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Alvaro E. Galvis*

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Case Report

Diagnosis of hereditary hemorrhagic telangiectasia in a pediatric patient admitted with diabetes: the utility of genetic testing

Beatrice Batoczki [1], Alvaro E. Galvis[1,2,3*], Iris S. Pecson [1], Evan Vidal[2], and Craig T. Nakamura [1]

[1] Children´s Lung Specialists Las Vegas, Nevada, USA

[2] Children´s Hospital of Orange County, Department of Infectious Diseases, USA.

[3] University of California, Irvine. School of Medicine. Irvine, California, USA.

***Correspondence Author:** Alvaro E. Galvis MD, PhD. Children´s Hospital of Orange County, Department of Infectious Diseases 1201 W. Veta Ave. Orange, CA 92868, USA

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Abstract

Background: Hereditary hemorrhagic telangiectasia (HHT) formerly known as Osler-Weber-Rendu syndrome is a rare autosomal dominant disorder characterized by vascular dysplasia and a wide spectrum of clinical manifestations.

Case presentation: We report the case of an undiagnosed pediatric patient who presented hypoxemia on clinical exam as the only suggestive feature for the presence of HHT.

Conclusions: Although HHT diagnosis is based on the finding of characteristic clinical features genetic testing should also be implemented when a family history of the disease is present to help confirm or refute the diagnosis.

Keywords: hereditary hemorrhagic telangiectasia; osler-weber-rendu syndrome; dominant disorder

Background

Hereditary hemorrhagic telangiectasia (HHT), formerly known as Osler-Weber-Rendu syndrome is a rare vascular disorder with an autosomal dominant (AD) inheritance, characterized by vascular dysfunction and a broad spectrum of clinical manifestations. Its incidence ranges from 1/5000 to 1/8000 [1,2].

Mucocutaneous telangiectasias are a typical feature of the condition. These are more frequently found in the oral and nasal cavities, being the latter responsible for epistaxis, the primary symptom of HHT. Gastrointestinal telangiectasias are oftentimes also common, causing bleeding which can result in iron deficiency anemia. More severe complications such as hemorrhage or stroke are generally caused by arteriovenous malformations (AVMs) mainly in the brain, lung, and liver [3,4,5].

HHT diagnosis is typically made by the finding of the characteristic clinical features of the entity; however molecular diagnostics can be used to confirm its presence, establish the subtype of HHT and for early diagnosis in relatives who are at genetic risk, allowing the establishment of appropriate treatment; reducing in such way the morbidity and mortality of the disease [6].

Case report

The patient is a 9-year old female that presented to the clinic for evaluation of polydipsia and polyuria over the course of three weeks as well as significant unintentional weight loss. Twenty four hours prior to the visit the patient complained of decreased energy, malaise and displayed labored breathing. A capillary glucose test was performed reporting a critical range high limit; oxygen saturation ranged from 84-88%. She was transferred to the pediatric ER. The initial laboratory workup showed a pH of 7.07, glucose 535 mg/dL. The diagnosis of diabetic ketoacidosis was established, fluid resuscitation was started and the patient was later transferred to the PICU to continue proper management.

Due to low oxygen saturation, a CT angiogram of the chest was performed revealing multiple pulmonary arteriovenous malformations (AVMs) being the largest situated on the left upper lobe measuring 18x14x13 mm.

The patient was born at 34 weeks gestation and had a 3-week stay in the NICU.

PMH was significant for one episode of lightheadedness one year before diagnosis, being referred at the time to the cardiology clinic for evaluation without findings of structural abnormalities.

FH was remarkable for HHT in father and paternal uncle; type 2 diabetes mellitus in the maternal side of the family and epistaxis in brother and sister.

Discussion

HHT originates due to gene coding mutations, with three genes being responsible for up to 85% of clinical cases: 1) HHT type 1 mutation of

ENG coding for endoglin, 2) HHT type 2 mutation of ACVRL1 coding for activin receptor-like kinase (ALK) and 3) the combined disorder of juvenile polyposis/HHT mutation in MADH4 that codes for transcription factor SMAD4. All of the above mutations are involved in the encoded proteins which mediate the transforming growth factor-beta superfamily signaling, resulting in an impairment of blood vessel formation and/or an imbalance in proangiogenic and antiangiogenic factors [4].

The diagnosis of HHT is based on the Curacao criteria: recurrent and spontaneous nosebleeds; mucocutaneous telangiectasias at fingertips, lips, oral mucosa or tongue; visceral AVMs (gastrointestinal, pulmonary, hepatic, cerebral, or spinal), and first-degree family history of HHT. If three or more of these features are met, an HHT diagnosis can be made and genetic testing for confirmation is justified [4]. However current recommendations advise that genetic testing may also be used in asymptomatic children with an affected parent to confirm or reject diagnosis [6].

Epistaxis is the most common sign in HHT, about 95% of diagnosed individuals will eventually present recurrent epistaxis. The average age of onset is 12 years and the frequency in affected individuals ranges from several episodes per year to several per day with intensity going from a couple of drops to exaggerated bleeding.

Telangiectasias of the face, oral cavity and hands also present in approximately 95% of HHT patients, with punctuate or macular character and are generally recognized later than epistaxis [6].

Bleeding of gastrointestinal telangiectasias usually begins after the age of 50-years-old in around one-quarter of patients diagnosed with HHT and has a slow and persistent character increasing its severity over time may leading to iron deficiency anemia [3,6].

Pulmonary arteriovenous malformations (PAVMs) pose a risk for the occurrence of cerebrovascular ischemia or cerebral abscess formation due to serving as a potential passage for paradoxical embolism. Besides, PAVMs serve as a physiological right to left shunt resulting in the possibility of patients presenting high output heart failure, dyspnea, platypnea and/or secondary polycythemia. The inherent friability of the abnormal vasculature can lead to PAVMs to increase in size or hemorrhage giving rise to hemoptysis and hemothorax [3].

Approximately 90% of patients with PAVMs suffer from HHT in contrast; only around 30 to 50% of HHT patients will present PAVMs. PAVMs generally manifest around the fifth decade of life and clinical signs or symptoms tend to be absent before the presence of complications [3].

Mortality or significant morbidity as a consequence of stroke or cerebral abscess formation has been estimated to be around 23% in patients with untreated PAVMs over a mean follow-up period of 4.5 to 10 years. The risk for cerebral complications is regularly regarded as significant when the feeding artery of the PAVM exceeds 3mm in diameter and may increase in the presence of multiple PAVMs. Over two-third of neurological manifestations in HHT are associated to PAVMs, while the remaining one third is related to cerebral or spinal AVMs that may result in subarachnoid hemorrhage or seizures; hence screening for PAVMs in asymptomatic HHT patients and establishment of treatment when the diameter of the feeding vessel exceeds 3 mm is warranted [3,5,6].

Hepatic abnormalities can present in up to 74% of patients diagnosed with HHT but only around 8% of affected individuals will exhibit symptoms [6].

It is important to discern between lesions that require a symptomatically/expectant approach and those that should be treated even in asymptomatic affected individuals. Usually, telangiectasias of the skin, oral and gastrointestinal mucosa, and liver should be treated when symptoms appear; in contrast AVMs of the brain and lungs usually receive treatment in asymptomatic patients considering their sudden rise and the significant morbidity and mortality related to them [6].

The use of humidifiers and moisturizer application to the nasal mucosa can help reduce the severity of epistaxis [4]. However, interventions such as laser ablation should be taken into consideration in the presence of anemia related to epistaxis or when the latter interferes with normal activities. In more severe cases surgical treatment would be warranted. Estrogen-progesterone at doses used for oral contraception and other agents such as bevacizumab and thalidomide have proved to reduce epistaxis, however further studies are necessary.

GI tract treatment will only be required when aggressive iron therapy fails to maintain hemoglobin in its normal range. In such cases, lesions can be treated with endoscopic application heater probe, bicap or laser.

Mild to severe iron deficiency anemia can present even with optimal treatment of epistaxis and GI lesions. Iron replacement therapy including parenteral delivery when needed is the preferred treatment approach. The target ferritin level in HHT patients who suffer from chronic anemia should remain between 50-100 ng/mL [6].

Percutaneous image-guided embolotherapy is the recommended treatment for all adults and symptomatic children to avoid complications derived from PAVMs. A follow-up CT should be done 6-12 months post-occlusion and if no reperfusion or new PAVMs are noted follow-up is recommended at 5-year intervals [3,6].

Cerebral AVMs larger than one centimeter can be treated using surgery, embolotherapy or stereotactic radiosurgery [6].

In most patients with symptomatic hepatic involvement, intensive medical therapy will be enough to manage high output cardiac failure secondary hepatocyte dysfunction and the hepatic involvement, nevertheless, in those individuals who do not respond to medical management, liver transplant is the standard therapy [6].

This report seeks to emphasize the importance of the medical history as an instrument to help healthcare providers to identify and establish proper management of diseases.

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