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Safety of thalidomide and bevacizumab in patients with hereditary hemorrhagic telangiectasia.


Collaborators: (2)

Federici P, Crocione C.

Abstract

BACKGROUND:

Hereditary hemorrhagic telangiectasia (HHT) is a multisystemic inherited vascular dysplasia that leads to nosebleeds and visceral arteriovenous malformations (AVMs). Anti-angiogenic drugs thalidomide and bevacizumab have been increasingly used off-label with variable results. The HHT working group within the ERN for Rare Multisystemic Vascular Diseases (VASCERN), developed a questionnaire-based retrospective capture of adverse
events (AEs) classified using the Common Terminology Criteria for Adverse Events.

RESULTS:

Sixty-nine HHT patients received bevacizumab, 37 (50.6%) for high output cardiac failure/hepatic AVMs, and 32 (49.4%) for bleeding; the 69 patients received bevacizumab for a mean of 11 months for a total of 63.8 person/years treatment. 67 received thalidomide, all for epistaxis and/or gastrointestinal bleeding; they received thalidomide for a mean of 13.4 months/patient for a total of 75 person/years treatment. AEs were reported in 58 patients, 33 with bevacizumab, 37 with thalidomide. 32 grade 1-3 AEs related to bevacizumab were reported with an average incidence rate of 50 per 100 person-years. 34 grade 1-3 AEs related to thalidomide were reported with an average incidence rate of 45.3 per 100 person-years. Bevacizumab AEs were more common in females (27 AEs in 46 women) than males (6 in 23, p < 0.001). Thalidomide AEs occurred at more similar rates in males (25 AEs in 41 men, 60.9%) and females (12 in 26 (46.2%), but were more common in ENG patients (17 in 17) than in ACVRL1 (14 in 34, p < 0.0001). For bevacizumab, the most common reports were of joint pains (7/69, 10%), headache (3/69, 4.4%) and proteinuria (2/69, 3%), and for thalidomide, peripheral neuropathy (12/67, 18%); drowsiness (8/67, 12%); and dizziness (6/67, 9%). Fatal adverse events were more common in males (p = 0.009), and in patients with ENG pathogenic variants (p = 0.012). One fatal AE was possibly related to bevacizumab (average incidence rate: 1.5 per 100 person-years); 3 fatal AEs were possibly related to thalidomide (average incidence rate: 4 per 100 person-years).

CONCLUSIONS:

With potential increase in use of Bevacizumab and Thalidomide in HHT patients, data presented support appropriate weighing of the toxicities which can arise in HHT settings and the practice recommendations for their prevention and management.

Similar articles


**Sclerotherapy and Topical Nasal Propranolol: An Effective and Safe Therapy for HHT-Epistaxis.**

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Abstract

OBJECTIVES:

Epistaxis is the most frequent clinical manifestation of hereditary hemorrhagic telangiectasia (HHT). Several topical, systemic, and surgical treatments have been tried, but none have been completely effective. The aim of the present study is to evaluate whether a combined treatment sclerotherapy and topical therapy with propranolol 0.5% nasal formulation would reduce the epistaxis due to HHT and improve patient’s quality of life.

METHODS:

An observational cross-sectional study was carried out. The primary outcome measure was frequency and severity of epistaxis as measured by the epistaxis severity score (ESS) at baseline (4 weeks before therapy) and at least 4 weeks after the treatment was implemented. Quality of life was analyzed using EuroQol-5D (EQ-5D) scale and visual analogue (VAS) scale before and after treatment.

RESULTS:

A total of 38 consecutive patients subjected to the combined treatment were evaluated (mean age: 57.2 years, standard deviation [SD] = 13.9; 60.5% women). The mean time of treatment was 37.1 weeks (SD = 14.9). Combined therapy significantly reduces frequency and severity of epistaxis, with an ESS improvement of 5 points from 6.9 ± 2.6 to 1.9 ± 1.3 (P < 0.05); however, the EQ-5D scale increased from 0.66 ± 0.27 to 0.93 ± 0.12 (P < 0.05). The difference in VAS means showed an increase from 44.6 ± 28.3 to 82.5 ± 12.5 (P < 0.05). The increases in quality of life are in line with the drop in ESS.

CONCLUSION:

The study demonstrated that combined therapy (sclerotherapy and topical nasal propranolol) significantly reduced the epistaxis due to HHT and increased patients' quality of life.

LEVEL OF EVIDENCE:


Similar articles

Bevacizumab as Treatment for Epistaxis in
Hereditary Hemorrhagic Telangiectasia: A Literature Review.

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Abstract

BACKGROUND:

Severe, recurring epistaxis is the most common symptom of hereditary hemorrhagic telangiectasias (HHT). Current treatment modalities range from noninvasive treatments that frequently fail to achieve even short-term control to surgeries and systemic therapies that carry significant risk of complications. Recently, bevacizumab, a VEGF inhibitor, has been proposed as an alternative option to alleviate epistaxis symptoms in HHT.

OBJECTIVE:

To review the current literature regarding the use of bevacizumab for the treatment of epistaxis in patients with HHT and provide guidance on its usage for this indication.

METHODS:

A narrative literature review was performed to analyze various methods and dosages of bevacizumab administration for the treatment of HHT-related epistaxis, along with a review of current treatment modalities and their drawbacks.

RESULTS:

The current standard of care for HHT-related epistaxis consists of treatments that are largely ineffective or invasive with significant potential complications. Submucosal bevacizumab has demonstrated efficacy in reducing frequency, duration, and severity of epistaxis in those with HHT.

CONCLUSION:

Given the inadequacies and potential drawbacks of current treatments for epistaxis in HHT, there is a need for new therapeutic options. Submucosal bevacizumab has been effective with a limited risk profile in a number of studies and should now be considered as a treatment option for refractory epistaxis. Controlled studies are recommended to quantify optimal dosing, treatment schedule, and specific subpopulations that will respond best to this treatment.

Similar articles
Does severe bleeding in HHT patients respond to intravenous bevacizumab? Review of the literature and case series.

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Abstract

BACKGROUND:

Hereditary Haemorrhagic Telangiectasia (HHT) is an autosomal dominant genetic disorder, with a wide variety of clinical manifestations due to the presence of multiple arteriovenous manifestations. Severe bleeding from the gastrointestinal (GI) tract and/or epistaxis presents a significant problem in a subgroup of patients and systemic bevacizumab, an angiogenesis inhibitor, has been suggested to benefit these patients.

OBJECTIVE:

To perform a review of the literature concerning the efficacy of systemic bevacizumab in treatment of bleeding from the nose or GI tract in patients with HHT, including patients from our own HHT-center.

METHODS:

A literature review was performed using the guideline “Preferred Reporting Items for systematic Reviews and MetaAnalysis statement” (PRISMA).

RESULTS:

After careful selection, we finally analysed the results of eight case series and 33 case reports. Among 195 patients 171 (88%) had reduced bleeding after bevacizumab.

CONCLUSIONS:

Based on the literature review and data from our own case series, systemic bevacizumab is very promising as treatment for HHT patients with severe epistaxis and/or GI-bleeding.
However, care should be taken using bevacizumab, a potent angiogenesis inhibitor; long-term side effects have not been studied in this population. A randomized controlled study is warranted to support the results in HHT patients.

**Injection of bevacizumab and cyanoacrylate glue for hereditary hemorrhagic telangiectasia**

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First published: 27 February 2019

[https://doi.org/10.1002/lary.27889](https://doi.org/10.1002/lary.27889)

**Abstract**

**Objectives/Hypothesis**

The objective of this study was to report for the first time on the results of submucosal injections of bevacizumab used in conjunction with cyanoacrylate glue sclerotherapy in hereditary hemorrhagic telangiectasia (HHT).

**Study Design**

Retrospective analytic chart review.

**Methods**

We performed a chart review that included all patients with HHT treated with intranasal bevacizumab and cyanoacrylate glue for refractory epistaxis at Lariboisiere University Hospital from 2013 with a minimum follow-up of 6 months. We injected 100 mg (25 mg/mL) of bevacizumab diluted in 2 mL of serum at the base of the telangiectasias, and sclerotherapy with an injection of cyanoacrylate glue was used adjunctively. Treatment efficacy was based on changes in Epistaxis Severity Scores (ESS) and the Bergler-Sadick Scale. Quality of life and patient satisfaction were evaluated using the Cantril Self-Anchorining Ladder (CL) and Likert scale, respectively.

**Results**

Thirty-one patients were included, with a mean follow-up of 26.6 months. The average ESS score significantly decreased from 7.82 to 3.89 (P < .05). The Bergler-Sadick score significantly improved (P < .05) following the treatment, including the frequency (from 2.74 to 1.64) and the quantity (from 2.54 to 1.51) scales. Quality of life was significantly improved (P < .05) using the CL score (from 4.16 to 7.22). The Likert satisfaction scale related to the treatment efficacy was high, with an average of 7.03 out of 10. No complications were noted.

**Conclusions**
Submucosal injections of bevacizumab in conjunction with cyanoacrylate glue sclerotherapy significantly reduced epistaxis and improved the quality of life in HHT. Prospective comparative studies are needed to further evaluate the significance of this treatment modality.

Level of Evidence

3b Laryngoscope, 2019


Recurrence of Hereditary Hemorrhagic Telangiectasia After Liver Transplantation: Clinical Implications and Physiopathological Insights.


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Abstract

Liver transplantation (LT) has been proposed as a curative treatment in hereditary hemorrhagic telangiectasia (HHT) with severe hepatic involvement. We provide a long-term evaluation of graft status after LT for HHT, with a focus on the risk of recurrence. The present study included all patients prospectively followed up after LT for HHT in the Lyon Liver Transplant Unit from 1993 to 2010, with a survival of more than 1 year. Protocol clinical, radiological, and histological examinations were performed at regular intervals.
Fourteen patients were included (13 women and one man). Median age at LT was 52.5 years (range: 33.1-66.7). In eight patients (seven female), disease recurrence was diagnosed by abnormal radiological features, suggestive of microcirculatory disturbances. Typical vascular lesions, including telangiectasia, were demonstrated by liver biopsy in five of these patients. The median interval between LT and diagnosis of recurrence was 127 months (range: 74-184). The risk of recurrence increased over time; estimated cumulative risk was 47.9% at 15 years. Liver tissue analysis found the coexistence of an angiogenic process combined with endothelial microchimerism, as shown by the presence of vascular lining cells of recipient origin. Conclusion: The present data show that disease recurrence occurs, usually after a long delay, in a significant number of patients treated by LT for liver complications of HHT. This strongly supports the necessity of a lifelong follow-up and suggests that therapeutic strategy needs discussion and evaluation, especially of the role of potential adjuvant treatments to LT, such as antiangiogenic medications, when recurrent disease appears.

Similar articles


Identification of two distinct hereditary hemorrhagic telangiectasia patient subsets with different hepatic perfusion properties by combination of contrast-enhanced ultrasound (CEUS) with perfusion imaging quantification.

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Abstract

BACKGROUND:

Hereditary hemorrhagic telangiectasia (HHT) is marked by arteriovenous fusion comprising hepatic vascular malformations (HVaMs) with the chance of bleeding.

AIMS:
We investigated HVaMs in HHT patients by combination of contrast-enhanced ultrasound (CEUS) with perfusion imaging quantification to be able to sub-classify a high risk cohort of asymptomatic HHT patients.

METHODS:

The imaging characteristics on CEUS in 34 patients (aged 21-84 years; mean 58.9) with HHT were retrospectively evaluated. Real-time contrast harmonic imaging, sulfur hexafluoride-filled microbubbles and motion adjustment were utilized. Cine loops of the liver were digital stored, perfusion was quantified using a software reading DICOM data’s.

RESULTS:

HVaMs were diagnosed in 31 out of 34 patients. Significant uppermost peak enhancement (PE), wash-in area under the curve (WiAUC) and wash-in perfusion index (WiPI) were identified in the shunt region (100%), next in the hilar region (PE 32.6%; WiAUC 33.9%; WiPI 34.1%), and the lowest in the hepatic parenchyma (PE 10.2%; WiAUC 12.0%; WiPI 9.5%). The perfusion parameters in the shunt region compared to the other regions were significantly increased in one subgroup of patients. Consistent with this, the intrahepatic portal vein diameter and Buscarini grading was significantly higher, while portal vein peak velocity was significantly lower in this patient subset. By statistical analysis, we could correlate PE and WiPI to these clinical parameters, while WiAUC showed no clinical association.

CONCLUSIONS:

For the first time we combined CEUS findings with motion adjustment software to quantitative determine perfusion parameters of a cohort of HHT patients. Hereby, we could identify a subset of HHT patients with two markedly increased parameter values in the shunt region compared to the hilus/hepatic parenchyma. This could contribute to sub-classify a high-risk group of HHT patients with therapeutic indication.

Author information:


**Diagnostic yield of capsule endoscopy for small bowel arteriovenous malformations in patients with hereditary hemorrhagic telangiectasia: a systematic review and meta-analysis.**

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Abstract

**Background and study aims** Small bowel arteriovenous malformations (AVMs) pose a bleeding risk and have traditionally been diagnosed by invasive enteroscopic procedures in patients with hereditary hemorrhagic telangiectasia (HHT). Capsule endoscopy (CE) is emerging as a safe and non-invasive alternative for small intestinal evaluation, but its diagnostic yield and utility in diagnosing small bowel AVMs in HHT patients are understudied. The aim of this study was to meta-analyze the utility of CE for diagnosing AVMs in HHT patients. **Methods** A meta-analysis and systematic review of the literature on CE in HHT patients identified in the PubMed, EMBASE, Scopus, and Cochrane databases from inception to March 2018 were conducted. Summary effects were estimated using a random effects model. **Results** After applying exclusion criteria, five studies (n=124 patients) were eligible for meta-analysis. The pooled diagnostic yield for visualization of small bowel AVMs by CE was 77.0% (95% CI 65.8-85.4%, P<0.001). **Conclusions** CE has a good diagnostic yield for small bowel AVMs in HHT. It can be regarded as a sufficient, noninvasive diagnostic modality for identifying small bowel AVMs in HHT patients.

**Similar articles**


**Abdominal manifestations of hereditary hemorrhagic telangiectasia: a series of 333 patients over 15 years.**

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Abstract

PURPOSE:

Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant multi-organ vascular disorder that commonly affects the gastrointestinal tract and the liver resulting in telangiectasias and arteriovenous malformations (AVMs). Previous studies looking at the prevalence of liver and abdominal organ involvement in HHT have been limited by differing imaging techniques and sample size limitations. We sought to define the prevalence of HHT related abdominal vascular abnormalities using optimized multiphasic contrast-enhanced abdominal computed tomography (CT) exams in a large cohort of HHT patients.

METHODS:

Between January 2001 and May 2015; we identified a total of 333 consecutive HHT patients who had undergone a dedicated HHT protocol multiphase abdominal CT at our institution. The CT exams were reviewed by three board certified abdominal radiologists for the presence of vascular abnormalities involving the liver, pancreas, spleen, and other abdominal organs. Vascular abnormalities involving the liver were further categorized as telangiectasias, large confluent vascular masses, perfusion abnormalities, or hepatic shunts.

RESULTS:

In patients with abdominal vascular abnormalities, the liver was the most commonly involved organ, with 180 out of 333 (54.1%) patients demonstrating at least one hepatic vascular abnormality (telangiectasia, confluent vascular mass, transient perfusion abnormalities, and hepatic shunts), with most (70.0%) demonstrating multiple hepatic vascular abnormalities. The other most common organs involved included the pancreas (18.0%), spleen (6.3%), and small bowel (4.5%).

CONCLUSION:

In patients with the clinical diagnosis of HHT, greater than half demonstrate an abdominal vascular abnormality, with the most commonly involved organ being the liver. These may be under recognized on routine or single phase contrast-enhanced CT of the abdomen. This supports the use of optimized multiphasic abdominal CT exams as an important tool for the evaluation and screening of patients with HHT.

Similar articles

Long-Term Single-Center Retrospective Follow-Up After Embolization of Pulmonary Arteriovenous Malformations Treated Over a 20-year Period: Frequency of Re-canalization with Various Embolization Materials and Clinical Outcome.

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Abstract

PURPOSE:

The present study is a register-based observational study of an unselected consecutive patient cohort with pulmonary arteriovenous malformations (PAVMs) from a single national hereditary hemorrhagic telangiectasia and PAVM embolization center. The aim was to investigate the frequency of re-embolizations and the clinical outcome after embolization with the use of different embolization materials further, to define which PAVM morphology and size of feeding arteries that most often were re-embolized, and to estimate the clinical outcome of the patients including those that were re-embolized.

METHODS:

The population was included from 1996 until 2016 and was made up of a total of 136 patients with 322 PAVMs. Median follow-up was 38.3 (0.3-241 months).

RESULTS:

The re-embolization rate was 9.3%. None of the PAVMs treated with detachable silicone balloons were re-embolized, while 4.5% treated with vascular plugs and 11.7% treated with coils were re-embolized (p=0.07). In total, 16/74 complex PAVMs were re-embolized...
compared with 14/248 simple PAVMs. In big-sized feeding arteries ≥ 6mm, 16/112 were re-embolized compared with 14/210 with smaller-sized feeding arteries. Out of the 30 re-embolized PAVMs, 23 resulted in a successful clinical outcome.

CONCLUSIONS:

Our results suggest that standard coils probably should not be the first choice for embolization of PAVMs, and vascular plug alone or in combination with coils might be a better primary option for embolization in these patients.

LEVEL OF EVIDENCE:

Level 3A, non-randomized case controlled cohort/follow-up study.

Similar articles


Growth of Pulmonary Arteriovenous Malformations in Pediatric Patients with Hereditary Hemorrhagic Telangiectasia.

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Abstract

The evolution of pulmonary arteriovenous malformations (PAVMs) over time in children with hereditary hemorrhagic telangiectasia (HHT) is not well-defined. Herein we demonstrate that, although new PAVMs did not evolve in children with HHT, existing PAVMs exhibit quantitative growth over time highlighting the need for ongoing follow-up throughout childhood.
Retrospective Comparison of Pulmonary Arteriovenous Malformation Embolization with the Polytetrafluoroethylene-Covered Nitinol Microvascular Plug, AMPLATZER Plug, and Coils in Patients with Hereditary Hemorrhagic Telangiectasia.

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Abstract

PURPOSE:

To evaluate effectiveness of the polytetrafluoroethylene-covered nitinol mesh microvascular plug (MVP) and compare it with other devices in pulmonary arteriovenous malformation (PAVM) embolization in patients with hereditary hemorrhagic telangiectasia (HHT).

MATERIALS AND METHODS:

Twenty-five patients (average age 35 y; range, 15-56 y) with hereditary hemorrhagic telangiectasia (HHT) and de novo PAVM embolization with at least 1 MVP between November 2015 and May 2017 were retrospectively evaluated. Retrospective data were also obtained from prior embolization procedures in the same patient population with other embolic devices dating back to 2008. Technical success, complications, PAVM persistence rates, and category of persistence were analyzed.
RESULTS:

In 25 patients, 157 PAVMs were treated: 92 with MVP, 35 with AMPLATZER vascular plug (AVP), 6 with AVP plus coils, and 24 with coils. The per-PAVM technical success rates were 100% with MVP; 97%, AVP; 100%, AVP plus coils; and 100%, coils. PAVM persistence rates and median follow-up were as follows: MVP, 2% (1/92) (510 d); AVP, 15% (3/20) (1,447 d); AVP plus coils, 20% (1/5) (1,141 d); coils, 46.7% (7/15) (1,141 d). Persistence owing to recanalization for MVP, AVP, AVP plus coils, and coils was 2%, 15%, 0%, and 33%. No difference was found between persistence rates of MVP vs AVP (P = .098). Embolization with a vascular plug (MVP or AVP) with or without coils had a statistically significant lower persistence rate (5.4%) than embolization with coils alone (46.7%) (P = .022).

CONCLUSIONS:

PAVM embolization with MVP had a high technical success rate and a low persistence rate comparable to AVP and lower than coil embolization alone.


Prevention of serious infections in hereditary hemorrhagic telangiectasia: roles for prophylactic antibiotics, the pulmonary capillaries-but not vaccination.

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Localization and age distribution of telangiectases in children and adolescents with hereditary hemorrhagic telangiectasia: A retrospective cohort study.

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Abstract

BACKGROUND:

The location of telangiectases in hereditary hemorrhagic telangiectasia (HHT), as set forth in the consensus diagnostic (Curaçao) criteria, is based primarily on adults.

OBJECTIVE:

Document the locations and numbers of telangiectases in a cohort of pediatric patients with
HHT.

METHODS:

A retrospective chart review using a standardized data collection form for site and number of telangiectases was performed for pediatric patients with HHT (age, 0-18 years) from 2005 to 2016.

RESULTS:

Of 90 pediatric patients with HHT, 71% had one or more telangiectases. Of all the telangiectases counted (N = 319), cutaneous telangiectases were more common (73%) than oral telangiectases (27%). The hands were the most frequent site, accounting for 33% of all telangiectases. Adolescents were more likely than children to have cutaneous telangiectases (85% vs 50% [Q = 0.005]). The most frequent sites in children younger than 10 years were the hands excluding the fingers (27%), fingers (25%), and face (23%). Only 23% of subjects (21 of 90) presented with multiple (≥3) telangiectases at locations considered characteristic for the current consensus diagnosis guidelines (lips, oral cavity, and fingers).

LIMITATIONS:

Ascertained bias based on recruitment.

CONCLUSIONS:

In this pediatric population, telangiectases at sites not included as "characteristic" by the Curaçao diagnostic criteria were common. The Curaçao criteria in regard to both number and location of telangiectases may be inadequate in the pediatric HHT population.

Similar articles

Hospitalizations with hereditary hemorrhagic telangiectasia and pulmonary hypertension in the United States from 2000 to 2014.

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Abstract

BACKGROUND:

Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant disease that causes widespread abnormal vasculature development, resulting in multiple complications including pulmonary hypertension (PH). Despite the potential severity of PH, there is a lack of data on hospitalization characteristics and outcomes in the HHT-PH population. The purpose of this analysis was to describe trends and outcomes of HHT-PH hospitalizations within the National (Nationwide) Inpatient Sample (NIS).

METHODS:

Adult hospitalizations (age ≥18 years) with a principal or secondary diagnosis of HHT were identified from the 2000-2014 NIS. Records were stratified by a concurrent PH diagnosis. Trends, characteristics, and outcomes of hospitalizations with HHT and PH were analyzed.

RESULTS:

There were 55,189 adult hospitalizations with HHT from 2000 to 2014, of which 4602 (8.3%) had a concurrent diagnosis of PH. HHT-PH hospitalizations rose steadily from 165 (5.1%) in 2000 to 540 (13.8%) in 2014 (p < 0.001). They were more common in females (vs. HHT without PH, 71.6% vs. 59.2%, p < 0.001) and were associated with a higher comorbidity burden (total 4.0 ± 0.1 vs. 2.4 ± 0.03, p < 0.001). Inpatient mortality was higher in HHT-PH hospitalizations than in HHT without PH (3.5% vs. 1.8%, p < 0.001). On multivariable logistic regression, the diagnosis of PH remained significantly associated with a higher risk of inpatient death (odds ratio 1.71, 95% confidence interval 1.11-2.63, p = 0.015) in HHT hospitalizations.

CONCLUSIONS:

HHT-PH hospitalizations rose from 2000 to 2014. Notably, HHT patients with a concurrent PH diagnosis were at significantly higher risk of in-hospital mortality.

Similar articles


**Living with Hereditary Haemorrhagic Telangiectasia: stigma, coping with unpredictable symptoms, and self-advocacy.**

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Abstract

OBJECTIVE:

Hereditary Haemorrhagic Telangiectasia (HHT) is a genetic condition causing frequent nose bleeds, skin lesions (telangiectasia) and arteriovenous malformations. Approximately, 50% of people experience life-threatening HHT symptoms including haemorrhages in the brain, lungs and liver. This study aimed to gain a qualitative understanding of the psychosocial impact of HHT over time.

DESIGN:

Using a phenomenological framework, a rigorous narrative analysis was performed on 20 semi-structured interviews with individuals with HHT aged 20s-60s.

MAIN OUTCOME MEASURES:

Qualitative themes explaining life experiences prior to and following a clinical diagnosis of HHT.

RESULTS:

Narratives highlighted four psychosocial themes: (i) the psychological impact of visible symptoms was significant and related to experiences of social stigma, (ii) individuals struggled to identify triggers of symptoms in order to reduce unpredictability, (iii) an illness identity was rejected by minimising HHT when talking about the present self, and by positive reframing as 'lucky' and (iv) self-advocacy was necessitated due to lack of expert coordinated care.

CONCLUSION:

HHT has a demanding impact on social, physical and psychological well-being. These findings have significant implications for health care, as narratives about interactions with health professionals often used the terms 'frustrating' and 'not being heard'.

PMID: 30931645

Similar articles


Identification of Retinal Vascular Lesions Using Ultra-Widefield Angiography in
Hereditary Hemorrhagic Telangiectasia Patients.

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Abstract

PURPOSE:
To determine the presence and to characterize location of retinal vascular lesions in patients with hereditary hemorrhagic telangiectasia (HHT).

DESIGN:
Prospective cross-sectional pilot descriptive study.

PARTICIPANTS:
Eighteen patients (age range, 22-65 years) with a clinical diagnosis of HHT.

METHODS:
Patients completed the 25-item National Eye Institute Visual Function Questionnaire and underwent a single study visit with dilated ophthalmic examination, OCT angiography (OCTA), and fluorescein angiography (FA) with widefield imaging.

MAIN OUTCOME MEASURES:
Presence of retinal vascular abnormalities in 1 or more quadrants identified on widefield FA, Visual Function Questionnaire scores, retinal vessel architecture on FA and OCTA, and dilated ophthalmic examination findings.

RESULTS:
Of the 18 patients recruited, fine telangiectatic vessels with capillary dilation and tortuosity were identified in 78% by FA imaging.
CONCLUSIONS:

In the first FA and OCTA analysis of the retina of unrelated HHT patients, we found a high rate of temporal and nasal telangiectasias. These telangiectasias were more apparent in older patients, suggesting that they may appear in later stages of HHT development. No abnormalities of the macular vasculature and architecture were identified, explaining the generally well-preserved visual acuity. Temporal and nasal telangiectasias may have clinical significance in a patient's risk for retinal hemorrhage and likely warrant periodic surveillance by annual FA imaging.

Benefits of Treating Arteriovenous Malformations in Hereditary Hemorrhagic Telangiectasia: A Retrospective Analysis of 14 Patients

M. Neil Woodall, Peter Nakaji, Robert F. Spetzler

Background

Arteriovenous malformations (AVMs) are a cardinal feature of hereditary hemorrhagic telangiectasia (HHT). However, whether to treat brain AVMs in patients with HHT remains questionable because of the possible risks.

Methods

We performed a retrospective study of patients with HHT who had been treated for brain AVMs at our institution from January 1, 2003, to December 31, 2016. An institutional database was queried for the phrases “hereditary hemorrhagic telangiectasia” and “HHT,” and those patients who had been treated during the study period were identified. Data were extracted regarding presentation, AVM characteristics, treatment modality, and treatment outcomes.

Results

We identified 14 patients (10 males, 4 females) with HHT who had had AVMs ($n = 27$) from the institutional database. The mean age of the patients was 43 years (range, 2–64). Of the 27 brain AVMs, 13 were Spetzler-Martin grade I, 12 were grade II, and 2 were grade III; none were grade IV or V. Treatment was by microsurgery only (11 AVMs in 10 patients), embolization followed by microsurgery (2 AVMs in 2 patients), and radiosurgery only (12 AVMs in 2 patients). AVM obliteration was achieved in 100% of the patients. No new fixed neurologic deficits developed after treatment of unruptured HHT AVMs.

Conclusions
The risk of treatment of brain AVMs in patients with HHT is quite low for appropriately selected patients with treatment individualized to radiosurgery, microsurgery, or a combination of embolization and microsurgery.

**Molecular Biology**


**Angiopoietin-2 Inhibition Rescues Arteriovenous Malformation in a Smad4 Hereditary Hemorrhagic Telangiectasia Mouse Model.**

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Abstract

**BACKGROUND:**

Hereditary hemorrhagic telangiectasia is an autosomal dominant vascular disorder caused by heterozygous, loss-of-function mutations in 4 transforming growth factor beta (TGFβ) pathway members, including the central transcriptional mediator of the TGFβ pathway, Smad4. Loss of Smad4 causes the formation of inappropriate, fragile connections between arteries and veins called arteriovenous malformations (AVMs), which can hemorrhage leading to stroke, aneurysm, or death. Unfortunately, the molecular mechanisms underlying AVM pathogenesis remain poorly understood, and the TGFβ downstream effectors responsible for hereditary hemorrhagic telangiectasia-associated AVM formation are currently unknown.

**METHODS:**

To identify potential biological targets of the TGFβ pathway involved in AVM formation, we performed RNA- and chromatin immunoprecipitation-sequencing experiments on BMP9 (bone morphogenetic protein 9)-stimulated endothelial cells (ECs) and isolated ECs from a Smad4-inducible, EC-specific knockout (Smad4-iECKO) mouse model that
develops retinal AVMs. These sequencing studies identified the angiopoietin-Tek signaling pathway as a downstream target of SMAD4. We used monoclonal blocking antibodies to target a specific component in this pathway and assess its effects on AVM development.

RESULTS:

Sequencing studies uncovered 212 potential biological targets involved in AVM formation, including the EC surface receptor, TEK (TEK receptor tyrosine kinase) and its antagonistic ligand, ANGPT2 (angiopoietin-2). In Smad4-iECKO mice, Angpt2 expression is robustly increased, whereas Tek levels are decreased, resulting in an overall reduction in angiopoietin-Tek signaling. We provide evidence that SMAD4 directly represses Angpt2 transcription in ECs. Inhibition of ANGPT2 function in Smad4-deficient mice, either before or after AVMs form, prevents and alleviates AVM formation and normalizes vessel diameters. These rescue effects are attributed to a reversion in EC morphological changes, such as cell size and shape that are altered in the absence of Smad4.

CONCLUSIONS:

Our studies provide a novel mechanism whereby the loss of Smad4 causes increased Angpt2 transcription in ECs leading to AVM formation, increased blood vessel calibers, and changes in EC morphology in the retina. Blockade of ANGPT2 function in an in vivo Smad4 model of hereditary hemorrhagic telangiectasia alleviated these vascular phenotypes, further implicating ANGPT2 as an important TGFβ downstream mediator of AVM formation. Therefore, alternative approaches that target ANGPT2 function may have therapeutic value for the alleviation of hereditary hemorrhagic telangiectasia symptoms, such as AVMs.

Similar articles


Activin Receptor-Like Kinase 1 Combined With VEGF-A Affects Migration and Proliferation of Endothelial Cells From Sporadic Human Cerebral AVMs.

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Abstract

Heterozygous loss of activin receptor-like kinase 1 (Alk1) can lead to hereditary hemorrhagic telangiectasia (HHT), which is a kind of vascular disease characterized by direct connections between arteries and veins with the lacking of capillaries, and develops into arteriovenous malformations (AVMs) in later stage. However, the changes of Alk1 in human sporadic cerebral AVMs (cAVMs) remain unknown. In the present study, we used endothelial cells (ECs) derived from human cAVMs (cAVM-ECs) specimens, to explore the characteristics of cAVM-ECs and the relationship between Alk1 and human sporadic cAVMs. Our data showed that there were obvious morphological changes in cAVM-ECs, and they could trans-differentiate into mesenchyme-like cells easily in a short period. In addition, the abilities of migration of cAVM-ECs were poorer than that in human aortic endothelial cells (HA-ECs). The abilities of proliferation of cAVM-ECs in patients with different ages were lower than HA-ECs. Immunofluorescent staining and Western blot showed that the levels of Alk1 mRNA and protein in the HA-ECs were both higher than that in cAVM-ECs. In addition, the levels of Alk1 mRNA had no significant differences between different ages in cAVM-ECs groups. The levels of VEGF-A mRNA in the cAVM were higher than HA-ECs. Besides, levels of VEGF-A mRNA expression were lower in older cAVM patients. Therefore, we conclude that Alk1 might induce the formation of sporadic human cAVMs through affecting migration and proliferation of endothelial cells combined with VEGF-A.

Similar articles


Deregulation of Drosha in the pathogenesis of hereditary hemorrhagic telangiectasia.

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Abstract
PURPOSE OF REVIEW:

The TGFβ (transforming growth factor β) superfamily - a large group of structurally related and evolutionarily conserved proteins - profoundly shapes and organizes the vasculature during normal development and adult homeostasis. Mutations inactivating several of its ligands, receptors, or signal transducers set off hereditary hemorrhagic telangiectasia (HHT), a disorder that causes capillary networks to form incorrectly. Drosha, an essential microRNA-processing enzyme, also interfaces with TGFβ signal transducers, but its involvement in vascular conditions had not been tested until recently. This review summarizes current evidence that links mutations of Drosha to HHT.

RECENT FINDINGS:

Genetic studies have revealed that rare missense mutations in the Drosha gene occur more commonly among HHT patients than in healthy people. Molecular analyses also indicated that Drosha enzymes with HHT-associated mutations generate microRNAs less efficiently than their wild-type counterpart when stimulated by TGFβ ligands. In zebrafish or mouse, mutant Drosha proteins cause the formation of dilated, leaky blood vessels deprived of capillaries, similar to those typically found in patients with HHT.

SUMMARY:

Recent evidence suggests that Drosha-mediated microRNA biogenesis contributes significantly to the control of vascular development and homeostasis by TGFβ. Loss or reduction of Drosha function may predispose carriers to HHT and possibly other vascular diseases.


**Loss-of-Function in SMAD4 Might Not Be Critical for Human Natural Killer Cell Responsiveness to TGF-β.**

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Abstract

We characterized the NK cell phenotype and function in three family members with Hereditary Hemorrhagic Telangiectasia (HHT) due to heterozygous SMAD4 mutations. Loss-of-function mutation in this gene did not induce developmental effects to alter CD56<sup>bright</sup> or CD56<sup>dim</sup> NK cell subset proportions in peripheral blood; and did not result in major differences in either their IL-15-induced proliferation, or their cytokine secretion response to TGF-β1. These data suggest that SMAD4 plays a redundant role in downstream TGF-β signaling in NK cells.

Characterization of a family mutation in the 5' untranslated region of the endoglin gene causative of hereditary hemorrhagic telangiectasia.

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Abstract

Hereditary hemorrhagic telangiectasia (HHT) is a vascular disease characterized by nose and gastrointestinal bleeding, telangiectases in skin and mucosa, and arteriovenous malformations in major internal organs. Most patients carry a mutation in the coding region of the endoglin (ENG) or activin A receptor type II-1 (ACVRL1) gene. Nonetheless, in around 15% of patients, sequencing analysis and duplication/deletion tests fail to pinpoint mutations in the coding regions of these genes. In these cases, it has been shown that sequencing of the 5′-untranslated region (5′UTR) of ENG may be useful to identify novel mutations in the ENG non-coding region. Here we report the genetic characterization and functional analysis of the heterozygous mutation c.-142A>T in the 5′UTR region of ENG found in a family with several members affected by HHT. This variant gives rise to a new initiation codon of the protein that involves the change in its open reading frame. Transfection studies in monkey cells using endogl in expression vectors demonstrated that c.-142A>T mutation results in a clear reduction in the levels of the endoglin protein. These results support the inclusion of the 5′UTR of ENG in the standard genetic testing for HHT to increase its sensitivity.

Similar articles


Decreased Expression of Vascular Endothelial Growth Factor Receptor 1 Contributes to the Pathogenesis of Hereditary Hemorrhagic Telangiectasia Type 2.

Thalgott JH1, Dos-Santos-Luis D2,3, Hosman AE4, Martin S2,3, Lamandé N2,3, Bracquart D2,3, Srun S2,3, Galair G1, de Boer HC1, Tual-Chalot S5, Kroon S4, Arthur HM5, Cao Y6, Snijder RJ6, Disch F4, Mager JJ4, Rabelink TJ4, Mummery CL7, Raymond K1,8, Lebrin F1,2,3,9.

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6. Department of Microbiology, Tumor and cell Biology, Karolinska Institute, Stockholm,
Abstract

BACKGROUND:

Hereditary Hemorrhagic Telangiectasia type 2 (HHT2) is an inherited genetic disorder characterized by vascular malformations and hemorrhage. HHT2 results from ACVRL1 haploinsufficiency, the remaining wild-type allele being unable to contribute sufficient protein to sustain endothelial cell function. Blood vessels function normally but are prone to respond to angiogenic stimuli, leading to the development of telangiectasic lesions that can bleed. How ACVRL1 haploinsufficiency leads to pathological angiogenesis is unknown.

METHODS:

We took advantage of Acvrl1+/− mutant mice that exhibit HHT2 vascular lesions and focused on the neonatal retina and the airway system after Mycoplasma pulmonis infection, as physiological and pathological models of angiogenesis, respectively. We elucidated underlying disease mechanisms in vitro by generating Acvrl1+/− mouse embryonic stem cell lines that underwent sprouting angiogenesis and performed genetic complementation experiments. Finally, HHT2 plasma samples and skin biopsies were analyzed to determine whether the mechanisms evident in mice are conserved in humans.

RESULTS:

Acvrl1+/− retinas at postnatal day 7 showed excessive angiogenesis and numerous endothelial "tip cells" at the vascular front that displayed migratory defects. Vascular endothelial growth factor receptor 1 (VEGFR1; Flt-1) levels were reduced in Acvrl1+/− mice and HHT2 patients, suggesting similar mechanisms in humans. In sprouting angiogenesis, VEGFR1 is expressed in stalk cells to inhibit VEGFR2 (Flk-1, KDR) signaling and thus limit tip cell formation. Soluble VEGFR1 (sVEGFR1) is also secreted, creating a VEGF gradient that promotes orientated sprout migration. Acvrl1+/− embryonic stem cell lines recapitulated the vascular anomalies in Acvrl1+/− (HHT2) mice. Genetic insertion of either the membrane or soluble form of VEGFR1 into the ROSA26 locus of Acvrl1+/− embryonic stem cell lines prevented the vascular anomalies, suggesting that high VEGFR2 activity in Acvrl1+/− endothelial cells induces HHT2 vascular anomalies. To confirm our hypothesis, Acvrl1+/− mice were infected by Mycoplasma pulmonis to induce sustained airway inflammation. Infected Acvrl1+/− tracheas showed excessive angiogenesis with the formation of multiple telangiectases, vascular defects that were prevented by VEGFR2 blocking antibodies.

CONCLUSIONS:

Our findings demonstrate a key role of VEGFR1 in HHT2 pathogenesis and provide mechanisms explaining why HHT2 blood vessels respond abnormally to angiogenic signals.
This supports the case for using anti-VEGF therapy in HHT2.


**Phenotype of CM-AVM2 caused by variants in EPHB4: how much overlap with hereditary hemorrhagic telangiectasia (HHT)?**

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15. Department of Pathology, University of Utah, Salt Lake City, UT, USA.
16. Department of Radiology, HHT Center, University of Utah, Salt Lake City, UT, USA.
Abstract

PURPOSE:

EPHB4 variants were recently reported to cause capillary malformation-arteriovenous malformation 2 (CM-AVM2). CM-AVM2 mimics RASA1-related CM-AVM1 and hereditary hemorrhagic telangiectasia (HHT), as clinical features include capillary malformations (CMs), telangiectasia, and arteriovenous malformations (AVMs). Epistaxis, another clinical feature that overlaps with HHT, was reported in several cases. Based on the clinical overlap of CM-AVM2 and HHT, we hypothesized that patients considered clinically suspicious for HHT with no variant detected in an HHT gene (ENG, ACVRL1, or SMAD4) may have an EPHB4 variant.

METHODS:

Exome sequencing or a next-generation sequencing panel including EPHB4 was performed on individuals with previously negative molecular genetic testing for the HHT genes and/or RASA1.

RESULTS:

An EPHB4 variant was identified in ten unrelated cases. Seven cases had a pathogenic EPHB4 variant, including one with mosaicism. Three cases had an EPHB4 variant of uncertain significance. The majority had epistaxis (6/10 cases) and telangiectasia (8/10 cases), as well as CMs. Two of ten cases had a central nervous system AVM.

CONCLUSIONS:

Our results emphasize the importance of considering CM-AVM2 as part of the clinical differential for HHT and other vascular malformation syndromes. Yet, these cases highlight significant differences in the cutaneous presentations of CM-AVM2 versus HHT.

PMID: 30760892

Similar articles


Endoglin is a conserved regulator of vasculogenesis in zebrafish - implications for hereditary haemorrhagic telangiectasia.

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Abstract

Hereditary haemorrhagic telangiectasia (HHT) is a progressive vascular disease with high mortality and prevalence. There is no effective treatment of HHT due to the lack of comprehensive knowledge of its underlying pathological mechanisms. The majority of HHT1 patients carry endoglin (ENG) mutations. Here, we used Danio rerio (zebrafish) as an in vivo model to investigate the effects of endoglin knockdown on vascular development. According to phylogenetic analyses and amino acid sequence similarity analyses, we confirmed that endoglin is conserved in vertebrates and descended from a single common ancestor. Endoglin is highly expressed in the vasculature beginning at the segmentation period in zebrafish. Upon endoglin knockdown by morpholinos, we observed disruption in the intersegmental vessels (ISVs) and decreased expression of several vascular markers. RNA sequencing (RNA-Seq) results implied that the BMP-binding endothelial regulator (bmper) is a gene affected by endoglin knockdown. Rescue experiments demonstrated that overexpression of bmper significantly increased the number of endothelial cells (ECs) and reduced the defects at ISVs in zebrafish. Moreover, there was enhanced tube formation in ENG mutant ECs derived from a HHT patient after human recombinant BMPER (hrBMPER) stimulation. Taken together, our results suggest that bmper, a potential downstream gene of ENG, could be targeted to improve vascular integrity in HHT.

CASE REPORT


Borovac-Pinheiro A1, Cavichioli FS1, Costa ML1, Surita FG1.
Hereditary Hemorrhagic Telangiectasia.

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Dyspnea and Near Syncope in a Young Female Following Delivery.

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Significant Hematochezia and Intracranial Bleeding in Neonatal Hereditary Hemorrhagic Telangiectasia.

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Abstract

Hereditary hemorrhagic telangiectasia (HHT) is an underreported autosomal dominant vascular dysplasia. Neonatal presentations of HHT are rare, as this disorder typically presents in adolescence or beyond with epistaxis. We report a female neonate with hematochezia on the 1st day of life secondary to multiple gastrointestinal arteriovenous malformations (AVMs) along with intracranial hemorrhage. We describe her clinical course and management, as well as her novel family mutation in ENG. This is the first reported HHT case with significant gastrointestinal bleeding in the newborn. We review neonatal HHT and raise the consideration for more directed prenatal imaging and delivery options for fetuses at high risk of HHT.

Lactulose to the Rescue: A Case of Toxic Hepatic Encephalopathy Caused by Portosystemic Shunting and Epistaxis in a Patient with Hereditary Hemorrhagic Telangiectasia.

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Abstract

Hereditary hemorrhagic telangiectasia (HHT) is an uncommon autosomal dominant disorder characterized by telangiectasias and arteriovenous malformations. Multiple organ systems are involved including the skin, lungs, gastrointestinal tract, and brain. Hepatic encephalopathy is an extremely rare complication of HHT and early diagnosis and treatment can be life-saving. We present a rare case of hepatic encephalopathy caused by HHT-induced portosystemic shunting treated with lactulose.