RO Bibliography

2nd trimester 2020

TOPICS

1. Prevalence and Diagnostic Value of Nail Fold Capillary Microscopy in Hereditary Hemorrhagic Telangiectasia: A Retrospective Study

Vasc Med. 2020 Apr 17;1358863X20910479.

Authors

Steven Kroon [1], Veronique Mm Vorselaars [2], Anna E Hosman [1], Martijn C Post [1 2], Repke J Snijder [1], Johannes J Mager [1]

Affiliations

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

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- DOI: 10.1177/1358863X20910479

Abstract

Abnormal vasculature is a key feature of hereditary hemorrhagic telangiectasia (HHT) and can also present in the nail fold capillary beds. However, the exact prevalence and the clinical diagnostic value in HHT are still largely unknown. The nail fold can be easily and noninvasively inspected with a capillary microscope. We therefore retrospectively assessed the prevalence and diagnostic value of abnormal nail fold capillaries in all patients who were screened between January 2000 and July 2017 for the presence of HHT and underwent capillary microscopy in St Antonius Hospital, The Netherlands. Capillary microscopy results and clinical characteristics were extracted from medical files and the prevalence of abnormal nail fold capillaries was calculated and the diagnostic value of the Curaçao criteria with and without capillary microscopy results was assessed. Of the 1761 individuals screened, 923 (52%) were diagnosed with a clinical and/or genetic HHT diagnosis. In these patients, capillary microscopy was normal in 23% (n = 218), enlarged loops were seen in 11% (n = 99), and giant loops in 66% (n = 606). The sensitivity and specificity of the Curaçao criteria for the diagnosis of HHT without capillary microscopy results were 96% and 90%, respectively. The addition of the presence of giant loops to the Curaçao criteria led to a small increase in sensitivity to 97% without affecting the specificity. In conclusion, the prevalence of nail fold abnormalities in patients with HHT is high. Capillary microscopy can be a useful, easy, and noninvasive diagnostic tool in HHT.

2. Trauma Can Induce Telangiectases in Hereditary Hemorrhagic Telangiectasia

J Clin Med. 2020 May 17;9(5):1507.

Authors

Urban Geisthoff [1] [2], Ha-Long Nguyen [3], Rolf Lefering [4], Steffen Maune [5], Kruthika Thangavelu [1], Freya Droege [6]

Affiliations

- [1] Department of Otorhinolaryngology, Head and Neck Surgery, University Hospital Marburg, Philipps-Universität Marburg, Baldingerstrasse, 35043 Marburg, Germany.
- [2] Morbus Osler-Selbsthilfe e.V. (German HHT Self-Help Group), 89264 Weissenhorn, Germany.
- [3] Laboratory of Human Molecular Genetics, de Duve Institute, Université catholique de Louvain, 1200 Brussels, Belgium.
- [4] Institute for Research in Surgical Medicine (IFOM), University of Witten/Herdecke, Campus Merheim, 51109 Cologne, Germany.
- [5] Department of Otorhinolaryngology, Hospitals of the City of Cologne, University of Witten/Herdecke, 51067 Cologne, Germany.
- [6] Department of Otorhinolaryngology, Head and Neck Surgery, Essen University Hospital, University Duisburg-Essen, Hufelandstrasse 55, 45122 Essen, Germany.

- PMID: 32429545
- PMCID: PMC7290907
- DOI: 10.3390/jcm9051507

Abstract

Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant disease of the fibrovascular tissue resulting in visceral vascular malformations and (muco-) cutaneous telangiectases with recurrent bleedings. The mechanism behind the disease is not fully understood; however, observations from HHT mouse models suggest that mechanical trauma may induce the formation of abnormal vessels. To assess the influence of environmental trauma (mechanical or light induced) on the number of telangiectases in patients with HHT, the number of telangiectases on the hands, face, and lips were counted on 103 HHT patients possessing at least three out of four Curaçao criteria. They were then surveyed for information concerning their dominant hand, exposure to sunlight, and types of regular manual work. Patients developed more telangiectases on their dominant hand and lower lip (Wilcoxon rank sum test: $p < 0.001$). Mechanical stress induced by manual work led to an increased number of telangiectases on patients' hands (Mann-Whitney U test: $p < 0.001$). There was also a positive correlation between sun exposure and the number of telangiectases on the lips (Mann-Whitney U test: 0.027). This study shows that mechanical and UV-induced trauma strongly influence the formation of

telangiectases in HHT patients. This result has potential implications in preventive measures and on therapeutic approaches for HHT.

Therapeutic strategy

1. Review of Pharmacological Strategies With Repurposed Drugs for Hereditary Hemorrhagic Telangiectasia Related Bleeding

J Clin Med. 2020 Jun 6;9(6):E1766.

Authors

Virginia Albiñana [1 2], Angel M Cuesta [1 2], Isabel de Rojas-P [1], Eunate Gallardo-Vara [3], Lucía Recio-Poveda [1 2], Carmelo Bernabéu [1 2], Luisa María Botella [1 2]

Affiliations

- [1] Centro de Investigaciones Biológicas Margarita Salas, Consejo Superior de Investigaciones Científicas (CSIC), 9 Ramiro de Maeztu Street, 28040 Madrid, Spain.
- [2] Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), Institute of Health Carlos III, 28040 Madrid, Spain.
- [3] Yale Cardiovascular Research Center, Section of Cardiovascular Medicine, Department of Internal Medicine, Yale University School of Medicine, 300 George Street, New Haven, CT 06511, USA.

- PMID: 32517280
- DOI: 10.3390/jcm9061766

Abstract

The diagnosis of hereditary hemorrhagic telangiectasia (HHT) is based on the Curaçao criteria: epistaxis, telangiectases, arteriovenous malformations in internal organs, and family history. Genetically speaking, more than 90% of HHT patients show mutations in *ENG* or *ACVRL1/ALK1* genes, both belonging to the TGF-β/BMP9 signaling pathway. Despite clear knowledge of the symptoms and genes of the disease, we still lack a definite cure for HHT, having just palliative measures and pharmacological trials. Among the former, two strategies are: intervention at "ground zero" to minimize by iron and blood transfusions in order to counteract anemia. Among the later, along the last 15 years, three different strategies have been tested: (1) To favor coagulation with antifibrinolytic agents (tranexamic acid); (2) to increase transcription of *ENG* and *ALK1* with specific estrogen-receptor modulators (bazedoxifene or raloxifene), antioxidants (N-acetylcysteine, resveratrol), or immunosuppressants (tacrolimus); and (3) to impair the abnormal angiogenic process with antibodies (bevacizumab) or blocking drugs like

etamsylate, and propranolol. This manuscript reviews the main strategies and sums up the clinical trials developed with drugs alleviating HHT.

Publication types

- Review

EPISTAXIS

2. Efficacy and Safety of a 0.1% Tacrolimus Nasal Ointment as a Treatment for Epistaxis in Hereditary Hemorrhagic Telangiectasia: A Double-Blind, Randomized, Placebo-Controlled, Multicenter Trial

J Clin Med. 2020 Apr 26;9(5):1262.

Authors

Sophie Dupuis-Girod [1] [2], Anne-Emmanuelle Fargeton [1], Vincent Grobost [3], Sophie Rivière [4], Marjolaine Beaudoin [1], Evelyne Decullier [5] [6], Lorraine Bernard [5], Valentine Bréant [7], Bettina Colombet [7], Pierre Philouze [8], Sabine Bailly [2], Frédéric Faure [9], Ruben Hermann [9]

Affiliations

- [1] Hospices Civils de Lyon, Hôpital Femme-Mère-Enfants, Service de Génétique et Centre de Référence de la Maladie de Rendu-Osler, F-69677 Bron, France.
- [2] Inserm, CEA, Laboratory Biology of Cancer and Infection, University, Grenoble Alpes, F-38000 Grenoble, France.
- [3] Service de Médecine Interne, CHU Estaing, 63100 Clermont-Ferrand, France.
- [4] Service de Médecine Interne CHU de Montpellier, Hôpital St Eloi, and Centre d'Investigation Clinique, Inserm, CIC 1411, F-34295 Montpellier CEDEX 7, France.
- [5] Hospices Civils de Lyon, Pôle Santé Publique, F-69003 Lyon, France.
- [6] Université Lyon 1, 69008 Lyon, France.
- [7] Hospices Civils de Lyon, Pharmacie, Hôpital Louis Pradel, F-69677 Bron, France.
- [8] Hospices Civils de Lyon, Hôpital de la Croix Rousse, Service ORL, F-69317 Lyon, France.
- [9] Hospices Civils de Lyon, Hôpital E. Herriot, Service ORL, F-69437 Lyon, France.

- PMID: 32357559
- PMCID: PMC7287684
- DOI: 10.3390/jcm9051262

Abstract

Hereditary hemorrhagic telangiectasia is a rare but ubiquitous genetic disease. Epistaxis is the most frequent and life-threatening manifestation and tacrolimus, an immunosuppressive agent, appears to be an interesting new treatment option because of its anti-angiogenic properties. Our objective was to evaluate, six weeks after the end of the treatment, the efficacy on the duration of nosebleeds of tacrolimus nasal ointment, administered for six weeks to patients with hereditary hemorrhagic telangiectasia complicated by nosebleeds, and we performed a prospective, multicenter, randomized, placebo-controlled, double-blinded, ratio 1:1 phase II study. Patients were recruited from three French Hereditary Hemorrhagic Telangiectasia (HHT) centers between May 2017 and August 2018, with a six-week follow-up, and we included people aged over 18 years, diagnosed with hereditary hemorrhagic telangiectasia and epistaxis (total duration > 30 min/6 weeks prior to inclusion). Tacrolimus ointment 0.1% was self-administered by the patients twice daily. About 0.1 g of product was to be administered in each nostril with a cotton swab. A total of 50 patients was randomized and treated. Mean epistaxis duration before and after treatment in the tacrolimus group were 324.64 and 249.14 min, respectively, and in the placebo group 224.69 and 188.14 min, respectively. Epistaxis duration improved in both groups, with no significant difference in our main objective comparing epistaxis before and after treatment (p = 0.77); however, there was a significant difference in evolution when comparing epistaxis before and during treatment (p = 0.04). Toxicity was low and no severe adverse events were reported. In conclusion, tacrolimus nasal ointment, administered for six weeks, did not improve epistaxis in HHT patients after the end of the treatment. However, the good tolerance, associated with a significant improvement in epistaxis duration during treatment, encouraged us to perform a phase 3 trial on a larger patient population with a main outcome of epistaxis duration during treatment and a longer treatment time.

3. Safety and Efficacy of Blue Light Laser Treatment in Hereditary Hemorrhagic Telangiectasia

Lasers Surg Med. 2020 Jun 23.

Authors

Mattis Bertlich [1], Fatemeh Kashani [1], Bernhard G Weiss [1], Robert Wiebringhaus [1], Friedrich Ihler [1], Saskia Freytag [2], Olivier Gires [1 3], Thomas Kühnel [4], Frank Haubner [1]

Affiliations

- [1] Department of Otorhinolaryngology, Head and Neck Surgery, University Hospital Munich, Marchioninistr. 15, Munich, 81377, Germany.
- [2] Epigenetics and Genomics, The Harry Perkins Institute of Medical Research, 6

Verdun St, Nedlands, Western Australia, 6009, Australia.
- [3] Clinical Cooperation Group "Personalized Radiotherapy in Head and Neck Cancer", Helmholtz Zentrum, Marchioninistr. 25, Munich, 81377, Germany.
- [4] Department of Otorhinolaryngology, Head and Neck Surgery, University Hospital Regensburg, Franz-Josef-Strauß-Allee 11, Regensburg, 93047, Germany.

- PMID: 32573010
- DOI: 10.1002/lsm.23289

Abstract

Background and objectives: Hereditary hemorrhagic telangiectasia (HHT) is a hereditary condition that is associated with arteriovenous malformations. A common site for these malformations is the nasal mucosa, which is associated with severe epistaxis and debilitation for affected patients. We evaluated the efficacy and safety of blue light laser technology in treating these endonasal manifestations in a retrospective chart analysis. Additionally, we compared blue light laser technology to bipolar coagulation in an animal model.

Study design/materials and methods: We performed a retrospective chart analysis of all patients that were diagnosed with HHT and received endonasal blue light laser treatment between 10/2017 and 04/2019. In addition, we performed bipolar or blue light laser coagulation of all macroscopically visible vessels on thyroid gland lobes (n = 4) from Dunkin-Hartley Guinea Pigs. Hematoxylin-eosin (HE) staining was then used to visualize depth and area of coagulation surrounding these vessels.

Results: One hundred and fifty-one treatments in 23 patients were analyzed. Under regular blue light laser treatment, quality of life (QOL), indicated on a visual analog scale from 1 to 10, gradually increased significantly from 5.6 ± 0.5 (before the first treatment) to 7.5 ± 0.9 (after the second treatment). Following this, QOL remained steady throughout additional treatments. Adverse effects were not recorded. HE staining showed that coagulation depth (162 ± 56 vs. 586 ± 192 µm) and area (74 ± 35 vs. 1015 ± 449 μm^2) were significantly lower after laser treatment.

Conclusion: Blue light laser therapy is safe and efficient in treating HHT. Damage to the surrounding tissue is significantly lower compared with bipolar coagulation.

4. In-Office KTP Laser for Treating Hereditary Hemorrhagic Telangiectasia-Associated Epistaxis

Laryngoscope. 2020 Jun 18.

Authors

Vincent Wu [1], Erika Kell [1], Marie E Faughnan [2 3], John M Lee [1 3]

Affiliations

- [1] Division of Rhinology, Department of Otolaryngology-Head and Neck Surgery, St. Michael's Hospital, Unity Health Toronto, University of Toronto, Toronto, Ontario, Canada.
- [2] Toronto HHT Centre, Division of Respirology, Department of Medicine, St. Michael's Hospital, Unity Health Toronto, University of Toronto, Toronto, Ontario, Canada.
- [3] Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, Ontario, Canada.

- PMID: 32557619
- DOI: 10.1002/lary.28824

Abstract

Objective: To evaluated the efficacy and safety of in-office potassium titanyl phosphate (KTP) laser treatment for the management of epistaxis in hereditary hemorrhagic telangiectasia (HHT) patients.

Methods: A retrospective case series of all HHT patients over age of 18 who underwent in-office KTP laser treatment from July 1, 2017 to December 31, 2019 was performed. The primary outcome measure was the epistaxis severity score (ESS) pre- and post-procedure. Secondary outcome measures included patient reported pain (on a 10-point Likert-type scale), and procedural adverse events and complications.

Results: A total of 16 patients underwent KTP in-office laser treatment during the review period. There was both a clinically and statistically significant decrease in the ESS after in-office laser treatment, baseline ESS -7.24, SD 1.71, follow up ESS -4.92, SD 1.83 (mean difference 2.94, 95% confidence interval, 1.83-4.04, $P < .0001$). There were no reported adverse events or complications associated with the procedure. The mean pain score reported was 0.19, SD 0.75. The average blood loss was 10.8 mL, SD 37.3. The majority of patients (62.5%, 10/16) had no blood loss during the procedure.

Conclusion: Clinically and statistically significant decreases were noted in the ESS of HHT patients after in-office KTP laser photocoagulation. The procedure was well tolerated by patients, without any adverse events or complications.

Level of evidence: 4 Laryngoscope, 2020.

5. FID Score: An Effective Tool in Hereditary Haemorrhagic Telangiectasia - Related Epistaxis

Rhinology. 2020 Jun 25.

Authors

F Pagella [1 2], E Maiorano [1 2], E Matti [1], C Tinelli [3], A De Silvestri [3], S Ugolini [1 2], R Lizzio [1], C Oliveri [4], A Pusateri [5], G Spinozzi [1]

Affiliations

- [1] Department of Otorhinolaryngology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy.
- [2] Department of Otorhinolaryngology, Università degli Studi di Pavia, Pavia, Italy.
- [3] Clinical Epidemiology and Biometry Unit, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy.
- [4] Molecular Medicine Department, General Biology and Medical Genetics Unit, University of Pavia, Italy.
- [5] Otorhinolaryngology Unit, ASST Papa Giovanni XXIII, Bergamo, Italy.

- PMID: 32584331
- DOI: 10.4193/Rhin20.078

Abstract

Background: Hereditary haemorrhagic telangiectasia (HHT) is a rare disease characterized by a multisystemic vascular dysplasia and epistaxis, that is the most common cause of disability and social impairment. Patient management strictly depends on the severity of this symptom; therefore, it is of paramount importance for the clinicians to effectively grade epistaxis severity. The aim of this report was to validate the Frequency, Intensity and Duration score (FID) for grading epistaxis severity in patients with HHT; we studied repeatability and external validity comparing FID score with Epistaxis Severity Score (ESS).

Methods: This is a descriptive, observational study that included 264 adult HHT patients with epistaxis. Diagnosis of HHT was established with Curaçao criteria or positivity at genetic testing. Nosebleed severity was evaluated according to the FID score and the ESS. The first 30 patients were included in the validation of the FID score, which was graded on days 0, 1, 3 and 7. In the remaining 234 patients, a comparison between the ESS and FID score was performed.

Results: The statistical analysis performed in order to validate the FID score showed very good agreement between scores calculated on different days; analysis comparing the FID score with the ESS revealed a high correlation between the two grading systems.

Conclusions: The FID score is a quick, easy and precise tool for evaluating HHT-related epistaxis and could be a possible alternative to the ESS. The FID score meets the need for an intuitive and smart grading system that is easy to manage in clinicians' hands.

GASTROINTESTINAL BLEEDING

6. An International Survey to Evaluate Systemic Bevacizumab for Chronic Bleeding in Hereditary Haemorrhagic Telangiectasia

Haemophilia. 2020 May 20.

Authors

Hanny Al-Samkari [1], Hasan A Albitar [2], Scott E Olitsky [3], Marianne S Clancy [3], Vivek N Iyer [4]

Affiliations

- [1] Division of Hematology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA.
- [2] Department of Internal Medicine, Mayo Clinic, Rochester, MN, USA.
- [3] Cure HHT, Monkton, MD, USA.
- [4] Division of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, MN, USA.

- PMID: 32432841
- DOI: 10.1111/hae.14034

Abstract

Introduction: Systemic bevacizumab is a novel targeted therapy for severe epistaxis and chronic gastrointestinal bleeding in hereditary haemorrhagic telangiectasia (HHT), but published data are very limited.

Aim: We conducted a survey-based study to characterize current treatment practices and physician-reported safety and effectiveness of systemic bevacizumab for bleeding in (HHT).

Methods: A 27-item survey was sent to physician centre directors of 31 International HHT Centers of Excellence.

Results: Response rate was 84%. Approximately half of centres had treated >10 HHT patients with systemic bevacizumab for chronic bleeding for a total of 291 patients treated. All centres utilize a 5 mg/kg dose for induction treatment and most administer six doses (range, 4-8) every 2 weeks. However, maintenance

regimens varied considerably between centres. Bevacizumab was highly effective, with 86% reporting significant (>50%) improvement in GI bleeding and/or epistaxis and haemoglobin rise in most patients treated with bevacizumab; 52% reported haemoglobin normalization in most patients. All centres reported adverse event rates <30% and two-thirds of centres reported adverse event rates <10%. Discontinuation for adverse events or inefficacy was rare. Bleeding severity thresholds for initiation of bevacizumab were highly variable, and it is typically administered by haematologists (76% of centres). Two-thirds of centres reported obtaining insurance approval for bevacizumab for most or all patients but 48% reported difficulty in obtaining coverage.

Conclusion: Systemic bevacizumab is widely used to treat bleeding in HHT with excellent physician-reported effectiveness and safety. There is considerable variation in maintenance treatment practices and thresholds for initiation of bevacizumab among HHT centres.

7. Management Of Gastrointestinal Bleeding In Rendu-Osler Disease

Rev Recent Clin Trials. 2020 Jun 3.

Authors

Annalisa Tortora [1], Clelia Marmo [1], Antonio Gasbarrini [1], Guido Costamagna [1], Maria Elena Riccioni [1]

Affiliation

- [1] Department of Gastroenterological, Fondazione Policlinico Gemelli IRCCS, Endocrino-Metabolic, and Nefrourological Science, Rome. Italy.

- PMID: 32493201
- DOI: 10.2174/1574887115666200603160033

Abstract

Background: Hereditary hemorrhagic telangiectasia (HHT, or Rendu-Osler-Weber disease) is a rare inherited syndrome, characterized by artero-venous malformations (AVMs or telangiectasia) with autosomal dominant transmission. AVMs can occur in any organ of the body, most commonly occur in nose, pulmonary, hepatic and cerebral circulations. In patients with HHT we report teleangectasia of mucosa of gastrointestinal tract.

Methods: Research and online content related to HHT online activity is reviewed, and DOC writing excerpts are used to illustrate key themes.

Results: Patients with HHT have a high rate of complications related to bleeding;

of them gastrointestinal bleeding accounts for 10.8%. Several therapy, both medical and endoscopic, was utilized to reduce the need of transfusions and hospitalization.

Conclusion: A combination of medical and endoscopic therapy is probably the best option.

Epidemiology

1. SMAD4 Mutation and the Combined Juvenile Polyposis and Hereditary Hemorrhage Telangiectasia Syndrome: A Single Center Experience

Int J Colorectal Dis. 2020 Jun 15.

Authors

Nicholas M McDonald [1], Guilherme Piovezani Ramos [2], Seth Sweetser [3]

Affiliations

- [1] Department of Internal Medicine, Mayo Clinic College of Medicine, Rochester, MN, USA.
- [2] Division of Gastroenterology and Hepatology, Mayo Clinic College of Medicine, Rochester, MN, USA. Ramos.Guilherme@mayo.edu.
- [3] Division of Gastroenterology and Hepatology, Mayo Clinic College of Medicine, Rochester, MN, USA.

- PMID: 32556653
- DOI: 10.1007/s00384-020-03670-3

Abstract

Purpose: Mutations of the SMAD4 gene can result in a distinct syndrome with combined clinical features of both juvenile polyposis syndrome (JPS) and hereditary hemorrhagic telangiectasia (HHT). Even though it is known that patients with the overlap syndrome are at increased risk for colorectal malignancies and bleeding, the outcomes of this patient population have not been extensively studied.

Methods: Retrospective study aiming to describe the phenotype and clinical outcomes of patients with genetically confirmed JP-HHT combined syndrome in a single large tertiary center in North America.

Results: A total of 22 patients were identified, the majority females (59%) with a median age diagnosis at 24 years. Polyps were more commonly seen in the lower gastrointestinal (GI) tract, and tubular adenomas were seen in 50%. Epistaxis and pulmonary arteriovenous malformations (AVM) were the most common manifestations of HHT, with a median Curacao score of 3 [1-4]. Hospitalization for gastrointestinal bleeding and cerebrovascular events occurred at a rate of 28% and 4%, respectively. Two patients had GI malignancies, one rectal and one small bowel adenocarcinoma. Overall mortality was 14%.

Conclusions: Patients with the combined JP-HHT syndrome remain at risk for life-threatening vascular complications and gastrointestinal malignancies; close follow-up is necessary to minimize morbidity and mortality in this patient population.

2. Disease Expression in Juvenile Polyposis Syndrome: A Retrospective Survey on a Cohort of 221 European Patients and Comparison With a Literature-Derived Cohort of 473 SMAD4/BMPR1A Pathogenic Variant Carriers

Genet Med. 2020 May 13.

Authors

Robert Blatter [1], Benjamin Tschupp [1], Stefan Aretz [2] [3], Inge Bernstein [4], Chrystelle Colas [5] [6], D Gareth Evans [7], Maurizio Genuardi [8] [9], Frederik J Hes [10], Robert Hüneburg [3] [11], Heikki Järvinen [12], Fiona Lalloo [7], Gabriela Moeslein [13], Laura Renkonen-Sinisalo [12], Nicoletta Resta [14], Isabel Spier [2] [3], Dora Varvara [14], Hans Vasen [15], Andrew R Latchford [16], Karl Heinimann [17]

Affiliations

- [1] Institute for Medical Genetics and Pathology, University Hospital Basel, and Research Group Human Genomics, Department of Research, University of Basel, Basel, Switzerland.
- [2] Institute of Human Genetics, University Hospital Bonn, Bonn, Germany.
- [3] National Center for Hereditary Tumour Syndromes, University Hospital, Bonn, Germany.
- [4] Department of Surgical Gastroenterology, Aalborg University Hospital, Aalborg, and Danish HNPCC Registry, Department of Surgical Gastroenterology, Hvidovre University Hospital, Hvidovre, Denmark.
- [5] Department of Oncogenetics and Angiogenetics, Pitie-Salpetriere Hospital, Sorbonne Université, Paris, France.
- [6] Department of Genetics, Institut Curie, Université de Recherche Paris Sciences et Lettres, Paris, France.
- [7] Department of Genomic Medicine, Manchester Universities NHS Foundation Trust and Division of Evolution and Genomic Sciences, University of Manchester, Manchester, United Kingdom.
- [8] Fondazione Policlinico Universitario A. Gemelli IRCCS, UOC Genetica Medica, Rome, Italy.

- [9] Università Cattolica del Sacro Cuore, Istituto di Medicina Genomica, Rome, Italy.
- [10] Department of Clinical Genetics, Leiden University Medical Center, Leiden, The Netherlands.
- [11] Department of Internal Medicine I, University Hospital Bonn, Bonn, Germany.
- [12] Department of Surgery, Helsinki University Central Hospital, Helsinki University, Helsinki, Finland.
- [13] Center for Hereditary Tumors, HELIOS Klinikum Wuppertal, University Witten-Herdecke, Wuppertal, Germany.
- [14] Division of Medical Genetics, Department of Biomedical Sciences and Human Oncology (DIMO), University of Bari "Aldo Moro", Bari, Italy.
- [15] Department of Gastroenterology and Hepatology, Leiden University Medical Centre, Leiden, The Netherlands.
- [16] Polyposis Registry, St. Mark's Hospital, Harrow, United Kingdom. andrew.latchford@nhs.net.
- [17] Institute for Medical Genetics and Pathology, University Hospital Basel, and Research Group Human Genomics, Department of Research, University of Basel, Basel, Switzerland. karl.heinimann@usb.ch.

- PMID: 32398773
- DOI: 10.1038/s41436-020-0826-1

Abstract

Purpose: Juvenile polyposis syndrome (JPS) is a rare, autosomal-dominantly inherited cancer predisposition caused in approximately 50% of cases by pathogenic germline variants in SMAD4 and BMPR1A. We aimed to gather detailed clinical and molecular genetic information on JPS disease expression to provide a basis for management guidelines and establish open access variant databases.

Methods: We performed a retrospective, questionnaire-based European multicenter survey on and established a cohort of SMAD4/BMPR1A pathogenic variant carriers from the medical literature.

Results: We analyzed questionnaire-based data on 221 JPS patients (126 kindreds) from ten European centers and retrieved literature-based information on 473 patients. Compared with BMPR1A carriers, SMAD4 carriers displayed anemia twice as often (58% vs. 26%), and exclusively showed overlap symptoms with hemorrhagic telangiectasia (32%) and an increased prevalence (39% vs. 13%) of gastric juvenile polyps. Cancer, reported in 15% of JPS patients (median age 41 years), mainly occurred in the colorectum (overall: 62%, SMAD4: 58%, BMPR1A: 88%) and the stomach (overall: 21%; SMAD4: 27%, BMPR1A: 0%).

Conclusion: This comprehensive retrospective study on genotype-phenotype correlations in 694 JPS patients corroborates previous observations on JPS in general and SMAD4 carriers in particular, facilitates recommendations for clinical management, and provides the basis for open access variant SMAD4 and BMPR1A databases.

3. Curaçao Diagnostic Criteria for Hereditary Hemorrhagic Telangiectasia Is Highly Predictive of a Pathogenic Variant in ENG or ACVRL1 (HHT1 and HHT2)

Genet Med. 2020 Apr 17.

Authors

Jamie McDonald [1] [2], Pinar Bayrak-Toydemir [3] [4], Desiree DeMille [4], Whitney Wooderchak-Donahue [3] [4], Kevin Whitehead [5] [6] [7]

Affiliations

- [1] Department of Radiology, University of Utah, Salt Lake City, UT, USA. Jamie.mcdonald@hsc.utah.edu.
- [2] Department of Pathology, University of Utah, Salt Lake City, UT, USA. Jamie.mcdonald@hsc.utah.edu.
- [3] Department of Pathology, University of Utah, Salt Lake City, UT, USA.
- [4] ARUP Institute for Clinical and Experimental Pathology, Salt Lake City, UT, USA.
- [5] Division of Cardiovascular Medicine, Department of Medicine, University of Utah, Salt Lake City, UT, USA.
- [6] Program in Molecular Medicine, University of Utah, Salt Lake City, UT, USA.
- [7] George E. Wahlen Veterans Affairs Medical Center, Salt Lake City, UT, USA.

- PMID: 32300199
- DOI: 10.1038/s41436-020-0775-8

Abstract

Purpose: Determine the variant detection rate for ENG, ACVRL1, and SMAD4 in individuals who meet consensus (Curaçao) criteria for the clinical diagnosis of hereditary hemorrhagic telangiectasia.

Methods: Review of HHT center database for individuals with three or more HHT diagnostic criteria, in whom molecular genetic analysis for ENG, ACVRL1, and SMAD4 had been performed.

Results: A variant known or suspected to be causal was detected in ENG in 67/152 (44.1%; 95% confidence interval [CI], 36.0-52.4%), ACVRL1 in 79/152 (52.0%; 95% CI, 43.7-60.1%), and SMAD4 in 2/152 (1.3%; 95% CI, 0.2-4.7%) family probands with definite HHT. Only 4/152 (2.6%; 95% CI, 0.7-6.6%) family probands did not have a variant in one of these genes.

Conclusion: Previous reports of the variant detection rate for ENG and ACVRL1 in HHT patients have come from laboratories, which receive samples from clinicians with a wide range of expertise in recognizing clinical manifestations of

HHT. These studies suggest a significantly lower detection rate (~75-85%) than we have found in patients who meet strictly applied consensus criteria (96.1%). Analysis of SMAD4 adds an additional detection rate of 1.3%. HHT as defined by the Curaçao criteria is highly predictive of a causative variant in either ENG or ACVRL1.

4. Current HHT Genetic Overview in Spain and Its Phenotypic Correlation: Data From RiHHTa Registry

Orphanet J Rare Dis. 2020 Jun 5;15(1):138.

Authors

Rosario Sánchez-Martínez [1 2], Adriana Iriarte [2 3], José María Mora-Luján [2 3], José Luis Patier [2 4], Daniel López-Wolf [2 5], Ana Ojeda [2 6], Miguel Angel Torralba [2 7], María Coloma Juyol [2 8], Ricardo Gil [2 9], Sol Añón [2 10], Joel Salazar-Mendiguchía [11 12 13], Antoni Riera-Mestre [14 15 16], RiHHTa Investigators of the Rare Diseases Working Group from the Spanish Society of Internal Medicine

Collaborators

- **RiHHTa Investigators of the Rare Diseases Working Group from the Spanish Society of Internal Medicine**:

  C Alonso-Cotoner, S Añón, M Beneyto, M M Bermejo-Olano, P Cerdà, F Cruellas, A De Los Santos, L Díez, A Fernández, J S García-Morillo, R Gil, J F Gómez-Cerezo, V Gómez Del Olmo, A González-García, A Iriarte, P Iglesias, M C Juyol, N López-Osle, M López, D López-Wolf, J M Mora-Luján, M Moreno, A Ojeda, J L Patier, J A Pérez de León, M L Perez, A Riera-Mestre, S Rivera, S Rodríguez, R Sánchez-Martínez, M A Torralba, R Zarrabeitia

Affiliations

- [1] Internal Medicine Department, Hospital General Universitario de Alicante - ISABIAL, Alicante, Spain.
- [2] Rare Diseases Working Group, Spanish Society of Internal Medicine, Madrid, Spain.
- [3] Hereditary Hemorrhagic Telangiectasia Unit, Internal Medicine Department, Hospital Universitari de Bellvitge - IDIBELL, Feixa Llarga s/n. 08907 L'Hospitalet de Llobregat, Barcelona, Spain.
- [4] Department of Internal Medicine, Systemic and Orphan Diseases Unit, University Hospital Ramón y Cajal, University of Alcalá, IRYCIS, Madrid, Spain.
- [5] Internal Medicine Department, Hospital Universitario Fundación Alcorcón, Madrid, Spain.
- [6] Internal Medicine Department, Hospital Insular Universitario de Gran Canaria, Gran Canaria, Spain.
- [7] Internal Medicine Department, Hospital Clínico Universitario Lozano Blesa, Zaragoza, Spain.
- [8] Internal Medicine Department, Hospital Universitario Miguel Servet, Zaragoza, Spain.

- [9] Internal Medicine Department, Hospital La Fe, Valencia, Spain.
- [10] Internal Medicine Department, Hospital Arnau de Vilanova, Valencia, Spain.
- [11] Health in Code, A Coruña, Spain.
- [12] Clinical Genetics Program, Hospital Universitari de Bellvitge - IDIBELL, Barcelona, Spain.
- [13] Genetics Department, Universitat Autònoma de Barcelona, Barcelona, Spain.
- [14] Rare Diseases Working Group, Spanish Society of Internal Medicine, Madrid, Spain. ariera@bellvitgehospital.cat.
- [15] Hereditary Hemorrhagic Telangiectasia Unit, Internal Medicine Department, Hospital Universitari de Bellvitge - IDIBELL, Feixa Llarga s/n. 08907 L'Hospitalet de Llobregat, Barcelona, Spain. ariera@bellvitgehospital.cat.
- [16] Faculty of Medicine and Health Sciences, Universitat de Barcelona, Barcelona, Spain. ariera@bellvitgehospital.cat.

- PMID: 32503579
- PMCID: PMC7275435
- DOI: 10.1186/s13023-020-01422-8

Abstract

Background: Hereditary hemorrhagic telangiectasia (HHT) is a rare vascular disease with autosomal dominant inheritance. Disease-causing variants in endoglin (ENG) and activin A receptor type II-like 1 (ACVRL1) genes are detected in more than 90% of cases submitted to molecular diagnosis.

Methods: We used data from the RiHHTa (Computerized Registry of Hereditary Hemorrhagic Telangiectasia) registry to describe genetic variants and to assess their genotype-phenotype correlation among HHT patients in Spain.

Results: By May 2019, 215 patients were included in the RiHHTa registry with a mean age of 52.5 ± 16.5 years and 136 (63.3%) were women. Definitive HHT diagnosis defined by the Curaçao criteria were met by 172 (80%) patients. Among 113 patients with genetic test, 77 (68.1%) showed a genetic variant in ACVRL1 and 36 (31.8%) in ENG gene. The identified genetic variants in ACVRL1 and ENG genes and their clinical significance are provided. ACVRL1 mutations were more frequently nonsense (50%) while ENG mutations were more frequently, frameshift (39.1%). ENG patients were significantly younger at diagnosis (36.9 vs 45.7 years) and had pulmonary arteriovenous malformations (AVMs) (71.4% vs 24.4%) and cerebral AVMs (17.6% vs 2%) more often than patients with ACVRL1 variants. Patients with ACVRL1 variants had a higher cardiac index (2.62 vs 3.46), higher levels of hepatic functional blood tests, and anemia (28.5% vs 56.7%) more often than ENG patients.

Conclusions: ACVRL1 variants are more frequent than ENG in Spain. ACVRL1 patients developed symptomatic liver disease and anemia more often than ENG patients. Compared to ACVRL1, those with ENG variants are younger at diagnosis and show pulmonary and cerebral AVMs more frequently.

5. The Italian National Rare Diseases Registry: A Model of Comparison and Integration With Hospital Discharge Data

J Public Health (Oxf). 2019 Mar 1;41(1):46-54.

Authors

Yllka Kodra [1], Giada Minelli [2], Adele Rocchetti [1], Valerio Manno [2], Annamaria Carinci [2], Susanna Conti [2], Domenica Taruscio [1], National Rare Diseases Registry Collaborating Group

Affiliations

- [1] National Centre for Rare Diseases, Istituto Superiore di Sanità, Rome, Italy.
- [2] Service of Statistics, Istituto Superiore di Sanità, Rome, Italy.

- PMID: 29294017
- DOI: 10.1093/pubmed/fdx176

Abstract

Background: Italy has been the first country at European level to implement a population-based public health registry dedicated to rare diseases. This study describes the current situation of the Italian National Rare Diseases Registry (NRDR) and compares its data with those from the National Hospital Discharge Database (HDD).

Methods: Three rare diseases were analysed: Huntington disease (HD), Hereditary Haemorragic Telangiectasia (HHT) and Prader-Willi Syndrome (PWS), selected for their different characteristics. The two sources (NRDR and HDD) were linked: incidence rate ratio (IRR), sensitivity and predictive positive value (PPV) were calculated.

Results: Incidence rates from NRDR and from HDD were compared by age groups, and IRR calculated: 1.08 for HD, 1.41 for HHT, 1.21 for PSW. For HD, sensitivity was 0.52 and PPV 0.48; for HHT sensitivity was 0.71 and PPV 0.52; for PWS the sensitivity was 0.71 and PPV 0.58. We found a strong regional variability in the results.

Conclusions: The integrated use of the two sources helps tracking those cases that are not captured by the Registry; further, it is a precious tool to accurately describe clinical histories of rare disease affected individuals, in terms of concomitant pathologies and medical procedures performed during hospitalization.

Publication types

- Comparative Study

6. Antithrombotic Therapy in Hereditary Hemorrhagic Telangiectasia: Real-World Data From the Gemelli Hospital HHT Registry

J Clin Med. 2020 Jun 2;9(6):E1699.

Authors

Eleonora Gaetani [1,2], Fabiana Agostini [1,2], Igor Giarretta [1,2], Angelo Porfidia [1,3], Luigi Di Martino [1,2], Antonio Gasbarrini [1,2], Roberto Pola [1,4], On Behalf Of The Multidisciplinary Gemelli Hospital Group For Hht [1]

Affiliations

- [1] Multidisciplinary Gemelli Hospital Group for HHT, Fondazione Policlinico Universitario A. Gemelli IRCCS Università Cattolica del Sacro Cuore, 00168 Rome, Italy.
- [2] Department of Translational Medicine and Surgery, Fondazione Policlinico Universitario A. Gemelli IRCCS Università Cattolica del Sacro Cuore, 00168 Rome, Italy.
- [3] Division of Internal Medicine, Fondazione Policlinico Universitario A. Gemelli IRCCS Università Cattolica del Sacro Cuore, 00168 Rome, Italy.
- [4] Department of Cardiovascular Sciences, Fondazione Policlinico Universitario A. Gemelli IRCCS Università Cattolica del Sacro Cuore, 00168 Rome, Italy.

- PMID: 32498318
- DOI: 10.3390/jcm9061699

Abstract

Although Hereditary Hemorrhagic Telangiectasia (HHT) is characterized by an overwhelming bleeding propensity, patients with this disease may also present medical conditions that require antithrombotic therapy (AT). However, precise information on indications, dosage, duration, effectiveness, and safety of AT in HHT patients is lacking. We performed a retrospective analysis of the HHT Registry of our University Hospital and found 26 patients who received AT for a total of 30 courses (19 courses of anticoagulant therapy and 11 courses of antiplatelet therapy). Indications to treatments included: atrial fibrillation, venous thrombosis and pulmonary embolism, heart valve replacement, retinal artery occlusion, secondary prevention after either stroke or myocardial infarction, and thromboprophylaxis for surgery. The total time of exposure to antiplatelet therapy was 385 months and to anticoagulant therapy 169 months. AT was generally well tolerated, with no fatal bleedings and no significant changes in hemoglobin levels. However, we found three major bleedings, with an incidence rate of 6.5 per 100 patients per year. When only patients treated with anticoagulants were considered, the incidence rate of major bleedings increased to 21.6 per 100 patients per year. Our study indicates that major bleeding may occur in HHT patients receiving AT, with a substantially increased rate in those treated with anticoagulants. Further studies are needed to fully estimate the tolerability of antithrombotic drugs in HHT.

7. Ocular Lesions in Hereditary Hemorrhagic Telangiectasia: Genetics and Clinical Characteristics

Orphanet J Rare Dis. 2020 Jun 29;15(1):168.

Authors

Inés Gómez-Acebo [1 2 3], Sara Rodríguez Prado [4 5], Ángel De La Mora [4 5], Roberto Zarrabeitia Puente [4 6 7], Beatriz de la Roza Varela [5], Trinidad Dierssen-Sotos [8 4 9], Javier Llorca [8 4 9]

Affiliations

- [1] Facultad de Medicina, Universidad de Cantabria, Avda. Herrera Oria s/n, 39011, Santander, Spain. ines.gomez@unican.es.
- [2] IDIVAL, Santander, Spain. ines.gomez@unican.es.
- [3] CIBER Epidemiología y Salud Pública (CIBERESP), Madrid, Spain. ines.gomez@unican.es.
- [4] IDIVAL, Santander, Spain.
- [5] Department of Ophthalmology, Hospital Sierrallana, Torrelavega, Cantabria, Spain.
- [6] Department of Internal Medicine, Hospital Sierrallana, Torrelavega, Cantabria, Spain.
- [7] Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), Madrid, Spain.
- [8] Facultad de Medicina, Universidad de Cantabria, Avda. Herrera Oria s/n, 39011, Santander, Spain.
- [9] CIBER Epidemiología y Salud Pública (CIBERESP), Madrid, Spain.

- PMID: 32600370
- PMCID: PMC7322834
- DOI: 10.1186/s13023-020-01433-5

Abstract

Background: The aim of our study is to study the association between eye lesions in Hereditary Hemorrhagic Telangiectasia (HHT) and other signs of the disease, as well as to characterize its genetics.

Methods: A cross-sectional study was conducted of a cohort of 206 patients studied in the HHT Unit of Hospital de Sierrallana, a reference centre for Spanish patients with HHT. Odds ratios for several symptoms or characteristics of HHT and ocular lesions were estimated using logistic regression adjusting for age and sex.

Results: The ocular involvement was associated with being a carrier of a mutation for the ENG gene, that is, suffering from a type 1 HHT involvement (OR = 2.09; 95% CI [1.17-3.72]). p = 0.012). In contrast, patients with ocular lesions have less frequently mutated ACVRL1/ALK1 gene (OR = 0.52; 95% CI [0.30-3.88], p = 0.022).

Conclusions: In conclusion, half of the patients with HHT in our study have ocular involvement. These eye lesions are associated with mutations in the ENG gene and ACVRL1/ALK1 gene. Thus, the ENG gene increases the risk of ocular lesions, while being a carrier of the mutated ACVRL1/ALK1 gene decreases said risk.

Molecular Biology

1. Mutational and Phenotypic Characterisation of Hereditary Hemorrhagic Telangiectasia

Blood. 2020 Jun 23;blood.2019004560.

Authors

Claire Shovlin [1], Ilenia Simeoni [2], Kate Downes [2], Zoe Frazer [1], Karyn Megy [2], María Bernabéu-Herrero [3], Abigail Yan Le Shurr [1], Jennifer Brimley [4], Dilipkumar Patel [5], Loren Kell [6], Jonathan C Stephens [2], Isobel Grace Turbin [1], Micheala A Aldred [7], Christopher J Penkett [2], Willem Hendrik Ouwehand [2], Luca Jovine [8], Ernest Turro [2]

Affiliations

- [1] Imperial College London, London, United Kingdom.
- [2] University of Cambridge, Cambridge, United Kingdom.
- [3] Imperial College London, United Kingdom.
- [4] Imperial College Healthcare NHS Trust, London, United Kingdom.
- [5] imperial college, london, United Kingdom.
- [6] University College London, United Kingdom.
- [7] Indiana University School of Medicine, Indianapolis, Indiana, United States.
- [8] Karolinska Institutet, Huddinge, Sweden.

- PMID: 32573726
- DOI: 10.1182/blood.2019004560

Abstract

Hereditary hemorrhagic telangiectasia (HHT) is a vascular dysplasia inherited as an autosomal dominant trait. Care delivery is impeded by requirements for laborious, repeated phenotyping, and gaps in knowledge regarding the relationships between causal DNA variants in ENG, ACVRL1, SMAD4 and GDF2, and clinical manifestations. To address, we analysed DNA samples from 183 previously uncharacterised, unrelated HHT and suspected HHT cases using the ThromboGenomics high-throughput sequencing platform. We identified 168

heterozygous variants, 127 unique. Applying modified ACMG Guidelines, 106 were classified as pathogenic/likely pathogenic, 21 as non-pathogenic (variants of uncertain significance/benign). Unlike the protein products of ACVRL1 and SMAD4, the extracellular ENG amino acids are not strongly conserved. Our inferences of the functional consequences of causal variants in ENG were therefore informed by the crystal structure of endoglin. We then compared the accuracy of predictions of the causal gene blinded to the genetic data using two approaches: subjective clinical predictions and statistical predictions based on eight Human Phenotype Ontology (HPO) terms. Both approaches had some predictive power but they were insufficiently accurate to be used clinically in isolation from genetic testing. The distributions of red cell indices from larger HHT and control populations differed by causal gene but not sufficiently for clinical use in isolation of genetic data. We conclude that parallel sequencing of the four known HHT genes, MDT review of variant calls sequencing results in the context of detailed clinical information, and statistical and structural modelling are all required to provide a framework to better prognosticate and treat HHT.

2. Arterial Endoglin Does Not Protect Against Arteriovenous Malformations

Angiogenesis. 2020 Jun 6.

Authors

Esha Singh [1], Rachael E Redgrave [1], Helen M Phillips [1], Helen M Arthur [2]

Affiliations

- [1] Centre for Life, Biosciences Institute, Newcastle University, Newcastle, NE1 3BZ, UK.
- [2] Centre for Life, Biosciences Institute, Newcastle University, Newcastle, NE1 3BZ, UK. helen.arthur@newcastle.ac.uk.

- PMID: 32506200
- DOI: 10.1007/s10456-020-09731-z

Abstract

Introduction: Endoglin (ENG) forms a receptor complex with ALK1 in endothelial cells (ECs) to promote BMP9/10 signalling. Loss of function mutations in either ENG or ALK1 genes lead to the inherited vascular disorder hereditary haemorrhagic telangiectasia (HHT), characterised by arteriovenous malformations (AVMs). However, the vessel-specific role of ENG and ALK1 proteins in protecting against AVMs is unclear. For example, AVMs have been described to initiate in arterioles, whereas ENG is predominantly expressed in venous ECs. To

investigate whether ENG has any arterial involvement in protecting against AVM formation, we specifically depleted the Eng gene in venous and capillary endothelium whilst maintaining arterial expression, and investigated how this affected the incidence and location of AVMs in comparison with pan-endothelial Eng knockdown.

Methods: Using the mouse neonatal retinal model of angiogenesis, we first established the earliest time point at which Apj-Cre-ERT2 activity was present in venous and capillary ECs but absent from arterial ECs. We then compared the incidence of AVMs following pan-endothelial or venous/capillary-specific ENG knockout.

Results: Activation of Apj-Cre-ERT2 with tamoxifen from postnatal day (P) 5 ensured preservation of arterial ENG protein expression. Specific loss of ENG expression in ECs of veins and capillaries led to retinal AVMs at a similar frequency to pan-endothelial loss of ENG. AVMs occurred in the proximal as well as the distal part of the retina consistent with a defect in vascular remodelling during maturation of the vasculature.

Conclusion: Expression of ENG is not required in arterial ECs to protect against AVM formation.

3. Generation and Genetic Repair of 2 iPSC Clones From a Patient Bearing a Heterozygous c.1120del18 Mutation in the ACVRL1 Gene Leading to Hereditary Hemorrhagic Telangiectasia (HHT) Type 2

Stem Cell Res. 2020 May 28;46:101786.

Authors

Marga J Bouma [1], Valeria Orlova [2], Francijna E van den Hil [2], Hans-Jurgen Mager [3], Frank Baas [4], Peter de Knijff [5], Christine L Mummery [6], Harald Mikkers [7], Christian Freund [6]

Affiliations

- [1] LUMC hiPSC Hotel, Leiden University Medical Center, Leiden, 2333 ZC, The Netherlands; Department of Anatomy and Embryology, Leiden University Medical Center, Leiden, 2333 ZC, The Netherlands. Electronic address: m.j.bouma@lumc.nl.
- [2] Department of Anatomy and Embryology, Leiden University Medical Center, Leiden, 2333 ZC, The Netherlands.
- [3] Department of Cardiology, St. Antonius Hospital, Nieuwegein, 3435 CM, The Netherlands.
- [4] Department of Clinical Genetics, Leiden University Medical Center, Leiden, 2333 ZC, The Netherlands.

- [5] Department of Human Genetics, Leiden University Medical Center, Leiden, 2333 ZC, The Netherlands.
- [6] LUMC hiPSC Hotel, Leiden University Medical Center, Leiden, 2333 ZC, The Netherlands; Department of Anatomy and Embryology, Leiden University Medical Center, Leiden, 2333 ZC, The Netherlands.
- [7] LUMC hiPSC Hotel, Leiden University Medical Center, Leiden, 2333 ZC, The Netherlands; Department of Cell and Chemical Biology, Leiden University Medical Center, Leiden, 2333 ZC, The Netherlands.

- PMID: 32485642
- DOI: 10.1016/j.scr.2020.101786

Abstract

Fibroblasts from a patient carrying a heterozygous 18bp deletion in exon 8 of the ACVRL1 gene (c.1120del18) were reprogrammed using episomal vectors. The in-frame deletion in ACVRL1 causes the loss of 6 amino acids of the protein, which is associated with Hereditary Hemorrhagic Telangiectasia (HHT) type 2 (Letteboer et al., 2005). CRISPR-Cas9 editing was used to genetically correct the mutation in the induced pluripotent stem cells (iPSCs). The top5-predicted off-target sites were not altered. Patient and isogenic iPSCs showed high pluripotent marker expression, in vitro differentiation capacity into all three germ layers and displayed a normal karyotype. The obtained isogenic pairs will enable proper in vitro disease modelling of HHT (Roman and Hinck, 2017).

4. Low Grade Mosaicism in Hereditary Haemorrhagic Telangiectasia Identified by Bidirectional Whole Genome Sequencing Reads Through the 100,000 Genomes Project Clinical Diagnostic Pipeline

J Med Genet. 2020 Apr 17;jmedgenet-2019-106794.

Authors

Jessica M Clarke [1 2], Mary Alikian [1 2], Sihao Xiao [2 3], Dalia Kasperaviciute [4], Ellen Thomas [1 4], Isobel Turbin [1 3], Kike Olupona [1], Elna Cifra [1], Emanuel Curetean [1], Teena Ferguson [1], Julian Redhead [1], Genomics England Research Consortium; Claire L Shovlin [5 2 3]

Affiliations

- [1] West London Genomic Medicine Centre, Imperial College Healthcare NHS Trust, London, UK.
- [2] Genomics England Respiratory Clinical Interpretation Partnership (GeCIP), London, UK.
- [3] NHLI Cardiovascular Sciences, Imperial College London, London, UK.
- [4] Genomics England, London, UK.

- [5] West London Genomic Medicine Centre, Imperial College Healthcare NHS Trust, London, UK c.shovlin@imperial.ac.uk.

- PMID: 32303606
- DOI: 10.1136/jmedgenet-2019-106794

Abstract

No abstract available

5. Whole-Mount In Situ Hybridization in Zebrafish Embryos and Tube Formation Assay in iPSC-ECs to Study the Role of Endoglin in Vascular Development

J Vis Exp. 2020 May 28;(159).

Authors

Yong Wang[#1], Ding Zhang[#2], Fang Zhou[2], Meijun Zhou[2], Qiujie Li[1], Jingyu Chen[3], Jun Yang[4]

Affiliations

- [1] Department of Physiology and Department of Cardiology of the Second Affiliated Hospital, Zhejiang University School of Medicine.
- [2] Department of Cell Biology, State Key Laboratory of Medical Molecular Biology, Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences and Peking Union Medical College.
- [3] Wuxi Lung Transplant Center, Wuxi People's Hospital affiliated to Nanjing Medical University; chenjy@wuxiph.com.
- [4] Department of Physiology and Department of Cardiology of the Second Affiliated Hospital, Zhejiang University School of Medicine; Department of Cell Biology, State Key Laboratory of Medical Molecular Biology, Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences and Peking Union Medical College; yangjunimb@hotmail.com.

[#] Contributed equally.

- PMID: 32538908
- DOI: 10.3791/60498

Abstract

Vascular development is determined by the sequential expression of specific genes, which can be studied by performing in situ hybridization assays in zebrafish during different developmental stages. To investigate the role of endoglin(eng) in vessel formation during the development of hereditary hemorrhagic telangiectasia (HHT),

morpholino-mediated targeted knockdown of eng in zebrafish are used to study its temporal expression and associated functions. Here, whole-mount in situ RNA hybridization (WISH) is employed for the analysis of eng and its downstream genes in zebrafish embryos. Also, tube formation assays are performed in HHT patient-derived induced pluripotent stem cell-differentiated endothelial cells (iPSC-ECs; with eng mutations). A specific signal amplifying system using the whole amount In Situ Hybridization - WISH provides higher resolution and lower background results compared to traditional methods. To obtain a better signal, the post-fixation time is adjusted to 30 min after probe hybridization. Because fluorescence staining is not sensitive in zebrafish embryos, it is replaced with diaminobezidine (DAB) staining here. In this protocol, HHT patient-derived iPSC lines containing an eng mutation are differentiated into endothelial cells. After coating a plate with basement membrane matrix for 30 min at 37 °C, iPSC-ECs are seeded as a monolayer into wells and kept at 37 °C for 3 h. Then, the tube length and number of branches are calculated using microscopic images. Thus, with this improved WISH protocol, it is shown that reduced eng expression affects endothelial progenitor formation in zebrafish embryos. This is further confirmed by tube formation assays using iPSC-ECs derived from a patient with HHT. These assays confirm the role for eng in early vascular development.

Publication types

- Video-Audio Media

6. Identification of a Novel ACVRL1 Gene Mutation (c.100T>A, p.Cys34Ser) in a Japanese Patient With Possible Hereditary Hemorrhagic Telangiectasia (Osler-Weber-Rendu Disease)

Acta Med Okayama. 2020 Apr;74(2):165-169. doi: 10.18926/AMO/58276.

Authors

Hiroshi Umemura [1], Katsuhiro Miura [2], Hiromu Naruse [1], Yoshihiro Hatta [2], Masami Takei [2], Tomohiro Nakayama [1]

Affiliations

- [1] Division of Laboratory Medicine, Department of Pathology and Microbiology, Nihon University School of Medicine, Itabashi-ku, Tokyo 173-8610, Japan.
- [2] Division of Hematology and Rheumatology, Department of Medicine, Nihon University School of Medicine, Itabashi-ku, Tokyo 173-8610, Japan.

- PMID: 32341592
- DOI: 10.18926/AMO/58276

Abstract

Hereditary hemorrhagic telangiectasia (HHT; also known as Osler-Weber-Rendu disease) is an autosomal dominant genetic disorder that causes frequent epistaxis, mucocutaneous telangiectasia, and visceral arteriovenous malformations. Four genes (ENG, ACVRL1, SMAD4, and GDF2) have been identified as pathogenic in HHT. We describe the case of a 50-year-old Japanese man highly suspected of having HHT due to recurrent epistaxis, mucocutaneous telangiectasia, and a family history. Genomic analysis revealed a novel missense mutation of c.100T>A, p.Cys34Ser in the patient's ACVRL1 gene. We used 6 freeware programs to perform an in silico analysis of this mutation. The results demonstrated the mutation's high pathogenicity.

Publication types

- Case Reports

7. Hereditary Haemorrhagic Telangiectasia (HHT) Marked by ACVRL1C1120T Variant Displays Hypopigmented Naevi and Frequent Bleeding Episodes if CYP2C9 Co-Mutated: Clinical Notes & Rationale of Patient Registry

Folia Biol (Praha). 2020;66(1):1-6.

Authors

L Minarik [1], K Vargova [2], N Dusilkova [1 2], V Kulvait [1], A Jonasova [3], O Kodet [4], T Stopka [1 3]

Affiliations

- [1] Biocev, First Faculty of Medicine, Charles University, Vestec, Czech Republic.
- [2] Institute of Pathological Physiology, First Faculty of Medicine, Charles University, Prague, Czech Republic.
- [3] First Department of Medicine, Department of Haematology, First Faculty of Medicine, Charles University and General University Hospital in Prague, Czech Republic.
- [4] Department of Dermatology and Venereology, First Faculty of Medicine, Charles University and General University Hospital in Prague, Czech Republic.

- PMID: 32512653

Abstract

Hereditary haemorrhagic telangiectasia (HHT) exhibits considerable phenotypic heterogeneity. Therefore, precise mutation screening and evaluation of patient risk must be determined in every HHT family. We present an HHT-2 case with an

initial life-threatening bleeding episode that led to identification of a relatively large HHT family. Exome sequencing of the family members determined HHT-associated ACVRL1C1120T variant resulting in Arg374Trp substitution at the Ser/Thr-kinase domain region. The affected members display typical epistaxis symptomatology from early childhood resulting in sideropoenia. In addition, the HHT patients also displayed dermatology findings such as facial teleangiectasias and trunk/limb white spots representing post-inflammatory hypopigmentation. Interestingly, co-segregating with modifying cytochrome P450 (CYP2C) variant in the HHT patients led to NSAID intolerance marked by increased frequency of bleeding episodes. No arterial-venous malformation of the visceral organs and brain or association with cancer were observed. The heterogeneity of clinical presentation and the role of other variants support the need of regular patient monitoring and development of a nation-wide patient registry.

Publication types

- Case Reports

PAVM

1. Approach to Pulmonary Arteriovenous Malformations: A Comprehensive Update

J Clin Med. 2020 Jun 19;9(6):E1927.

Authors

Shamaita Majumdar [1], Justin P McWilliams [1]

Affiliation

- [1] UCLA Department of Radiological Sciences, Los Angeles, CA 90095, USA.

- PMID: 32575535
- DOI: 10.3390/jcm9061927

Abstract

Pulmonary arteriovenous malformations (PAVMs) are abnormal direct vascular communications between pulmonary arteries and veins which create high-flow right-to-left shunts. They are most frequently congenital, usually in the setting of hereditary hemorrhagic telangiectasia (HHT). PAVMs may be asymptomatic or present with a wide variety of clinical manifestations such as dyspnea, hypoxemia,

or chest pain. Even when asymptomatic, presence of PAVMs increases patients' risk of serious, potentially preventable complications including stroke or brain abscess. Transcatheter embolotherapy is considered the gold standard for treatment of PAVMs. Though previous guidelines have been published regarding the management of PAVMs, several aspects of PAVM screening and management remain debated among the experts, suggesting the need for thorough reexamination of the current literature. The authors of this review present an updated approach to the diagnostic workup and management of PAVMs, with an emphasis on areas of controversy, based on the latest literature and our institutional experience.

2. CT Angiography Findings of Pulmonary Arteriovenous Malformations in Children and Young Adults With Hereditary Hemorrhagic Telangiectasia

AJR Am J Roentgenol. 2020 Jun;214(6):1369-1376.

Authors

Su-Mi Shin [1], Hee Kyung Kim [2 3], Eric J Crotty [2 3], Adrienne M Hammill [4 5], Katherine Wusik [6], Dong-Hoon Kim [7]

Affiliations

- [1] Department of Radiology, SMG-SNU Boramae Medical Center, Seoul, Republic of Korea.
- [2] Department of Radiology, Cincinnati Children's Hospital Medical Center, 3333 Burnet Ave, Cincinnati, OH 45229-3039.
- [3] Department of Radiology, University of Cincinnati College of Medicine, Cincinnati, OH.
- [4] Cancer and Blood Diseases Institute, Division of Hematology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH.
- [5] Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH.
- [6] Division of Human Genetics, Cincinnati Children's Hospital Medical Center, Cincinnati, OH.
- [7] Department of Pharmacology, Korea University College of Medicine, Seoul, Republic of Korea.

- PMID: 32255688
- DOI: 10.2214/AJR.19.22012

Abstract

OBJECTIVE. The purpose of this study was to evaluate the CT angiography (CTA) findings of pulmonary arteriovenous malformation (PAVMs) in patients

with hereditary hemorrhagic telangiectasia and to correlate these findings with those of graded contrast-enhanced transthoracic echocardiography (CE-TTE).

MATERIALS AND METHODS. A retrospective review was conducted of PAVMs visualized at CTA of patients with abnormal CE-TTE findings (3-point scale). Location, distribution, size, number, volume, grade, and relative attenuation (attenuation of PAVM divided by attenuation of aorta) of PAVMs were recorded. PAVMs were graded as follows on conventional and maximum-intensity-projection (MIP) images: 0, nodule, unlikely PAVM; 1, ground-glass opacity (GGO); 2, GGO with increased vascular network; 3, GGO or nodule with single vessel; 4, GGO or nodule with two or more vessels; 5, GGO or nodule with afferent and larger efferent vessels; 6, mature arteriovenous malformation. Correlation between PAVM grade and relative attenuation and between CTA variables and CE-TTE grades was assessed.

RESULTS. Forty patients (median age, 14.9 years; range, 0.6-27.9 years) had 117 PAVMs at CTA: 107 peripheral, eight central, and two both peripheral and central. None of the PAVMs was diffuse. Median size and volume were 0.4 cm (range, 0.1-4.4 cm) and 0.031 mL (range, 0.0009-10.019 mL). At CTA, seven PAVMs were grade 1, five grade 2, 28 grade 3, 62 grade 4, two grade 5, and 13 grade 6. MIP images showed 39 of 117 PAVMs were higher grade. Statistically significant correlation was found between relative attenuation and PAVM grade ($p < 0.001$, $r = 0.58$) in 40 patients and between all CTA variables and CE-TTE ($p < 0.05$, strongest correlation with highest grades [$p < 0.0001$, $r = 0.81$]) in 32 patients.

CONCLUSION. In children and young adults with hereditary hemorrhagic telangiectasia, grade 4 PAVMs were most common. Higher-grade PAVMs more often have right-to-left shunts.

CASE REPORTS

3. Pulmonary Arteriovenous Fistula Ruptured in an Adolescent Girl 1 Week After Her Mother's Rupture: A Report of a Case

Gen Thorac Cardiovasc Surg. 2020 Jun 18.

Authors

Suguru Mitsui 1 , Shunsuke Tauchi 2 , Yugo Tanaka 3 , Satoshi Tobe 1

Affiliations

- 1 Department of Thoracic Surgery, Akashi Medical Center, 743-33 Okubocho Yagi, Akashi, Hyogo, 674-0063, Japan.
- 2 Department of Thoracic Surgery, Akashi Medical Center, 743-33 Okubocho Yagi, Akashi, Hyogo, 674-0063, Japan. s-tauchi@amc1.jp.

- 3 Division of Thoracic Surgery, Graduate School of Medicine, Kobe University, Kobe, Hyogo, 650-0017, Japan.

- PMID: 32556901
- DOI: 10.1007/s11748-020-01410-6

Abstract

A 14-year-old girl was diagnosed with hemothorax associated with pulmonary arteriovenous fistula rupture, and emergency surgery was performed. One week before her surgery, her mother at 32 weeks of gestation underwent emergency surgery for hemothorax caused by pulmonary arteriovenous fistula rupture. Both were diagnosed with hereditary hemorrhagic telangiectasia. The indications for treatment of pulmonary arteriovenous fistulas in young patients remain controversial because the risk of complications concerning pulmonary arteriovenous fistula is lower in young patients than in adult patients. We recommend that aggressive treatment should be performed for pulmonary arteriovenous fistulas in patients with hereditary hemorrhagic telangiectasis with a family history of pulmonary arteriovenous fistula rupture even if the patient is asymptomatic and young, because such patients may have a high risk of pulmonary arteriovenous fistula rupture.

4. Hereditary Haemorrhagic Telangiectasia With Heritable Pulmonary Arterial Hypertension

Eur Heart J. 2020 May 26;ehaa431.

Authors

Wei-Wei Zhu [1], Xiu-Zhang Lv [1], Wen-Huan Li [2]

Affiliations

- [1] Department of Echocardiography, Beijing Chao Yang Hospital, Capital Medical University, Beijing 100020 , China.
- [2] Department of Radiology, Beijing Chao Yang Hospital, Capital Medical University, No. 8 Gongren Tiyuchang Nanlu, Chaoyang District, Beijing 100020 , China.

- PMID: 32457986
- DOI: 10.1093/eurheartj/ehaa431

5. Diffuse Endobronchial Telangiectasia

Int J Appl Basic Med Res. Apr-Jun 2020;10(2):137-139.

Authors

Mohan Rudrappa [1] [2], Laxmi Kokatnur [1]

Affiliations

- [1] Department of Medicine, Mercy Hospital, Joplin, Missouri, USA.
- [2] Louisiana State University Health Science Centre, Shreveport, LA, USA.

- PMID: 32566532
- PMCID: PMC7289210
- DOI: 10.4103/ijabmr.IJABMR_343_18

Abstract

Hemoptysis is one of the most common reasons for seeking emergency care. Infections and malignancy are the leading causes of hemoptysis although caused by various other pulmonary and extrapulmonary conditions. Most causes are self-limiting and do not warrant any aggressive investigation. Endobronchial telangiectasia can rarely cause hemoptysis and is seen in patients with hemorrhagic hereditary telangiectasia or scleroderma. Isolated diffuse endobronchial telangiectasia is rare and is only reported in one case in literature. We present another case of diffuse endobronchial telangiectasia in a young adult who presented with recurrent hemoptysis. Computer tomography scan was normal, but bronchoscopy showed multiple endobronchial arteriovenous malformations in the entire tracheobronchial tree.

1. European Reference Network for Rare Vascular Diseases (VASCERN) Position Statement on Cerebral Screening in Adults and Children With Hereditary Haemorrhagic Telangiectasia (HHT)

Orphanet J Rare Dis. 2020 Jun 29;15(1):165.

Authors

Omer F Eker [1], Edoardo Boccardi [2], Ulrich Sure [3], Maneesh C Patel [4], Saverio Alicante [5], Ali Alsafi [4], Nicola Coote [4], Freya Droege [3], Olivier Dupuis [6], Annette Dam Fialla [7], Bryony Jones [4], Ujwal Kariholu [4], Anette D Kjeldsen [7], David Lefroy [4], Gennaro M Lenato [8], Hans Jurgen Mager [9], Guido Manfredi [5], Troels H Nielsen [7], Fabio Pagella [10], Marco C Post [9], Catherine Rennie [4], Carlo Sabbà [11], Patrizia Suppressa [8], Pernille M Toerring [7], Sara Ugolini [10], Elisabetta Buscarini [12], Sophie Dupuis-Girod [6], Claire L Shovlin [13]

Affiliations

- [1] VASCERN HHT Reference Centre, Hospices Civils de Lyon, Lyon, France. omer.eker@chu-lyon.fr.
- [2] Niguarda Hospital, Milan, Italy and VASCERN HHT Reference Centre, Crema, Italy.
- [3] VASCERN HHT Reference Centre, Essen University Hospital, Essen, Germany.
- [4] VASCERN HHT Reference Centre, Imperial College Healthcare National Health Service Trust, London, UK.
- [5] VASCERN HHT Reference Centre, ASST Maggiore Hospital, Crema, Italy.
- [6] VASCERN HHT Reference Centre, Hospices Civils de Lyon, Lyon, France.
- [7] VASCERN HHT Reference Centre, Odense Universitetshospital, Syddansk Universitet, Odense, Denmark.
- [8] VASCERN HHT Reference Centre, "Frugoni" Internal Medicine Unit, University of Bari "A. Moro", Policlinico, Bari, Italy.
- [9] VASCERN HHT Reference Centre, St Antonius Ziekenhuis, Nieuwegein, Netherlands.
- [10] VASCERN HHT Reference Centre, University of Pavia, IRCCS Policlinico San Matteo Foundation, Pavia, Italy.
- [11] VASCERN HHT Reference Centre, "Frugoni" Internal Medicine Unit, University of Bari "A. Moro", Policlinico, Bari, Italy. carlo.sabba@uniba.it.
- [12] VASCERN HHT Reference Centre, ASST Maggiore Hospital, Crema, Italy. elisabetta.buscarini@asst-crema.it.
- [13] VASCERN HHT Reference Centre, Imperial College Healthcare National Health Service Trust, London, UK and Imperial College London, London, UK.

c.shovlin@imperial.ac.uk.

- PMID: 32600364
- PMCID: PMC7322871
- DOI: 10.1186/s13023-020-01386-9

Abstract

Hereditary haemorrhagic telangiectasia (HHT) is a multisystemic vascular dysplasia inherited as an autosomal dominant trait. Approximately 10 % of patients have cerebral vascular malformations, a proportion being cerebral arteriovenous malformations (AVMs) and fistulae that may lead to potentially devastating consequences in case of rupture. On the other hand, detection and treatment related-risks are not negligible, and immediate. While successful treatment can be undertaken in individual cases, current data do not support the treatment of unruptured AVMs, which also present a low risk of bleeding in HHT patients. Screening for these AVMs is therefore controversial.Structured discussions, distinctions of different cerebrovascular abnormalities commonly grouped into an "AVM" bracket, and clear guidance by neurosurgical and neurointerventional radiology colleagues enabled the European Reference Network for Rare Vascular Disorders (VASCERN-HHT) to develop the following agreed Position Statement on cerebral screening:1) First, we emphasise that neurological symptoms suggestive of cerebral AVMs in HHT patients should be investigated as in general neurological and emergency care practice. Similarly, if an AVM is found accidentally, management approaches should rely on expert discussions on a case-by-case basis and individual risk-benefit evaluation of all therapeutic possibilities for a specific lesion.2) The current evidence base does not favour the treatment of unruptured cerebral AVMs, and therefore cannot be used to support widespread screening of asymptomatic HHT patients.3) Individual situations encompass a wide range of personal, cultural and clinical states. In order to enable informed patient choice, and avoid conflicting advice, particularly arising from non-neurovascular interpretations of the evidence base, we suggest that all HHT patients should have the opportunity to discuss knowingly brain screening issues with their healthcare provider.4) Any screening discussions in asymptomatic individuals should be preceded by informed pre-test review of the latest evidence regarding preventative and therapeutic efficacies of any interventions. The possibility of harm due to detection of, or intervention on, a vascular malformation that would not have necessarily caused any consequence in later life should be stated explicitly.We consider this nuanced Position Statement provides a helpful, evidence-based framework for informed discussions between healthcare providers and patients in an emotionally charged area.

2. An Update on Medications for Brain Arteriovenous Malformations

Neurosurgery. 2020 May 20;nyaa192.

Authors

Daniel M S Raper [1], Ethan A Winkler [1], W Caleb Rutledge [1], Daniel L Cooke [2], Adib A Abla [1]

Affiliations

- [1] Department of Neurological Surgery, University of California, San Francisco, San Francisco, California.
- [2] Department of Radiology and Biomedical Engineering, University of California, San Francisco, San Francisco, California.

- PMID: 32433738
- DOI: 10.1093/neuros/nyaa192

Abstract

Despite a variety of treatment options for brain arteriovenous malformations (bAVMs), many lesions remain challenging to treat and present significant ongoing risk for hemorrhage. In Vitro investigations have recently led to a greater understanding of the formation, growth, and rupture of bAVMs. This has, in turn, led to the development of therapeutic targets for medications for bAVMs, some of which have begun testing in clinical trials in humans. These include bevacizumab, targeting the vascular endothelial growth factor driven angiogenic pathway; thalidomide or lenalidomide, targeting blood-brain barrier impairment; and doxycycline, targeting matrix metalloproteinase overexpression. A variety of other medications appear promising but either requires adaptation from other disease states or development from early bench studies into the clinical realm. This review aims to provide an overview of the current state of development of medications targeting bAVMs and to highlight their likely applications in the future.

3. [An Hereditary Hemorrhagic Telangiectasia of Late Revealed by a Cerebral Venous Thrombosis: A Case Report]

Rev Med Interne. 2020 Jun 19;S0248-8663(20)30115-6.

Authors

P Constant Dit Beaufils [1], S De Gaalon [2], O Espitia [3], G Ploton [3], S Mercier [4], R Liberge [5], J Connault [3]

Affiliations

- [1] Clinique neurologique, CHU de Nantes, Boulevard Jacques Monod, 44093 Nantes cedex 1, France. Electronic address: pacome.constantditbeaufils@chu-nantes.fr.
- [2] Clinique neurologique, CHU de Nantes, Boulevard Jacques Monod, 44093 Nantes cedex 1, France.
- [3] Service de médecine vasculaire, CHU de Nantes, Boulevard Jacques Monod, 44093 Nantes cedex 1, France.
- [4] Service de génétique clinique, CHU de Nantes, 1, Place Alexis Ricordeau, 44093 Nantes, France.
- [5] Service de radiologie et imagerie médicale, CHU de Nantes, 1, Place Alexis Ricordeau, 44093 Nantes, France.

- PMID: 32565074
- DOI: 10.1016/j.revmed.2020.03.013

Abstract

Introduction: Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant disease characterized by the triad of nose bleeding, telangiectasia and familial heredity.

Case report: We report the case of a patient who had idiopathic venous cerebral thrombosis complicated by a cerebral infarction treated with warfarin. In the context of a psoas hematoma by warfarine overdose and immobilization, the patient had deep vein thrombosis of the left lower limb with pulmonary embolism revealing a pulmonary arteriovenous malformation. After a reexamination, the patient clinical phenotype of HHT was confirmed genetically. The patient was treated with rivaroxaban allowing clinical improvement and partial recanalization of all thrombosis after six months. Thrombotic overisk has already been studied in HHT patients but the use of anticoagulants is at higher risk in these patients. However this patient experienced no adverse event with rivaroxaban.

Conclusion: This is the first case described of cerebral venous thrombosis treated with rivaroxaban revealing an HHT.

4. Comparison of MRI, MRA, and DSA for Detection of Cerebral Arteriovenous Malformations in Hereditary Hemorrhagic Telangiectasia

AJNR Am J Neuroradiol. 2020 Jun;41(6):969-975. doi: 10.3174/ajnr.A6549. Epub 2020 May 7.

Authors

M Vella [1], M D Alexander [2], M C Mabray [3], D L Cooke [4], M R Amans [4], C M Glastonbury [5], H Kim [6 7], M W Wilson [8], D E Langston [4 6], M B Conrad [8 6], S W Hetts [9 6]

Affiliations

- [1] From the Departments of Radiology and Biomedical Imaging (M.V.).
- [2] Department of Radiology, Division of Interventional Neuroradiology (M.D.A.), University of Utah, Salt Lake City, Utah.
- [3] Department of Radiology, Division of Neuroradiology (M.C.M.), University of New Mexico, Albuquerque, New Mexico.
- [4] Division of Neurointerventional Radiology (D.L.C., M.R.A., D.E.L., S.W.H.).
- [5] Division of Diagnostic Neuroradiology (C.M.G.).
- [6] Hereditary Hemorrhagic Telangiectasia Center of Excellence (H.K., D.E.L., M.B.C., S.W.H.).
- [7] Anesthesia and Perioperative Care (H.K.), University of California, San Francisco, San Francisco, California.
- [8] Division of Interventional Radiology (M.W.W., M.B.C.).
- [9] Division of Neurointerventional Radiology (D.L.C., M.R.A., D.E.L., S.W.H.) steven.hetts@ucsf.edu.

- PMID: 32381546
- DOI: 10.3174/ajnr.A6549

Abstract

Background and purpose: Patients with hereditary hemorrhagic telangiectasia (HHT) have a high prevalence of brain vascular malformations, putting them at risk for brain hemorrhage and other complications. Our aim was to evaluate the relative utility of MR imaging and MRA compared with DSA in detecting cerebral AVMs in the HHT population.

Materials and methods: Of 343 consecutive patients evaluated at the University of California, San Francisco HTT Center of Excellence, 63 met the study inclusion criteria: definite or probable hereditary hemorrhagic telangiectasia defined by meeting at least 2 Curacao criteria or positive genetic testing, as well as having at least 1 brain MR imaging and 1 DSA. MRIs were retrospectively reviewed, and the number of AVMs identified was compared with the number of AVMs identified on DSA.

Results: Of 63 patients, 45 (71%) had AVMs on DSA with a total of 92 AVMs identified. Of those, 24 (26%) were seen only on DSA; 68 (74%), on both DSA and MR imaging; and 5 additional lesions were seen only on MR imaging. Of the 92 lesions confirmed on DSA, 49 (53.3%) were seen on the 3D-T1 postgadolinium sequence, 52 (56.5%) were seen on the 2D-T1 postgadolinium sequence, 35 (38.0%) were seen on the SWI sequence, 24 (26.1%) were seen on T2 sequence, and 25 (27.2%) were seen on MRA. The sensitivity and specificity of MR imaging as a whole in detecting AVMs then confirmed on DSA were 80.0% and 94.4%, respectively, and the positive and negative predictive values were 97.3% and 65.4%, respectively.

Conclusions: This study reinforces the use of MR imaging as a primary screening tool for cerebral AVMs in patients with hereditary hemorrhagic telangiectasia and suggests that 3D-T1 postgadolinium and 2D-T1 postgadolinium performed at 3T are the highest yield sequences.

5. A Case Report of Hereditary Hemorrhagic Telangiectasia in a Family With Initial Presentation of Cerebral Abscess and Pulmonary Arteriovenous Malformation in the Proband

Neurol Sci. 2020 Jun 8.

Authors

Xiaojuan Han [1 2], Tingming Xie [3], Zenggang Yang [3], Yifeng Du [1 2], Shen Qi [4 5]

Affiliations

- [1] Department of Neurology, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, People's Republic of China.
- [2] Department of Neurology, Shandong Provincial Hospital, Cheeloo College of Medicine, Shandong University, No 324, Jingwu Road, 250012, Jinan, Shandong, People's Republic of China.
- [3] Department of Neurology, Mengyin County People's Hospital, Mengyin, China.
- [4] Department of Neurology, Shandong Provincial Hospital, Cheeloo College of Medicine, Shandong University, No 324, Jingwu Road, 250012, Jinan, Shandong, People's Republic of China. qishen007@163.com.
- [5] Department of Neurology, Shandong Zaozhuang Municipal Hospital, Jinan, People's Republic of China. qishen007@163.com.

- PMID: 32514857
- DOI: 10.1007/s10072-020-04500-8

Publication types

- Letter

1. Hereditary Hemorrhagic Telangiectasia: How to Efficiently Detect Hepatic Abnormalities Using Ultrasonography

J Med Ultrason (2001). 2020 May 10.

Authors

Hiroko Naganuma [1], Hideaki Ishida [2], Hidekatsu Kuroda [3], Yasuaki Suzuki [4], Masahiro Ogawa [5]

Affiliations

- [1] Department of Gastroenterology, Yokote Municipal Hospital, 5-31 Negishi-cho, Yokote, Akita, 013-8602, Japan. hiron@vesta.ocn.ne.jp.
- [2] Center of Diagnostic Ultrasound, Akita Red Cross Hospital, Akita, Japan.
- [3] Division of Hepatology, Department of Internal Medicine, Iwate Medical University, Iwate, Japan.
- [4] Department of Gastroenterology, Nayoro City General Hospital, Hokkaido, Japan.
- [5] Department of Gastroenterology and Hepatology, Nihon University Hospital, Tokyo, Japan.

- PMID: 32390074
- DOI: 10.1007/s10396-020-01022-w

Abstract

Introduction: Hereditary hemorrhagic telangiectasia (HHT) is a multiorgan genetic angiodysplastic affection characterized by visceral vascular malformations. It affects mainly the brains, lungs, gastrointestinal tract, and nasal mucosa. Unlike those organs, hepatic involvement, although very frequently occurring, is insufficiently recognized, mainly because of the complex vascular structure of this organ. Thus, treating HHT patients requires a solid understanding of these hepatic anomalies. It is especially important for any general clinicians to be able to recognize clinical findings in HHT, which leads to a high suspicion of HHT and have an index of suspicion for liver abnormalities of HHT. For this purpose, keen awareness of clinical as well as hepatic sonographic (US) findings is paramount.

Aim: The aim of this review is to summarize previously reported findings on the hepatic US through a thorough analysis of related articles, and to (a) determine the role of US in the diagnosis of hepatic involvement in HHT patients and (b) propose the most simple and easy way to detect HHT-related abnormalities during routine US examinations.

Conclusion: Hepatic US serves to diagnose the detailed complex hepatic changes typical of HHT, and contributes to increased diagnostic confidence of hepatic changes in HHT patients, with the most simple way not to overlook HHT-related abnormalities being to find hepatic artery dilatation.

Publication types

- Review

2. Hereditary Hemorrhagic Telangiectasia and Liver Involvement: Vascular Liver Diseases: Position Papers From the Francophone Network for Vascular Liver Diseases, the French Association for the Study of the Liver (AFEF), and ERN-rare Liver

Clin Res Hepatol Gastroenterol. 2020 Apr 7;S2210-7401(20)30079-6.

Authors

Christine Silvain [1], Thierry Thévenot [2], Isabelle Colle [3], Valérie Vilgrain [4], Sophie Dupuis-Girod [5], Elisabetta Buscarini [6], Dominique Valla [7], Sophie Hillaire [8], Danielle Dutheil [9], Olivier Sitbon [10], Christophe Bureau [11], Aurélie Plessier [7]

Affiliations

- [1] Department of Gastroenterology and Hepatology, University Hospital of Poitiers, 2, rue de la Milétrie - CS 90577, 86021 Poitiers, France. Electronic address: c.silvain@chu-poitiers.fr.
- [2] Department of Hepatology and intensive digestive care, Jean Minjoz Hospital, 3, boulevard Alexandre Fleming, 25030 Besançon, France.
- [3] Department of Gastroenterology and Hepatology, Algemeen Stedelijk Ziekenhuis ASZ campus Aalst, 9300 Aalst (Alost), Belgium.
- [4] Department of radiology, Beaujon Hospital, AP-HP, 100, boulevard du Général Leclerc, 92118 Clichy, France; French Network for Rare Liver Diseases (FILFOIE), Saint-Antoine Hospital, APHP, 184, rue du Faubourg Saint-Antoine, 75012 Paris, France.
- [5] Hospices Civils de Lyon, Department of genetic and Reference Center for Hereditary Hemorrhagic Telangiectasia, -Hôpital Femme Mère Enfant, 59, boulevard Pinel, 69677 Bron, France.
- [6] Department of Gastroenterology and Reference Center for Hereditary Hemorrhagic Telangiectasia, Maggiore Hospital, ASST Crema, Largo Ugo Dossena, 2, 26013 Crema CR, Italy.
- [7] Department of Hepatology and reference center of vascular liver diseases, Beaujon Hospital, AP-HP, 100, boulevard du Général Leclerc, 92118 Clichy, France; French Network for Rare Liver Diseases (FILFOIE), Saint-Antoine Hospital, APHP, 184, rue du Faubourg Saint-Antoine, 75012 Paris, France; Reference center of vascular liver diseases, European Reference Network (ERN) Rare-Liver.

- [8] Department of Internal Medicine, Foch Hospital, 40, rue Worth, 92150 Suresnes, France.
- [9] Association of patients with vascular liver diseases (AMVF), Beaujon Hospital, Department of Hepatology, 100, boulevard du Général Leclerc, 92118 Clichy, France; French Network for Rare Liver Diseases (FILFOIE), Saint-Antoine Hospital, APHP, 184, rue du Faubourg Saint-Antoine, 75012 Paris, France.
- [10] Université Paris-Saclay, AP-HP, INSERM UMR_S 999, Service de Pneumologie et Soins Intensifs Respiratoires, Hôpital Bicêtre, Le Kremlin Bicêtre, France.
- [11] Department of Gastroenterology and Hepatology, Rangueil Hospital, University Hospital of Toulouse, 1, avenue du Professeur Jean Poulhès, 31400 Toulouse, France; French Network for Rare Liver Diseases (FILFOIE), Saint-Antoine Hospital, APHP, 184, rue du Faubourg Saint-Antoine, 75012 Paris, France.

- PMID: 32276767
- DOI: 10.1016/j.clinre.2020.03.008

Abstract

No abstract available

Publication types

- Practice Guideline

3. Hereditary Hemorrhagic Telangiectasia of Liver: Pathophysiology With Role of Radiology in Diagnosis and Treatment

Indian J Radiol Imaging. Jan-Mar 2020;30(1):98-101.

Authors

Maheswaran Viyannan [1], Devanand Balalakshmoji [1], Venkatakrishnan Leelakrishnan [2]

Affiliations

- [1] Department of Radiology, PSG Institute of Medical Sciences and Research, Peelamedu, Coimbatore, Tamil Nadu, India.
- [2] Department of Med. Gastro, PSG Institute of Medical Sciences and Research, Peelamedu, Coimbatore, Tamil Nadu, India.

- PMID: 32476760
- PMCID: PMC7240902
- DOI: 10.4103/ijri.IJRI_367_19

Abstract

Hereditary hemorrhagic telangiectasia (HHT) or Osler-Weber-Rendu syndrome is a rare condition which can result in significant *systemic and hepatobiliary*

abnormalities. Liver involvement in HHT consists primarily of the consequence of various intrahepatic shunts. Even though these vascular shunts are present in the majority of patients with HHT, symptoms occur only in *minority* with clear predilection to *female gender*. The symptoms and imaging findings of liver vascular malformations can be easily overlooked or misdiagnosed which can result in delay in treatment or potentially harmful vascular interventions. In this case report, we discuss the pathophysiology of HHT in liver involvement, role of imaging in diagnosis, and the possible role of interventional radiologist in the treatment.

Publication types

- Case Reports

4. Liver Cirrhosis in a Patient With Hepatic Hereditary Hemorrhagic Telangiectasia and Budd-Chiari Syndrome: A Case Report

BMC Gastroenterol. 2020 Jun 3;20(1):169.

Authors

Bai-Guo Xu [1 2 3], Jing Liang [1 2 3], Ke-Feng Jia [2 3 4], Tao Han [5 6 7]

Affiliations

- [1] Department of Hepatology and Gastroenterology, the Third Central Clinical College of Tianjin Medical Universityssss, 83 Jintang Road, Hedong District, Tianjin, 300170, China.
- [2] Tianjin Key Laboratory of Extracorporeal Life Support for Critical Diseases; Artificial Cell Engineering Technology Research Center, Tianjin, China.
- [3] Tianjin Institute of Hepatobiliary Disease, Tianjin, China.
- [4] Department of Radiology, the Third Central Clinical College of Tianjin Medical University, Tianjin, 300170, China.
- [5] Department of Hepatology and Gastroenterology, the Third Central Clinical College of Tianjin Medical Universityssss, 83 Jintang Road, Hedong District, Tianjin, 300170, China. hantaomd@126.com.
- [6] Tianjin Key Laboratory of Extracorporeal Life Support for Critical Diseases; Artificial Cell Engineering Technology Research Center, Tianjin, China. hantaomd@126.com.
- [7] Department of Radiology, the Third Central Clinical College of Tianjin Medical University, Tianjin, 300170, China. hantaomd@126.com.

- PMID: 32493237
- PMCID: PMC7268624
- DOI: 10.1186/s12876-020-01311-1

Abstract

Background: Hereditary hemorrhagic telangiectasia (HHT) often involves the liver, and belongs to abnormal blood vessel disease. The etiology of Budd-Chiari syndrome (BCS) is not clear, but congenital vascular dysplasia is considered to be one of the causes. Liver cirrhosis due to hepatic hereditary hemorrhagic telangiectasia concomitant with BCS has not been reported. Here, we report a case of cirrhosis with hepatic hereditary hemorrhagic telangiectasia (HHHT) and BCS.

Case presentation: A 58-year-old woman with hepatic hereditary hemorrhagic telangiectasia showed decompensated liver cirrhosis, and abdominal imaging revealed Budd-Chiari syndrome. Disease has progressed considerably during 2.5 years after hospital discharge despite subsequent transjugular intrahepatic portosystemic shunting (TIPS). One hypothesis that might explain the coexistence of hepatic hereditary hemorrhagic telangiectasia and Budd-Chiari syndrome in this patient is ischemia and thrombosis of hepatic veins.

Conclusions: Further studies are required to evaluate the relationship between HHHT and BCS. Our observations already challenged the TIPS therapeutic strategy in BCS secondary to HHHT patients.

Publication types

- Case Reports

5. Hereditary Hemorrhagic Telangiectasia With Pulmonary Hypertension and Hepatic Vascular Malformations

Am J Med Sci. 2020 Apr 28;S0002-9629(20)30162-2.

Authors

Hui Chen [1], ShengYu Wang [2], Jing Zhou [2]

Affiliations

- [1] Department of Pulmonary and Critical Care Medicine, First Affiliated Hospital of Xi'an Medical University, Xi'an, Shaanxi, China. Electronic address: chenhui84278403@163.com.
- [2] Department of Pulmonary and Critical Care Medicine, First Affiliated Hospital of Xi'an Medical University, Xi'an, Shaanxi, China.

- PMID: 32418611
- DOI: 10.1016/j.amjms.2020.04.029

Publication types : Letter