Plug II is safe and effective for the occlusion of pulmonary arteriovenous malformations with no reintervention required up 5 years.

P-128
FOLLOW-UP OF THE PULMONARY RIGHT-TO-LEFT SHUNT WITH TRANSTHORACIC CONTRAST ECHOCARDIOGRAPHY IN HEREDITARY HEMORRHAGIC TELANGIECTASIA

VMM Vorselaars, S Velthuis, JJ Mager, R Snijder, MC Post

Dept. Cardiology and Dept. Pulmonology, St. Antonius Hospital, the Netherlands

Purpose: Pulmonary arteriovenous malformations (PAVMs) are associated with severe neurological complications in patients with hereditary hemorrhagic telangiectasia (HHT). Transthoracic contrast echocardiography (TTCE) is the first-line screening technique for the detection of pulmonary right-to-left shunts (RLS) and only moderate and large shunts seem to have clinical implications. Five years after the initial TTCE we evaluated the change in pulmonary RLS. *Methods:* All adult HHT patients underwent a second TTCE five years after the initial screening. HHT patients with a history of PAVM embolisation were excluded. Opacification of the left

Non-commercial use only

ventricle was graded with a three grade scale. The TTCE was compared to the TTCE performed at the initial screening. *Results:* In total 76 HHT patients (53% female, mean age 52.2±14.8 years) underwent a second TTCE at 5-years follow-up. The initial TTCE showed no pulmonary RLS in 42 (55.3%), a minimal RLS in 19 (25.0%), a moderate in 6 (7.9%), and a severe in 9 (11.8%) patients. At 5 year follow-up, TTCE showed no pulmonary RLS in 41 (53.9%), a minimal in 19 (25.0%), a moderate in 7 (9.2%), and a severe in 9 (11.8%) patients. Five patients (6.6%) without a shunt at baseline, showed a mild pulmonary RLS at follow up. In none of them a PAVM was seen on chest computed tomography (CT). In three patients (3.9%) with a minimal shunt at baseline, the shunt size increased to moderate at follow up without treatable PAVMs on chest CT. *Conclusions:* Five years follow up is feasible using TTCE and showed an increase in shunt size in 10% of HHT patients without the presence of treatable PAVMs on chest CT.

P-129
ESTIMATED PULMONARY ARTERY SYSTOLIC PRESSURE IN A GROUP OF 105 HHT PATIENTS DISCLOSES DIFFERENCES IN PATIENTS CARRYING ACVRL1 OR ENG MUTATIONS

F Ornati[1], C Canzonieri[2], L Lanzarini[1], F Pagella[3], E Matti[3], F Chu[3], G Manfredi[4], E Buscarini[4], M Comelli[5], C Danesino[2], C Olivieri[2] on behalf of HHT-NET

[1]*Department of Cardiology, Foundation I.R.C.C.S. Policlinico "S. Matteo", Pavia, Italy,* [2]*General Biology and Medical Genetics, Dept of Molecular Medicine, University of Pavia, Italy,* [3]*Department of Otorhinolaryngology, Foundation I.R.C.C.S. Policlinico "S. Matteo", Pavia, Italy,* [4]*Department of Gastroenterology, Maggiore Hospital, Crema, Italy,* [5]*Department Of Brain And Behavioral Sciences, University of Pavia, Italy*

We performed Doppler transthoracic echocardiography (TTE) to estimate Pulmonary artery systolic pressure (PASP) in a group of 253 HHT patients; PASP was assessable in 151. All patients were previously diagnosed with HHT according to Curaçao criteria. ACVRL1 and ENG were analyzed using denaturing High Performance Liquid Chromatography (dHPLC) and subsequent direct sequencing in 105 cases. We found 79 ACVRL1 and 26 ENG mutations; nonsense mutations (48/105) and missense mutations (36/105) were the most representative groups. The distribution of the mutations in both genes resembles the general distribution of mutations in the whole group of patients (n=365) studied in our lab. We plotted estimated PASP values vs age and observed that the yearly increase for PASP was 0.38 mmHg (C.I. 0.27-0.49) for patients carrying ACVRL1 mutations, while it was 0.23 mmHg (C.I. 0.05-0.42) for patients carrying ENG mutations. In particular, eleven HHT2 patients (6 female) showed very high systolic pressure values, ranging between 40 and 75 mmHg, and 4 HHT1 patients showed PASP levels ranging between 42 and 45 mmHg. In a small number of cases (18 ACVRL1, 3 in ENG) two or three subsequent TTE were performed one or two years after the first one; in 11 cases (10 ACVRL1) an increased value was observed. TTE easily identifies, among HHT patients, those for whom more invasive methods are indicated to confirm a diagnosis of PAH.

P-130
IMPACT OF PULMONARY ARTERIOVENOUS MALFORMATIONS (PAVMs) ON PULMONARY FUNCTION IN PATIENTS WITH HHT

C Rotenberg, S Blivet, D Cobarzan, A Beauchet, S Binsse, M Bonay, JH Blondel, I Bourgault, A Cordier, C Fagnou, L Gouya, G Lesur, A Ozanne, Y Retory, J Roume, P Lacombe, Th Chinet

Consultation Pluridisciplinaire Maladie de Rendu-Osler, Hôpital Ambroise Paré, Boulogne, HHT Center, Paris, France

Background: PAVMs are present in approximately 20-50% individuals with HHT. They may be isolated but are more often multiple. In approximately 5% of cases, PAVMs are diffuse. The goal of this study was to evaluate the influence of the presence of PAVMs on lung mechanical properties. *Methods:* we reviewed the files of all adult patients (age > 18 years) referred to our Center for evaluation of HHT between 2007 and 2012. The diagnosis of HHT was based on the Curacao criteria and/or the presence of a pathogenic mutation in the ALK-1 gene, the ENG gene or the smad4 gene. Exclusion criteria included: chronic cardiac or lung disease (i.e. asthma, COPD,…), current or past smoking (> 10 pack-years), history of thoracic surgery, history of treatment of PAVMs by embolisation, pregnancy and obesity (BMI > 30 kg/m^2). Chest high resolution CT-scan and pulmonary function tests were performed the same day in all patients as part of our routine work-up. Pulmonary functions tests included measurements of TLC, VC, FEV1, FRC, RV, FEV1/VC, FEF75. To study the effect of the number of PAVMs on lung function, patients were divided into 3 groups: no PAVM, 1-3 PAVMs, 4 PAVMs and more; lung function values were compared between the 3 groups. To study the influence of the location of PAVMs on lung function, patients were divided into 3 groups: no PAVM, unilateral PAVMs and bilateral PAVMs. Comparisons between groups were performed using analysis of variance. *Results:* 123 patients with HHT were included (age: 45.2±17.7 yrs – mean±SD -; males: 49%). Sixty patients had no PAVM, 41 had 1-3 PAVMS and 22 had at least 4 PAVMs. Thirty six patients had unilateral PAVMs and 27 bilateral PAVMs. We found no statistical difference between groups for all measures of lung function. *Conclusion:* our study found no evidence that the presence and location of PAVMs have a significant influence on lung mechanical function in adult patients with HHT.

Non commercial use only

EPISTAXIS AND GASTROINTESTINAL BLEEDING IN HHT

P-131
FIRST PREVALENCE REPORT OF ALLERGY MANIFESTATIONS IN HHT POPULATION

M Serra[1], R Zarrabeitia[2], ML Ojeda-Fernandez[3], HJ Benito[1], C Bernabeu[3], J Maritano Furcada[1], LM Botella[3]

[1]*Hospital Italiano de Buenos Aires.Unidad HHT.ARG(Argentine Rendu Study Group). Argentina,* [2]*Hospital de Sierrallana. Torrelavega. Spain. IFIMAV,* [3]*Centro de Investigaciones Biológicas, Consejo Superior de Investigaciones Científicas (CSIC), Madrid (Spain).Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), Instituto de Salud Carlos III (ISCIII), Madrid, Spain*

Hereditary hemorrhagic telangiectasia is a dominantly inherited genetic vascular disorder characterized by recurrent epistaxis, cutaneous telangiectases and visceral arteriovenous malformations (AVMs) affecting many organs. HHT is habitually revealed by nose bleeding and familial history, but in several case reports the clinical diagnosis of HHT is done by the identification of pulmonary arteriovenous malformations. Clinical exploration of HHT patients suffering epistaxis reveals in many cases symptoms compatible with allergic rhinitis and other allergic processes. In general, no data are available, so far, on the prevalence and incidence of allergic or vasomotor rhinitis, nor of other allergic processes, in HHT patients. In this sense, this is the first analysis of ongoing allergic processes in HHT patients. We have retrospectively studied two different cohorts of HHT patients: a total of 150 patients referred to the Spanish HHT reference center (Hospital de Sierrallana, Torrelavega) and 100 HHT patients referred to the Argentine HHT reference center (Hospital Italiano de Buenos Aires). The HHT syndrome was confirmed by clinical and genetic analysis. All principal allergic processes were analyzed, but special attention was paid to asthma and allergic rhinitis. In these cases, HHT-dependent mechanisms facilitating or mimicking the development of allergy might explain a higher incidence of allergic symptoms, mainly affecting the nose. Reports on the quality of life of HHT patients and the worsening of clinical HHT manifestation during the active allergic periods, are currently under analysis. These data will be useful to improve the aspects related to a better care to allergic HHT patients.

P-132
EFFICACY OF THALIDOMIDE IN THE TREATMENT OF SEVERE RECURRENT EPISTAXIS IN HEREDITARY HEMORRHAGIC TELANGIECTASIA (HHT): ONGOING RESULTS OF A PROSPECTIVE STUDY

CL Balduini[1], F Bellistri[1], F Pagella[2], F Chu[2], E Matti[2], G Spinozzi[2], F Ornati[3], C Canzonieri[4], C Olivieri[4], C Danesino[4], M Benazzo[2], R Invernizzi[1]

[1]*Department of Internal Medicine, Foundation IRCCS Policlinico San Matteo, Pavia, Italy,* [2]*Department of Otorhinolaryngology, Foundation IRCCS Policlinico San Matteo, Pavia, Italy,* [3]*Department of Cardiology, Foundation IRCCS Policlinico San Matteo, Pavia, Italy,* [4]*General Biology and Medical Genetics, Dept of Molecular Medicine, University of Pavia, Pavia, Italy*

Introduction: Hereditary hemorrhagic telangiectasia is an autosomal dominant disease affecting approximately 1:5000 people. Recurrent epistaxis is the most frequent symptom, affecting 95% of patients. Angiogenesis has been implicated in the pathogenesis of HHT and it has been suggested that antiangiogenic substances may be effective in the treatment of vascular malformations. In literature, oral administration of thalidomide has proved to lower the frequency of epistaxis. The aim of our prospective, non-randomized, phase II, open-label trial is to confirm the effectiveness of this drug in reducing epistaxis and to identify the lowest effective dose in patients refractory to standard therapies. Methods. HHT patients with at least one episode of overt bleeding/week requiring at least one blood transfusion during the last three months, refractory to mini-invasive surgical procedures are enrolled. Thalidomide is administered at a starting dose of 50 mg/day orally. In case of no response, dosage is increased by 50 mg/day every 4 weeks until complete (cessation of nose bleeding) or partial response (reduction in the severity of epistaxis less than complete response) to a maximum dose of 200 mg/day. After the achievement of complete/partial response patients are treated for 16 additional weeks. Monthly follow-up evaluates the epistaxis severity score, the transfusion need and reported adverse events. The study, which will enroll 34 patients, is currently recruiting participants. Results. Thirteen patients (7M; 6F), aged 45-80 years (median 67) have been enrolled. 10 have completed 16 weeks of treatment. Seven patients responded within 4 weeks of starting the drug: epistaxis cessation was observed in one case, an epistaxis reduction has been obtained in 12 cases. Six patients reported a partial response after 8 weeks. As a consequence, thalidomide therapy increased hemoglobin levels and abolished/greatly decreased the need for blood transfusions.Seven patients completed the treatment and remained stable during the immediate follow-up. Conclusions. Preliminary results strongly support the hypothesis that low-dose thalidomide is effective for the treatment of epistaxis in HHT patients who did not benefit from other available treatments.

P-133
HEYDE'S SYNDROME AND HEREDITARY HEMORRHAGIC TELANGIECTASIA: REPORT OF THREE CASES

PA Carrillo[1,2,3], N Causada Calo[2,3], MC Elizondo[2,5], M Serra[1,2,4]

[1]*HHT Unit. Hospital Italiano de Buenos Aires, (HIBA),* [2]*ARG (Argentine Rendu Study Group),* [3]*Departament of Gastroenterology. HIBA,* [4]*Internal Medicine. HIBA,* [5]*Internal Medicine Research Unit, HIBA, Argentina*

Introduction: Gastrointestinal bleeding (GIB) is an important cause of anemia in patients with Hereditary Hemorragic Telangiectasia (HHT). Its treatment is based

Non-commercial use only

on endoscopic coagulation and pharmacological therapy. Aortic stenosis (AS) is associated with gastrointestinal bleeding from angiodysplasia. This condition, known as Heyde's syndrome (HS), is related to type 2A Von Willebrand (VW) disease, caused by the high shear stress in the valve that breaks down VW multimers. Epistaxis is also reported in patients with AS. Aortic valve replacement (AVR) significantly reduces GIB. There are no studies evaluating this intervention in patients with HHT and HS. *Objective:* To describe three cases of HHT patients (Curaçao criteria 4/4) with HS who experienced severe GIB, one of them was treated with AVR. *Case 1:* A 83 year-old male, with history of moderate AS, experienced 4 episodes (in one year) of hematemesis with hemodynamic instability due to gastroduodenal telangiectasias. Five therapeutic upper endoscopies were performed (with epinephrine and argon plasma), he received more than 10 red cells units (RCU) and he was treated with tranexamic acid (3 g). Because of recurrent bleeding and severe epistaxis, he was started on thalidomide (100 mg). AVR was not considered because of comorbidities and advanced age. *Case 2:* A 73 year-old male, with history of severe AS, suffered multiple episodes of GIB and anemia. More than 20 therapeutic endoscopies were performed because of gastroduodeal and colonic telangiectasias. He underwent AVR and didn't experience bleeding of any source or anemia for 6 months. He suffered aortic valve restenosis and presented with new episodes of GIB, recurrent epistaxis and anemia. *Case 3:* A 73 year-old male, with history of severe AS and multiple hospital admissions for anemia and melena due to duodenal, jejunal and colonic telangiectasias underwent right-hemicolectomy for lower GIB. His lowest hemoglobin concentration was 5.5 g/dL and received more than 25 RCU. At present he is in evaluation for AVR. *Conclusion:* We describe three cases of HHT with Heyde's syndrome. Endoscopic treatment was complex and all patients required multiple interventions. Aortic valve replacement could be an approach for bleeding control in this group of patients.

P-134
LASER ENDOSCOPIC SURGERY FOR CHRONIC EPISTAXIS IN HEREDITARY HEMORRHAGIC TELANGIECTASIA

FA Urquiola[1,3], Y Lijdens[1,3], M Serra[2,3,4]

[1]*Department of otorhinolaryngology. Hospital Italiano de Buenos Aires. Argentina. (HIBA),* [2]*Internal Medicine. HIBA,* [3]*HHT Unit. HIBA,* [4]*ARG (Argentine Rendu Study Group)*

Introduction: Epistaxis occurs in more than 95% of the patients thus affecting their quality of life. Nowadays no cure exists but a wide variety of treatments have been developed to control nose bleeding, from local ointments to septal closure. *Aims:* The present study is the first series described in Argentina and was designed to evaluate the effectiveness of Nd-Yag laser in the treatment of nasal telangiectasias, shown in the improvement of the Sadick scale, hematocrit and quality of life. *Methods:* Sixty-three out of 144 patients from the HHT unit attended an appointment at the ENT department of the Hospital Italiano de Buenos Aires; from May 2010 to November 2012. We performed an unilateral endoscopic photocoagulation of the nasal telangiectasias with Nd-Yag Laser at 25W of power in a continuous mode. Age, sex and Sadick grade before and after treatment as well as the hematocrit and the improvement in the quality of life were taken into account. *Results:* Fifteen out of 63 patients were treated with laser with a total of 18 procedures (three patients received bilateral treatment with an interval of 2-4 months). The age range was 12-82 years. The follow up time was of 9 months and continuing. Sadick grades were individualized according to the intensity and frequency. Only 3 patients remained with a grade III according to the Sadick frequency, 11 achieved a Grade I and one achieved Grade II. In terms of intensity, 13 (86 %) patients achieved a Grade I, whereas one patient achieved Grade II and another one grade III. The total increase in hematocrit after treatment was 6.6. All patients reported an improvement in their quality of life. *Conclusions:* Photocoagulation with Nd-Yag laser is indicated for moderate to severe epistaxis in HHT disease. This treatment demonstrated an improvement in the frequency and intensity of nasal bleedings as well as in the hematocrit values. This is why photocoagulation with Nd-Yag laser is considered a valuable and effective therapeutic option to improve the quality of life not only from a clinical but also from a social and psychological perspective.

P-135
THE CENTRE FOR RARE DISORDERS SERVICES FOR THE HHT GROUP

GA Ruud, K Iversen

Centre for Rare Disorders, Oslo University Hospital - Rikshospitalet, Norway

The Centre for Rare Disorders is a national interdisciplinary competence unit which offers services regarding a selected range of rare disorders. HHT is one of the largest of the centre's assigned groups. The centre's tasks/duties are to assist is patients, their family and to health-, educational- and other support professionals. Anyone belonging to these groups is welcome to contact the centre without referral. The centre's main objectives are:

- Information
- Counselling
- Seminars
- Research and Development

The centre's experience is that for a patient group like HHT, the most important I work is on a system level: To contribute to a better medical treatment and follow up for the group as a whole, by facilitate an expert collaboration group, and by emphasizing information material and activities. Also bringing professionals and the lay organisation together has been fruitful for bettering the treatment and follow up of the group. Information comprises written materials such as brochures and booklets, films, articles, a web site and lectures. The main topics are medical

non commercial use only

knowledge and how to cope and live well with the disorder. We also offer information meetings for larger groups of health care professionals and other support staff, consisting of lectures, discussion and sharing of experiences. Counselling is given in meetings and consultations at the centre, in hospitals or other institutions, in patient's domicile and over the telephone. Seminars are offered both to patients, their family and professionals, both in separate and joined groups. The centre is also engaged in research and development projects. In all our activity we aim to have close contact and cooperation with the lay organisations.

P-136
HEREDITARY HEMORRHAGIC TELANGIECTASIA (HHT) IN URUGUAY

R Mezzano, F Lemos, A Tiscornia, S Pisano, B Boggia

Transfusion Medicine Pereira Rossell Hospital, Montevideo, Uruguay

Introduction: Syndrome Hereditary Hemorrhagic Telangiectasia (HHT) is a disorder caused by the presence of vascular changes in multiple sites of autosomal dominant economy causing various health complications of sufferers. Commonly manifested by recurrent epistaxis, gastrointestinal bleeding, iron deficiency anemia and mucocutaneous telangiectasias. He added the presence of arteriovenous malformations (AVMs) in multiple organs mainly in lung, liver and CNS, the latter determining substantial morbidity. The HHT has a worldwide distribution and racial. There are few records of prevalence and believes that there is considerable underreporting of the disease. Prevalence is estimated variable: 1:5000 1:8000 depending on the population studied. The frequency is similar in men and women. Being a hereditary disease, familial screening is useful in members of a family with HHT. Traditionally the diagnosis of the disease is based on clinical criteria (criteria Curacao), however at present genetic test may also be used. The latter are considered useful for diagnosis in children and young people who are not visible telangiectasias or epistaxis but have presented no risk of pulmonary AVMs, brain or liver. The aim of this paper is to present the prevalent symptoms of patients studied so far according to the criteria of Curacao. *Methodology:* Includes clinical evaluation (diagnostic criteria Curacao) and paraclinical in patients assisted in 5 care institutions. *Results:* There have been 17 people diagnosed with HHT adults and one teenager, who meet diagnostic criteria for referrals. Epistaxis 16 patients presented with different score Sadick. First-degree family history of 15 patients and 2 unknown family history. Arterio - venous malformations 5 patients were studied and 12 unknown whether suffering, no studies were requested. Mucocutaneous Telangiectasis 15 patients. The teenager has first-degree family history, epistaxis and telangiectasias. *Conclusion:* epistaxis and telangiectasias are most prevalent clinical manifestations. There's still an underdiagnosis of arteriovenous malformations (major cause of morbidity and mortality) for failure to request the necessary studies in Uruguay.

P-137
CUSTOMIZED NASAL BREATHING TUBES AS AN ALTERNATIVE TO YOUNG'S PROCEDURE IN HHT PATIENTS WITH EPISTAXIS - PRELIMINARY RESULTS

BJ Folz, AM Chirtesiu, CG Konnerth

Dept. of ORL, HNS, Karl Hansen Medical Center, Bad Lippspringe, Germany

Introduction: Epistaxis is a major concern in HHT patients. If conservative measure and endoscopic therapies do not lead to sufficient hemostasis in the nose, the patients are either treated by Dermoplasty or by closure of the nares (Young's procedure). After Young's procedure the patients usually lose their sense of smell and the ability to breathe through the nose. Methods: Three HHT patients received customized nasal breathing tubes. Endonasal casts for modelling of the tubes were taken during routine laser therapies for Epistaxis. The casts were then transformed by a prosthetician into customized silicone breathing tubes, which should shield the nasal mucosa from irritations of nasal airflow, dryness and crusting. Results: The average time period between necessity of further laser therapy sessions was extended by two months, if the patients wore their breathing tubes regularly. At the same time nasal patency was preserved and the sense of smell was not impaired. *Conclusion:* On a very preliminary basis it can be said that customized nasal breathing tubes can aid in prolonguing time intervals between laser therapies for telangiectases in the nose of HHT patients. It may be an alternative to Young's procedure, which is able to preserve the function of the nose.

P-138
NASAL HYGIENE EDUCATION AND EPISTAXIS MANAGEMENT: NURSING INTERVENTION FOR HHT PATIENTS

R Pantalone, E Leek, J Lee, ME Faughnan

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

Background: Epistaxis is the most common symptom of HHT, reported in approximately 90% of adults over age 50. There is consensus about need for lubrication and basic nasal hygiene for management of HHT-related epistaxis, though there no systematic clinical approach has been developed to educate patients. *Aim:* To assess needs for epistaxis education in the Toronto HHT Centre and to pilot a nursing-based epistaxis educational program. *Methods:* To address burden of disease, we collected Epistaxis Severity Score (ESS), hemoglobin (Hgb) and ferritin levels from consecutive patients over one year. In 14 patients, we assessed individual needs for epistaxis education and piloted an epistaxis education session administered by a registered nurse (RN). The RN received education from an HHT ENT expert. An epistaxis education order form was developed for communication between MD and RN, as well as a questionnaire to assess patient needs and feedback. *Results:* We included 90

Non-commercial use only

patients ; 51 were female (57%); mean age 53 yrs (± 13.3. range 17–82). Two patients (2 %) had no epistaxis, ESS was mild in 43/90 (48%), moderate in 32/90 (34%) and severe in 12/90 (13%). Mean Hgb was 126 g/L (± 22, range 69-164); mean ferritin was 50 μg/L (±52, range <10 - 376 μg/L). The pilot study included 14 patients; 9 were female and mean age was 53 years (± 11.3, range 35-82). ESS was mild in 5/14 (35%), moderate in 6/14 (43%) and severe in 3/14 (21%). Mean Hgb was 124.7g/L (± 25.1, range 80-157); mean ferritin was 45 (±38.9, range <10-124). Questionnaire revealed 8/14(57%) were not using nasal lubricant. Four reported self packing, of which 3 were using harmful methods. All patients reported positive need for epistaxis education and feedback from all patients was positive regarding usefulness of the education. *Conclusion:* There is a large burden of epistaxis in HHT Centre patients, with broad range of severity and unmet needs for patient education. A standardized approach to epistaxis education is feasible and preliminary assessment suggests it is useful.

P-139
NARROW BAND IMAGING (NBI): FIRST IMPRESSION ABOUT ITS USE IN THE STUDY OF NASAL TELANGIECTASIAS IN PATIENTS AFFECTED BY HHT

F Chu[1], F Pagella[1], E Matti[1], G Spinozzi[1], D Zaccari[1], C Olivieri[2], F Ornati[3], E Buscarini[4], C Danesino[2] on behalf of HHT-NET

[1]*Department of Otorhinolaryngology, Foundation IRCCS Policlinico San Matteo, Pavia, Italy,* [2]*General Biology and Medical Genetics, Dept of Molecular Medicine, University of Pavia, Pavia, Italy,* [3]*Department of Cardiology, Foundation IRCCS Policlinico San Matteo, Pavia, Italy,* [4]*Department of Gastroenterology, Maggiore Hospital, Crema, Italy*

Introduction: Hereditary hemorragic telangectasia (HHT) is an autosomal dominant disease affecting 1:5000 people. Epistaxis due to nasal telangiectasias is the most frequent symptom. We recently reported an endoscopic classification of nasal telangiectasias including three main morphological patterns: large, punctate and mixed. Narrow Band Imaging (NBI) has recently been introduced as a new optic device which uses reflected light to improve the contrast of superficial capillaries present in the mucosal layers. In this work we report the advantages, disadvantages and clinical implications of this novel technique in the study of the morphology of nasal telangiectasias in patients affected by HHT. Materials and *Methods:* we reviewed the video recordings of the nasal endoscopies performed in patients affected by HHT, both with white light and with the assistance of NBI. Results: From 1996 to 2012, 476 patients affected by HHT were hospitalized in our Clinic. 295 underwent nasal procedures for their epistaxis. In total we performed 488 procedures since some patients required more than one treatment. 13 patients (M:F=9:4; average age 49.7 years, range 14-81) underwent nasal endoscopy, both with white light and with the assistance of NBI, to assess the morphological pattern of nasal telangiectasias. In all patients, narrow-bandwidth filters permitted the morphology of nasal telangiectasias to be enhanced more clearly. In particular, the small and punctate telangiectasias were detected more easily while the large telangiectasias showed a very complex vasculature resulting from a thick and irregular nest of altered vessels. Intraoperatively, NBI was performed in 3 patients only; in 10 patients, bleeding from nasal telangiectasias darkened the screen so that the procedure was performed under endoscopic control, in white light. *Conclusions:* In our experience NBI has proved to be an effective tool for studying the morphology of nasal telangiectasias in patients affected by HHT, improving the diagnosis of this disease. In addition to this, the correlation between the morphology of nasal telangiectasias valued with NBI and genetics might, in the future, clarify some aspects of the genotype-phenotype relationship of HHT. Further studies are needed to verify the role of such a new optic device in Rendu Osler Weber disease.

P-140
THE RELATIONSHIP OF TIME AND AMBIENT AIR QUALITY TO EPISTAXIS SEVERITY SCORES IN HEREDITARY HEMORRHAGIC TELANGIECTASIA

CA Merlo[1,2], R Peng[2], JB Hoag[3], S Mitchell[1], G Robinson[1], DD Reh[1], PB Terry[1]

[1]*The Johns Hopkins University School of Medicine,* [2]*The Johns Hopkins Bloomberg School of Public Health,* [3]*Drexel University School of Medicine, Baltimore, MD, USA*

Introduction: Epistaxis among individuals with hereditary hemorrhagic telangiectasia (HHT) related epistaxis is common. Although there is a wide spectrum of severity, little is known about longitudinal changes in epistaxis and how ambient air may affect these changes over time. The purpose of this study was to examine longitudinal trends in epistaxis severity over time and to determine factors associated with worsening epistaxis. *Methods:* Individuals with HHT were prospectively recruited using the HHT Foundation International website (www.hht.org). Individuals were sent a monthly HHT-Related Epistaxis Questionnaire and an HHT Epistaxis Severity Score (HHT-ESS) was calculated. Subject demographics, geographic location, and time of year were collected. Data were merged with ambient air pollution data (particulate matter and ozone) from the EPA's Air Quality System and temperature data from the National Climatic Data Center. Descriptive analyses were performed with calculations of means and medians for continuous variables and proportions for categorical variables. Multiple linear regression models using generalized estimating equations were developed to assess the effect of geography, season, and ambient air characteristics on epistaxis severity over time. *Results:* One hundred seventy seven subjects over a twelve-month period were included. The mean (SD) age was 55.4 (11.6) years, and the mean (SD) HHT-ESS was 2.8 (0.3). Over time, the ESS remained constant within individuals with a change of -0.001 (p=0.68) per month during the study. The HHT-ESS was stable across the four sea-

Non commercial use only

sons: slightly lower in winter (-0.005; p=0.84), higher in summer (0.02; p=0.32) and fall (0.01; p=0.56). The HHT-ESS did not show strong associations with fine particulate matter (PM), ozone, temperature, or dew point temperature. A 1-unit increase in fine PM, ozone, temperature, and dew point temperature were associated with a 0.0035 (p=0.15), -0.31 (p=0.44), 0.0015 (p=0.21), and 0.0005 (p=0.35) change in HHT-ESS, respectively. *Conclusions:* Epistaxis severity remains constant in individuals with HHT over time with little seasonal variation and does not appear to be associated with outdoor ambient air characteristics. Further study investigating the indoor environment in this patient population is warranted.

P-141
SEPTODERMOPLASTY IN HHT: A MODIFIED TECHNIQUE.

J Rimmer[1], VJ Lund[1,2]

[1]*Royal National Throat Nose & Ear Hospital, London,* [2]*University College London, USA*

Introduction: Epistaxis is the most common symptom in patients with hereditary haemorrhagic telangiectasia (HHT) and may have a significant effect on their quality of life. There are a variety of surgical treatments available which aim to reduce the frequency and severity of bleeding. Septodermoplasty (SDP), first described by Saunders in 1964, is a technique in which the anterior septal mucosa is removed and replaced with a split-thickness skin graft (STSG). We describe a modified technique for SDP that provides improved visualisation of the surgical field. *Methods:* A prospective review of patients who underwent SDP using a modified technique from November 2012 to February 2013. *Results:* Six patients have undergone SDP using the modified technique since November 2012. There were 5 female and 1 male, with an average age of 54.6 years (range 39-66 years). Average follow-up was 9.7 weeks (range 1-14 weeks). Two of the cases were revision procedures. There was good visualisation of the operative field throughout, with reduced operative time compared to the previous technique. The procedure was effective in all cases and there were no complications. *Discussion:* Eighty-four SDPs have been undertaken in our department since 1987, in 61 patients. Cold steel and sharp dissection were previously used to excise septal mucosa but we describe a recent modification to the technique. We now employ a microdebrider to excise septal mucosa, which provides simultaneous suction and thereby improves visualisation of the operative field. This allows more precise removal of the relevant area of mucosa, and is particularly helpful in revision cases when the plane of dissection is more difficult to find. Outcomes were comparable and there were no complications. We recommend its use routinely when undertaking SDP.

ENDOGLIN, ALK1 AND SMAD4 IN TGF-BETA AND BMP PATHWAYS

P-142
ENDOTHELIAL CELLS DERIVED FROM HHT1 PATIENT SPECIFIC INDUCED PLURIPOTENT STEM CELLS (IPSCS) SHOW REDUCED ENDOGLIN (ENG) PROTEIN LEVELS AND ALTERED DOWNSTREAM SIGNALLING

K Gkatzis[1], V Orlova[1,2], C Freund[1], P ten Dijke[2], F Disch[3], K Westermann[3], H-J Mager[3], C Mummery[1]

[1]*Department of Anatomy and Embryology,* [2]*Department of Molecular Cell Biology, Leiden University Medical Center, Leiden, The Netherlands,* [3]*St Antonius Hospital, Nieuwegein, The Netherlands*

Endoglin (ENG, CD105) is a transmembrane glycoprotein, type III co-receptor for transforming growth factor (TGF)-β, present on the surface of endothelial cells (ECs) and subsets of haematopoietic cells, such as monocytes. Mutations in the ENG gene are associated with the development of Hereditary Haemorrhagic Telangiectasia Type (1) (HHT1), characterized by periodic heavy nosebleeds, micro telangiectasis and arterial-venous malformations (AVMs). To our knowledge, there is no human in vitro model to study pathogenesis of HHT(1). Recent advances in stem cell research have made it possible to reprogram somatic cells into pluripotent cells, known as induced pluripotent stem cells (iPSCs). iPSCs resemble human embryonic stem cells, including the ability to self-renew and differentiate towards all cell types of the body. Thus, HHT(1) patient specific iPSCs can serve as an unlimited source of endothelial cells (ECs) and can potentially be used to model HHT in vitro. We recently established several iPSC lines from HHT(1) patients with different ENG mutations. Here, we analyzed ENG protein expression levels on CD(14+) monocytes from peripheral blood and on ECs derived from iPSC lines generated from corresponding patients. Peripheral blood from HHT(1) patients and control individuals was studied by fluorescence-activated cell sorting (FACS). ENG protein levels were downregulated in most of the HHT(1) patient monocytes compared to healthy individuals. We next compared ENG expression levels on HHT(1)-iPSC ECs from patients with corresponding. Just as the patient monocytes, HHT(1) iPSC-ECs also demonstrated reduced levels of ENG protein as detected by FACS and Western Blot analysis. Reduced levels of ENG protein were also found to have an affect on downstream signaling upon stimulation with TGFβ/BMP ligands. Thus HHT(1) iPSC-ECs exhibit reduced ENG expression levels and as well as defective downstream signaling, demonstrating (i) their potential value in modelling HHT in vitro and (ii) that the essential features of HHT1 are not lost during reprogramming. This will facilitate further developments in patient specific drug screening and personalized medicine.

non-commercial use only

P-143
ALK-1 DEFICIENCY IS ASSOCIATED TO ALTERATIONS IN ARTERIAL PRESSURE REGULATION

M Gonzalez-Nuñez, B Oujo, F Pérez-Barriocanal, JM Lopez-Novoa

Unidad de Fisiología Renal y Cardiovascular, Departamento de Fisiología y Farmacología, Universidad de Salamanca, Instituto de Investigación Biomédica de Salamanca (IBSAL), Instituto Reina Sofía de Investigación Nefrológica, Spain

Activin receptor-like kinase-1 (ALK-1) is a type I receptor for TGF-β with serine/threonine kinase activity mainly expressed in vascular endothelial cells. A mutation in the gen that codifies for ALK-1 is the responsible for a disease called Hereditary Hemorrhagic Telangiectasia type 2 (HHT-2). We have previously demonstrated that endoglin (whose deficiency is related to HHT-1) plays a major role in vascular contractility regulation by regulating eNOS expression. As the alterations in the vascular reactivity seem to play a role in the HHT-2 and pulmonary hypertension, the aim of our study was to test the role of ALK-1 in the regulation of the vascular function. For this purpose we have used heterozygous mice (Alk-1+/-), a genotype similar to the disease, and their littermates Alk-1+/+. Arterial pressure (AP) was measured using telemetry methods to avoid the alterations induced by anesthesia. Alk-1+/- mice had a higher AP than control mice (Alk-1+/+). Echocardiographic studies revealed no differences in cardiac structure and function between Alk-1+/+ and Alk-1+/- mice, thus suggesting differences in peripheral vasoconstriction. Acetylcholine or nitroprusside treatment induced a similar decrease in AP in both mice strains, whereas L-NAME treatment induced the same AP increase in both groups, thus suggesting that ALK-1 effect on the AP is not nitric oxide-dependent. Administration of losartan or captopril reduced AP in a similar way in Alk-1+/- than in Alk-1+/+ mice. Treatment with AgII produces similar vasoconstrictor response, suggesting that the increase in AP is renin-angiotensin system-independent. However, plasma catecholamine concentration was higher in Alk-1+/- than in Alk-1+/+ mice, and the blockage of 1-adrenergic receptors was more effective decreasing AP in Alk-1+/- than in Alk-1+/+ mice, suggesting a hiperactivation of the sympathetic nervous system in the Alk-1+/- mice. In conclusion, ALK1-deficient mice show an increase in arterial pressure that seems to be dependent on a sympathetic activation.

P-144
ALTERATION IN ENDOGLIN-RELATED ANGIOGENESIS IN REFRACTORY CYTOPENIA WITH MULTILINEAGE DYSPLASIA

M del Rey[1,2], M Pericacho[2,3], S Velasco[3], E Lumbreras[1,2], JM Lopez-Novoa[2,3], JM Hernandez-Rivas[1,2,4], A Rodríguez-Barbero[2,3]

[1]*IBMCC, Centro de Investigación del Cáncer (CIC), Universidad de Salamanca-CSIC, Salamanca, Spain,* [2]*IBSAL, Instituto de Investigación Biomédica de Salamanca, Salamanca, Spain,* [3]*Departamento de Fisiología and Farmacología, Universidad de Salamanca, Salamanca, Spain,* [4]*Servicio de Hematología, Hospital Universitario de Salamanca, Salamanca, Spain*

Myelodysplastic Syndromes (MDS) are a heterogeneous group of hematopoietic malignancies, characterized by ineffective haematopoiesis, hypercellular bone marrow, dysplasia of at least one lineage and cytopenias in the peripheral blood. Myelodysplastic Syndromes are stem cell disorders; however, some studies have recently stressed the possibility that the bone marrow microenvironment may play a relevant role in the pathogenesis of these diseases. In addition, abnormalities in signal transduction, transcription activity, cell cycle control and angiogenesis have been related to MDS. The functional mechanisms involved in angiogenesis and the potential role of endoglin, recently described as a new marker for this process, have not been explored in Myelodysplastic Syndromes. In order to gain insight in MDS angiogenesis a combined analysis in bone marrow of gene expression levels, angiogenesis-related soluble factors and functional angiogenesis-related studies was carried out. Ninety-seven MDS patients and forty-two normal bone marrow samples were studied. The morphology of the capillary-like structures originated by two endothelial cells lines in the bone marrow environment of patients with refractory cytopenia with multilineage dysplasia (RCMD) was different from those of the remaining MDS. In addition, the bone marrow mononuclear cells from RCMD patients displayed over-expression of VEGF, HIF and FN1 while they showed reduced expression of endoglin in contrast to the normal endoglin expression of the remaining low-risk MDS and the high expression of endoglin in high-risk MDS subtype. Moreover, higher soluble endoglin and soluble FLT-1 levels in bone marrow microenvironment were observed in RCMD cases, which distinguished them from other individuals. Thus, the RCMD patients showed an abnormal angiogenesis characterized by an increased level of soluble endoglin. The RCMD has been recently proposed by the WHO classification as a specific MDS disorder and the present study showed these patients had a different pattern of angiogenesis. These results provide new insights in the molecular mechanisms of RCMD patients that could be endoglin-related. These observations could provide new therapeutic approaches for this specific subtype of MDS.

P-145
ENDOGLIN HAPLOINSUFFICIENCY PROMOTES FIBROBLAST ACCUMULATION DURING WOUND HEALING THROUGH AKT ACTIVATION

M Pericacho, S Velasco, M Prieto, E Llano, JM Lopez-Novoa, A Rodríguez-Barbero

Renal and Cardiovascular Physiopathology Unit, Instituto "Reina Sofía" de Investigación Nefrológica, Departamento de Fisiología y Farmacología, Universidad de Salamanca, Salamanca, Spain

Accurate regulation of dermal fibroblast function plays a crucial role in wound healing. Many fibrotic diseases are

Non-commercial use only

characterized by a failure to conclude normal tissue repair and the persistence of fibroblasts inside lesions. 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. In the present study we demonstrate that endoglin haploinsufficiency promotes fibroblast accumulation during wound healing. Moreover, scars from endoglin-heterozygous (Eng+/-) mice show persisting fibroblasts 12 days after wounding, which could lead to a fibrotic scar. Endoglin haploinsufficiency results in increased proliferation and migration of primary cultured murine dermal fibroblasts (MDFs). Moreover, Eng+/- MDF have diminished responses to apoptotic signals compared with control cells. Altogether, these modifications could explain the augmented presence of fibroblasts in Eng+/- mice wounds. Besides, ALK1 and ALK5 TGFβ signaling pathways are present, functional and independent of endoglin expression in dermal fibroblasts. We demonstrate that endoglin expression regulates Akt phosphorylation and that PI3K inhibition abolishes the differences in proliferation between endoglin haploinsufficient and control cells. Finally, persistent fibroblasts in Eng+/- mice wound co-localize with a greater degree of Akt phosphorylation. Thus, endoglin haploinsufficiency seems to promote fibroblast accumulation during wound healing through the activation of the PI3K/Akt pathway. These studies open new non-Smad signaling pathway for endoglin regulating fibroblast cell function during wound healing, as new therapeutic opportunities for the treatment of fibrotic wounds.

PEDIATRICS AND NATURAL HISTORY OF HHT

P-146
ASSESSING HHT CLINICAL DIAGNOSTIC CRITERIA IN CHILDHOOD - THE ISRAELI NATIONAL CENTER EXPERIENCE

M Mei-Zahav, N Goldschmidt, S Metzger, E Yaniv, H Blau, E Brockheimer

HHT Center, Schneider Children's Medical Center, Tel Aviv University, Israel

Introduction: The diagnosis of HHT in children is difficult. The late presentation of HHT symptoms and signs has challenged the use of HHT clinical diagnostic criteria (Curacao criteria) in childhood. *Objectives:* To assess the sensitivity of the HHT Curacao diagnostic criteria in patients before the age of 20 years. *Methods:* All patients referred to the Israeli HHT center were included. Diagnosis of definite and suspected HHT was made using the Curacao diagnostic criteria or genetic analysis when informative. Bubble echocardiography followed by chest CT when indicated was performed to detect pulmonary AVMs. Cerebral AVMs were detected by head MRI. Detailed history revealed the exact timing of symptoms. *Results:* 238 patients (mean 38±21 years) were referred to the Israeli national HHT center in 2006-2012. 138 patients were diagnosed with definite HHT. 113 (82%) were 20 years and older when screened. Familial genetic analysis confirmed the diagnosis of HHT1 in 23 patients, HHT2 in 34 and HHT4 in one. In 28% no mutation was found. Pulmonary AVMs were detected in 39% of patients with definite HHT. Cerebral AVMs were detected in 11%, mostly small and asymptomatic. Reviewing HHT symptoms of the adult patients before the age of 20y revealed that 35 (31%) did not have any symptoms suggestive of HHT and did not fulfill clinical diagnostic criteria of HHT. Pulmonary AVMs in seven patients and cerebral AVM in one would have been missed relying solely on the diagnostic criteria. Two patients who presented with strokes did not have any symptoms suggestive of HHT as children. 72 patients experience epistaxis in childhood, as young as one year of age. Most episodes of epistaxis in childhood were mild and infrequent. *Conclusions:* Clinical symptoms and signs are not sensitive in the diagnosis of HHT in children. Symptoms, when present, are usually mild. Diagnosis based solely on symptoms can result in life-threatening complications. Every child of a HHT patient should be screened for visceral AVMs regardless of symptoms.

P-147
HHT CENTER OF EXCELLENCE AT JOHNS HOPKINS HOSPITAL – ORGANIZATION, SCREENING, AND TREATMENT RESULTS IN CHILDREN AND ADULTS 2009-2013

Ul Haq Faheem, G Robinson, CA Merlo, JM Collaco, P Terry, S Mitchell

Johns Hopkins Hospital, Baltimore, MD, USA

Introduction: Purpose of this presentation is to highlight the organization of an HHT Center of Excellence, screening process, and results in terms of adult and pediatric patient volumes and management over a 4 year period. *Methods:* This retrospective study was carried out at the HHT Center of Excellence at Johns Hopkins Hospital which was established in 2009. A total of 249 patients were evaluated from March 2009 to March 2013, out of which 220 patients (90% Caucasian) underwent screening (56 children(</= 18 years) and 164 adults). *Results:* 45(70%) children and 153(83%) adults presented with epistaxis. Mucocutaneous telangiectases were identified in 14(22%) children and 138(75%) adults on clinical examination. Family history was positive in 57(89%) children and 131(71%) adults. Agitated saline echocardiography was performed in 54 pediatric patients and was positive in 17(31%) and 6(11%) were equivocal. All 23 underwent 3D CTA which identified pulmonary arteriovenous malformations (PAVMs) in 13(56%) out of which 12 had pulmonary angiography and 10 were amenable to embolization. Out of 164 adults, 132 had agitated saline echocardiography which was positive in 89(67%). 140 underwent 3D CTA which identified pulmonary arteriovenous malformations (PAVMs) in 75(54%) out of which 70 had pulmonary angiography and 64 were amenable to

non commercial use only

embolization. Cerebral MRI was positive for cerebral arteriovenous malformations (cAVMs) in 3(6%) out of 54 children and 13(8%) out of 154 adults. 17(27%) children were tested for genetic mutations and 8(47%) were found to have ACVRL mutation on chromosome 12 and 4(23%) were positive for ENG mutation on chromosome 9. Similarly 9(43%) had ACVRL mutation and 6(29%) adults were positive for ENG mutation out of the 21(11%) adults who had undergone genetic testing. *Conclusion:* Prevalence of PAVMs reported in HHT patients in international studies have a variable range from 5-50% however our data is consistent with a higher percentage of PAVMs in both pediatric and adult populations. Our patient prevalence of cAVMs is similar to the available data 5-20%. Our study population had more genetic mutations in ACVRL gene than ENG gene.

P-148
COMORBIDITIES IN HHT PATIENTS WITH EPISTAXIS

BJ Folz, AM Chirtesiu, CG Konnerth

Dept. of ORL,HNS; Karl Hansen Medical Center, Bad Lippspringe, Germany

Introduction: Hereditary Hemorrhagic Teleangiectasia (HHT, Morbus-Rendu-Osler-Weber) is a disorder of the entire vascular system. Typical findings of the disease are telangiectases of the skin and mucous membranes and arteriovenous malformations of the inner organs. Due to the systemic character of the disorder hemorrhages and other complications may occur everywhere in the body. Typical manifestations of HHT are Epistaxis, hemorrhages, stroke, abscesses, heart and liver failure and anemia. It is not clear, whether HHT patients suffer from a typical spectrum of comorbities. *Methods:* The charts of 57 HHT patients from a 5 year period (2007-2012) were prospectively analyzed for age, gender, signs and symptoms at presentation and comorbities. The investigation was performed with standardized evaluation protocol. *Results:* A total of 46 cases with comorbidities could be evaluated from a pool of 57 patients. In 31% of the cases multiple comorbidities could be found. The most frequent comorbidity was arterial hypertension (16/46). Further common diagnoses were: anemia (9/46), cardiac arrythmia (8/46), congestive heart disease (4/46), diseases of the cardiac valves (4/46) and coronary heart disease (3/46). Two patients had a history of stroke, 4 patients had suffered from a malignoma. Diabetes was evident in 6 patients, deep vein thrombosis was seen in 2 patients. Chronic renal failure was diagnosed in 2 patients, one patient each had a history of the following diagnoses: Depression, Gastritis, Morbus Meniére, Cushing Syndrome, Hepatitis B, Dementia, OSAS, Asthma and Allergies. *Conclusion:* HHT patients suffer from multiple disorders. It comes to no surprise, that the majority of comorbidities concern the cardio-vascular system. HHT patients with cardiac arrythmia are difficult to treat, because anticoagulant therapy may lead to deleterious nosebleeds. In this regard factor Xa inhibitors may become an alternative to Warfarin.

PATIENTS' ASSOCIATIONS WORKSHOP

P-149
CONSEQUENCES OF HHT ON WORKING LIFE

U Geisthoff, A Al-Habib, L Hoffmanns, S Maune

Department of ORL, Hospital of the City of Cologne, Cologne, Germany

Background: HHT can severely impair quality of life, life balance, physical and mental capacities of affected persons. However, so far no data exists on the consequences of HHT on working life and social security coverage. *Methods:* Patients were asked if HHT led to an early retirement or to an officially acknowledged reduction in earning capacity. They were also asked for medical reports and medical expert opinions on this subject. Findings on examination and the documents were analyzed with respect to the official German regulations for medical expert opinions. *Results:* 124 patients were included in the study. 4 patients had achieved a retirement ahead of time, 3 additional patients an officially acknowledged reduction of earning capacity between 20 % and 60 %. Reasons reported in the official decisions were mainly nosebleeds and anemia. However, analysis of the official German regulations for medical expert opinions showed the following relevant parameters related to HHT, which mostly were not considered in the expert opinions: disorders of the gastrointestinal system, the liver, the central nervous system, the respiratory organs, the skin, migraines, bleeding disorders, arteriovenous fistulae. Though multiple parameters were positive for numerous patients, most patients had not applied for an official reduction of workload. The reasons given for this included relatively low impediment by HHT, fear of being not successful and losing one's job instead (as had happened reportedly to 1 of the patients), and being retired already. *Conclusions:* HHT can lead to inability to work. Our results suggest that HHT is not well known to physicians performing medical expert opinions and that this might lead to an insufficient assessment of the disorder in medical expert opinions. A possible reason is the lack of literature and recommendations on medical expert opinions on HHT. Patients themselves seem to avoid applying for a reduction of workload or early retirement.

P-150
10TH ANNIVERSARY OF THE HHT UNIT IN SIERRALLANA HOSPITAL (SPAIN)

R Zarrabeitia[1], V Diez[1], J Bueno[1], JA Parra[2], J Zarauza[1], A Fontalba[2], B Señaris[1], M Bustamante[2], J Jordá[2], C Menéndez[1], JLF Forcelledo[1], J Calvo[1], R Megía[2], J Rodríguez Iglesias[2], C Morales[2], LM Botella[3]

[1]*Unidad HHT. Hospital Sierrallana (Torrelavega. Spain),* [2]*Hospital Universitario Marqués de Valdecilla (Santander. Spain),* [3]*Centro de Investigaciones Biológicas (CIB.CSIC. Madrid. Spain), Network of biomedical research on rare diseases (CIBERER 707),*

Non-commercial use only

Institute of education and research Marqués de Valdecilla (IFIMAV)

The clinical HHT Unit in Hospital Sierrallana was created in 2003 thanks to the collaboration with the basic research projects developed in Madrid (CIB) by Luisa Botella and Carmelo Bernabeu. The main objectives of the project were to create and develope a multidisciplinary team to diagnose and treat Spanish HHT population with the best standards. On 2004 the HHT Foundation international included the unit into the panel of expertise centres and that circumstance provided better knowledge by general population and collaboration with international groups. Nowadays the clinical unit can not be understood without taking into account the close collaboration with basic researchers and with the Spanish HHT Association of patients (www.asociacionhht.org). In the area of clinical research, the team is included into the CIBERER network and it is part of the IFIMAV Institute. In this last 10 years 588 new patients from all over the national territory have been attended in the three different types of services provided (consultancy/in hospital/family genetic testing). Among them, 394 have been confirmed of suffering the disease. Considering the numbers, we think that practically all the population from Cantabria has been evaluated by the unit, since the 87 HHT confirmed cases lead to a 1: 6,641 prevalence for Cantabria. Extrapolating the data, around 7,000 (6,944) HHT patients would be expected for Spain. HHT 2 patients were more prevalent (49.49%) than HHT 1 (43.91%) and Madh4/Smad 4 mutations were observed only in 2 patients (0.51%). Important milestones in the history of the unit have been the ISO 9001:2008 quality certification achieved in 2008, the organization of the 8th HHT Scientific Conference in Santander in 2009, and the designation of raloxifene as first orphan drug for HHT by the European Medicines Agency and the Food and Drug Administration. Nowadays the efforts are focussed on creating a Spanish network of clinical regional units to provide closer and better attention to the HHT population.

non commercial use only

Index of Authors

Akers A 18, 48
Al-Habib A 68
Al-Saleh SA 40
Alamowitch S 51
Albiñana V 9, 26, 53
Alcaraz C 9
Alicante S 5, 24, 36
Allinson KR 1
Ambrun A 22
Amirrasouli M 15
Andersen PE 17, 45
Angenendt H-W 58
Angriman F 54, 59
Ardelean DS 13, 24
Aristorena M 14, 50
Aronovitz MJ 39
Arthur HM 1, 13, 15
Auboiroux C 20
Azzopardi N 52

Babin E 10
Baca B 18, 48
Bachur CD 22
Bailly S 7, 20, 21, 38, 52
Balagny P 41
Balduini CL 61
Bandi JC 3
Bardel-Danjean C 48
Bauso D 3
Bayrak-Toydemir P 8, 19, 20, 43
Beauchet A 55, 60
Begbie ME 9
Bellistri F 61
Benazzo M 61
Benito HJ 61
Bensalah M 4, 54
Bergerot J-F 17
Bernabeu C 8, 9, 13, 14, 16, 19, 26, 37, 49, 50, 53, 61
Berthezene Y 17
Besada C 3
Bidart M 38
Binsse S 4, 6, 31, 41, 54, 55, 60
Blamire A 15
Blanco FJ 14, 16, 37, 50
Blau H 45, 67
Bletry O 23
Blivet S 4, 6, 31, 41, 54, 55, 60
Blondel J-H 4, 6, 31, 41, 54, 55, 60
Boccardi E 5, 11, 24, 36
Boersma LVA 27
Boggia B 63
Bogwitz M 46
Bonay M 4, 6, 31, 41, 54, 55, 60
Bonjean M 9
Bos WJ 58
Botella LM 8, 9, 13, 14, 19, 26, 37, 49, 50, 53, 61, 68
Bourgault I 4, 6, 31, 41, 54, 55, 60
Bovy N 19
Bracquart D 2
Brambilla G 5, 24
Bravo NC 46
Brilliant MH 25
Bruckheimer E 45, 67
Brusgaard K 45
Buecker A 4, 17, 33
Bueno J 68
Buonamico P 43
Busbridge B 28
Busbridge M 28, 31
Buscarini E 5, 11, 24, 30, 31, 36, 47, 60, 64
Bustamante M 68

Cabana A 3
Cabañas C 37
Cadranel J 12
Cajal AR 46
Calender A 20, 48
Calvo J 68
Canzonieri C 5, 11, 24, 36, 47, 60, 61
Carette MF 7, 10, 12, 23, 48, 51, 52
Carpenter S 40
Carrillo PA 61
Castrillo A 16
Causada Calo N 3, 61
Cerrutti D 13
Chagnon S 4, 6, 31, 54, 55
Chapuis F 22
Chinet T 4, 6, 31, 41, 54, 55
Chinet Th 55, 60
Chirtesiu AM 63, 68
Chiumarulo L 43
Cho T-H 17
Choe S 1, 12, 25
Choi E-J 12
Choquet H 18, 48
Chu F 11, 47, 60, 61, 64
Ciais D 38
Ciarleglio MM 4
Cirulli ET 49
Cobarzan D 55, 60
Colak E 5
Collaco JM 67
Comelli M 60
Comi AM 22
Connors SM 22
Corbi A 50
Cordier A 4, 6, 31, 41, 54, 55, 60
Corre R 7, 10, 52
Costa LD 46
Covella B 43
Crinò S 5, 24, 36
Cunningham T 1
Curado F 38
Curatolo AS 22

Daly GH 39
Danesino C 5, 11, 24, 30, 31, 36, 47, 60, 61, 64
Dani E 50
Davison B 15
De Grazia F 5, 24, 36
de las Casas-Engel M 50
De Mattia D 43
de Picciotto C 6
Decullier E 7, 9, 10, 22, 48, 51, 52
del Rey M 66

non commercial use only

Deng Y 4
Devlin HL 29, 34, 42
Díaz M 16
Dicuonzo F 42
Diederik AL 41, 56
Diez V 68
Disant F 22
Disch F 2, 65
Donaldson JW 21, 32
Donazzolo Y 22
Donovan JP 38
Dos-Santos-Luis D 2, 52
Douda D 13
Drabsch Y 2
Dubois M 6
Dubourg O 41
Duffau P 10, 23
Dupuis-Girod J 51
Dupuis-Girod S 7, 9, 10, 13, 17, 22, 23, 48, 52
Düwell A 37

Edery P 9, 10
Egana I 38
El Hajjam M 4, 6, 31, 41, 54, 55
Eleno N 37
Elizondo MC 3, 61
Epperla N 25
Eyries M 4, 6, 31, 48, 54, 55
Eyris M 12

Fagnou C 4, 6, 31, 41, 54, 55, 60
Fargeton AE 7, 22, 52
Faughnan ME 5, 29, 33, 40, 44, 63
Faure F 7, 22, 52
Favrole P 51
Feige J-J 38
Feige JJ 21
Fernández-Luna JL 9
Ferreyro B 54, 59
Finnamore HE 27, 28
Fogarty AW 21, 32
Folz BJ 37, 63, 68
Fontalba A 9, 68
Forcelledo JLF 68
Forner PA 5, 11, 24, 36
Foster FS 24
Freund C 2, 65

Gallardo-Vara E 50
Gallea M 51
Gallione CJ 49
Game L 9
Gandolfi S 5, 11, 24, 36
Garcia M Basalo
Garcia-Tsao G 4
Garrido-Martín EM 1
Gauthier, 41 A.
Gazzaniga P 5, 11, 24, 30, 31, 36
Geisthoff U 4, 17, 33, 58, 68
Genot E 38
Gentile E 57
Giess A 9
Gilbert-Dussardier B 7, 10, 23, 48, 52
Gilson C 28
Ginon I 7, 52
Giordano P 42, 43
Giraud S 7, 9, 10, 20, 21, 48
Giunta D 3
Gkatzis K 2, 65
Goldschmidt N 67
Golimstok A 3
Gonzalez-Nuñez M 16, 66
Gossage JR 23, 33
Gouya L 4, 6, 31, 54, 55, 60
Govani FS 9
Grimmer JF 19
Grosso M 5, 11, 24, 36
Guilhem A 13, 23
Guillot E 7
Guilpain P 13

Hall IP 21, 32
Han C 25
Hansen S 19
Haq Faheem UL 67
Harle JR 10, 23
Hart B 18, 48
Hatron PY 7, 10, 52
Henderson K 4, 18
Hermier M 17, 51
Hernandez-Rivas JM 66
Hickson M 27, 28
Hirschfield GM 5
Hoag JB 35, 64
Hoffmanns L 68
Honnorat J 17
Hosman AE 29, 34, 42
Howard LSGE 31
Hubbard RB 21, 32
Hughes CCW 15
Hughes JMB 31

Invernizzi R 61
Ishiguro T 10
Ito H 45
Iversen K 62

Jackson JE 27, 31, 58
Jerkic M 13, 14, 24
Jezkova K 39
Jiang Z 1
Jones MD 9
Jordá J 68

Kaminsky P 10, 23
Kapur NK 39
Karam C 4, 6, 31, 41, 54, 55
Karas RH 39
Kashiwagi J 1
Kasthuri RS 29
Kawagoshi A 45
Keavney B 15
Kerbe RS 24
Khalil A 12
Khan Y 18
Kim H 15, 18, 29, 33, 44, 48

non commercial use only

Kim J-H 15
Kim TK 5
Kim YH 1, 12, 25
Kirpalani A 5
Kitzis A 48
Kiyosue H 1
Kjeldsen AD 17, 45
Klatt R 49
Koculym A 5
Komiyama M 8, 10
Konnerth CG 37, 63, 68
Krings T 18
Kucharczyk M 54
Kühnel T 53
Kulinskaya E 27

Lacombe P 4, 6, 7, 10, 31, 41, 52, 54, 55, 60
Laeeq K 35
Laffan MA 27
Lamandé N 2
Lamribet K 21
Langa C 8, 16, 37
Lanier KE 22
Lanzarini L 11, 60
Laroche JP 47
Lastella P 42, 43, 50
Lastres P 13
Latino GA 40, 44
Laux DW 38
Lavigne C 10, 23
Le Couteur J 27, 28
Le Quellec A 13
Lebrin F 2, 12, 52
Lee J 63
Lee YJ 25
Leek E 63
Lemos F 63
Lenato GM 42, 43, 50
Lequellec A 23
Lerolle N 23
Lesca G 10, 20, 48
Lesur G 4, 6, 31, 41, 54, 55, 60
Letarte M 13, 14, 24, 39, 49
Letteboer TGW 49, 51
Levet S 38
Levy E Yeyati
Lewis T 19
Li W 8
Liang ZA 14
Lijdens Y 62
Lin D 44
Ling L 57, 59
Liso V 50
Livesey JA 27, 58
Llano E 16, 66
Londoni C 5, 24
Lopez-Gutierrez JC 1
Lopez-Novoa JM 16, 37, 66
Lorcerie B 7, 23, 47, 52
Lorcerie P 10
Lumbreras E 66
Lund VJ 35, 65
Lupinacci G 5, 24, 36

Mackey EE 39
Mager H-J 2, 65
Mager JJ 27, 30, 31, 32, 41, 51, 55, 56, 58, 59
Magro P 10
Mahmoud M 1
Mallet C 21, 38
Manfredi G 5, 11, 24, 30, 31, 36, 47, 60
Manning RA 27
Mansencal N 41
Mansfield CJ 38
Marchuk DA 49
Margiotta C 50
Marion D 7
Maritano Furcada J 61
Marnas E 47
Marro B 51
Martial JA 19
Martin S 2
Maruno M 1
Massmann A 4, 17, 33
Mathai S 35
Matsumoto S 1
Matti E 11, 47, 60, 61, 64
Maune S 58, 68
Mazzocca A 50
McDonald J 8, 19, 20, 36, 43
McKeever TM 21, 32
McLauchlin A 46
Meek JH 27
Megía R 68
Mei-Zahav M 45, 67
Menéndez C 68
Menozzi F 5, 24
Merlo CA 35, 64, 67
Mestice A 50
Metzger S 67
Mezzano R 63
Mitchell S 35, 64, 67
Mollet IG 9
Monaco RG 54, 57
Monod B 12
Montifar M 29
Morales C 68
Mori H 1
Morisaki H 8, 10
Morisaki T 8
Morrell NW 8
Morrison L 18, 48
Moses MA 22
Mukherjee B 31
Mummery C 2, 65
Murphy K 31

Nachtigal P 39
Napoli N 54
Nelson J 18, 48
Nemeckova I 39
Nepali P 39
Nicod-Tran A 4, 6, 31, 54, 55
Nishida T 18
Nissen H 17

non commercial use only

O'Fallon B 8, 19, 20
Oh SP 1, 12, 25
Ojeda-Fernandez ML 9, 13, 14, 19, 49, 50, 53, 61
Olivieri C 5, 11, 24, 36, 47, 60, 61, 64
Orlova V 2, 65
Ornati F 5, 11, 24, 36, 47, 60, 61, 64
Ortega I 23
Osuga K 8
Oujo B 16, 66
Ousager LB 45
Ozanne A 4, 6, 31, 41, 54, 55, 60

Paez C 10
Pagella F 5, 11, 36, 47, 60, 61, 64
Paintaud G 7, 22, 52
Palaniyar N 13
Pantalone R 63
Parra JA 68
Paruchuri V 39
Patatas K 57, 59
Pawlikowska L 48
Pendas AM 16
Peng R 64
Peralta O 57
Pérez-Barriocanal F 66
Pericacho M 66
Peter M 13, 24
Pfeiferová J 39
Phan D 15
Piccarreta P 42
Pisano S 63
Plant P 8, 19
Plauchu H 7, 17
Ploos van Amstel JK 49, 51
Pollak JS 4
Pongiglione G 5, 11, 24, 36
Portales P 13
Post MC 27, 30, 31, 32, 55, 58, 59
Prigoda-Lee N 49

Qiao X 39
Quaranta D 43
Quere I 47

Rabellino JM 57
Ramirez CV 46
Ratjen F 40
Recio-Poveda L 9, 13, 19, 26, 49
Redgrave R 15
Reh DD 35, 64
Rensing BJWM 27
Retory Y 6, 60
Ricard N 38
Rimmer J 35, 65
Rioufol C 22
Riviere S 7, 10, 13, 23, 47, 48, 52
Robinson G 35, 57, 59, 64, 67
Rodríguez Iglesias J 68
Rodríguez-Barbero A 66
Rohrmeier C 53
Roman BL 8, 38
Rossi E 37
Rotenberg C 60

Rottiers P 38
Roume J 4, 6, 31, 41, 54, 55, 60
Runo JR 8
Rushlow D 49
Ruud GA 62

Sabbà C 42, 43, 50
Saenz A 3
Salaria M 46
Samson G 22
Sangerardi M 42, 43
Sano M 45
Santana A 49
Santhirapala V 31, 58
Sanz-Rodriguez F 37
Satake M 45
Sato K 45
Saurin JC 7, 9, 23, 48
Scagliusi L 50
Scardapane A 42
Schneider GK 4, 17, 33
Schonewille WJ 31
Schwiertz V 22
Scoazec JY 20
Sellier J 4, 6, 31, 41, 54, 55
Señaris B 68
Serra M 3, 46, 49, 54, 57, 59, 61, 62
Shianna K 49
Shioya T 45
Shovlin CL 9, 27, 28, 29, 31, 34, 42, 58
Silva BM 34, 42
Simon A-C 23
Snijder R 2, 27, 30, 31, 32, 41, 51, 55, 56, 58, 59
Sotov V 13
Spinozzi G 61, 64
Srun S 2
Stefani C 3
Stevenson DA 8, 19, 43
Stocks J 19
Struman I 19
Subileau M 38
Suppressa P 42, 43, 50
Swaans MJ 27

Tabruyn SP 19
Tahon F 17
Tamas G 8
Tanoue S 1
Taylor J 46
ten Dijke P 2, 65
terBrugge K 18
Ternant D 7, 52
Terry P 67
Terry PB 35, 64
Thalgott J 2, 52
Tighe HC 31, 58
Tillet E 21
Tiscornia A 63
Tørring PM 17, 45
Tual-Chalot RRS 15
Tual-Chalot S 1

non commercial use only

Ulla M 57
Üner J 58
Upton PD 8, 38
Urquiola FA 62

Valbuena-Diez AC 16
Valerio R 43
Valette P-J 7
Van den Heuvel DAF 56
van den Hil L 2
Van Erkel AJM 51
Van Gent MWF 30, 31, 32
Van Kien AK 47
van Leersum M 56
van Strije MJL 58
van Strijen MJL 56
Varejckova M 39
Vázquez C 49
Velasco S 66
Velthuis S 27, 30, 31, 32, 55, 58, 59
Venance L 2, 52
Vercherat C 20
Vidaillet HJ 25
Vincent T 13
Vlachou PA 5
Vorselaars VMM 27, 32, 55, 58, 59
Vos JA 56, 58

Wainstein EJ 59
Ward PD 36, 43
Weise S 58
Westermann CJJ 30, 31, 32, 41, 49, 51, 55
Westermann K 2, 65
Whelan K 27, 28
White Jr RI 4, 18
Whitehead K 43
Whitehead KJ 36
Whitehouse AB 23
Wilson A 20
Wilson K 36, 43
Winship I 46
Wooderchak-Donahue W 8, 19, 20

Yamada O 8, 10
Yaniv E 67
Yeyati EL 54
Yin LX 35
Yin M 24
Young LH 4
Young S 8, 38
Young W 44
Young WL 29, 33

Zaccari D 64
Zambelli A 5, 24, 36
Zarauza J 68
Zarrabeitia R 9, 19, 26, 49, 53, 61, 68
Zemankova L 39
Zessler A 44
Zhai Z 15

non commercial use only

non commercial use only

non commercial use only