# Rendu-Osler-Weber Syndrome or Hereditary Hemorrhagic Telangiectasia (HHT): Report of two cases and review of literature

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**ABSTRACT**

Rendu-Osler-Weber syndrome, also known as __Hereditary Hemorrhagic Telangiectasia (HHT), is a vascular disorder with a prevalence estimated in one in 5-8.000 individuals. It is a dominant autosomic transmission determining multisystemic vascular dysplasia, which has been mapped to two genes, HHT1 and HHT2, determined by mutations of the endoglin (ENG) gene, localized to the chromosome 9, and by mutations of the activin receptor-like kinase 1 (ALK1) gene, localized on the chromosome 12. The 95% of affected present recurrent epistaxis, with a mean age of first event at about 12 years, generally the nosebleed frequency and severity increase with age and usually it is associated with pulmonary AVM and/or multiple telangiectases of gastrointestinal apparatus, of the hands, face, and oral cavity and others visceral involvement.
The first diagnosis of HHT is still based on the presence of clinical signs and family history; for the molecular diagnosis of HHT is necessary sequencing the entire coding regions of the ALK1 and ENG genes.
The genetic test is positive not in the 100% of all patients with clinical diagnosis of HHT, but it is also possible not find in the same family group the common mutation.
We review the litterature and report 2 cases with oral manifestation, on the tongue and on the inferior lip, without others systemic HHT lesions, treated in our Department for general odontoiatric problems.

**Key words:** Rendu-Osler-Weber syndrome. Hereditary Hemorrhagic Telangiectasia (HHT). Multisystemic vascular dysplasia. Arteriovenous malformations.

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## INTRODUCTION

Rendu-Osler-Weber syndrome, also known as Hereditary Hemorrhagic Telangiectasia (HHT), is a vascular disorder characterized by telangiectases and arteriovenous malformations (AVM), direct artery-to-vein connections predisposing to shunting and hemorrhage.

It is an autosomal dominant multisystemic vascular

dysplasia. Two genes, HHT1 and HHT2, are involved in its pathogenesis and determine two different forms of the same disease.

HHT1 is caused by mutations of the endoglin (*ENG*) gene, localized to the long arm of chromosome 9 (9q33-q34.1) (1, 2), while HHT2 is caused by mutations of the activin receptor-like kinase 1 (*ALK1*) gene, localized on the long arm of chromosome 12 (12q11-q14) (3).

We report 2 cases with oral manifestation, on the tongue and on the inferior lip, without others systemic HHT lesions.

## MATERIALS AND METHODS

Two patients affected by HHT, one male and one female, referred to our Institute (Fig. 1, 2). They were 57 and 49 years old, and are the first case of HHT in their family group. Clinical records, diagnostic parameters, treatment as well as follow-up data of these two patients were evaluated.

The diagnostic parameters taken in consideration, for a general screening, were: contrast echocardiography to screen for intrapulmonary shunts (29), computed tomography, imaging resonance of the brain, auscultation and ultrasound exams for a hepatic assessment. All the patients were diagnosed of HHT1 and HHT2 disease by molecular diagnosis.

The first case reported concern a female patient, 57 years old, with 3 necrotic roots. She had diagnosis of HHT1 by molecular analysis not many years before but the clinical diagnosis were supposed when the patient were 19 years old. The only one HHT manifestation with the epistaxis (15 times for each month) were in the oral cavity, especially on the tongue; in fact all the instrumental research for a systemic manifestation was not confirmed. She were the first case in her family with this kind of pathology, excluding one parent that live in other country.

The second case reported is a man, 49 years old, with the tooth 2.8 in dysodontiasis. He had diagnosis of HHT2 by molecular analysis recently, but in this case too there were clinical diagnosis 30 years ago. The epistaxis were present 18 times for month, while the principal manifestation were on the inferior lip. There were no others signs of HHT confirmed by the instrumental analysis. He was the first time that the pathology appears in his family.

To extract the necrotic roots and the 28 we perform an antibiotics prophylaxis using amoxicillin, with a dosage of 2 grams/day for 4 days before the extraction and for others 6 days after the surgical treatment. The avulsions were performed using normal procedures, using carbocaine as anesthetic and common tools. The hemorrhage was stopped using a simple suture and a compression gauze.

A follow-up to 3 months is sufficient to appraise the results and the good healing of tissue.

## DISCUSSION

The ENG and *ALK1* genes encode transforming growth factor-_ (TGF_) receptor proteins expressed on endothelial cells. The angiogenesis is regulated by endoglin and *ALK1* as positive regulators, and is constituted by the phase of activation and the phase of resolution. During the activation phase the mesenchymal cells differentiate into pericytes and smooth muscle cells, new vessels are formed for the proliferation and migration of endothelial cells, induced by *ALK1*, while ALK5 induced the resolution phase. The angiogenesis requires an *ALK1/ALK5* balance and endoglin appears necessary to maintain this equilibrium (4, 5). For a mechanism not yet known, genetic mutations in the ENG and ALK1 cause alterations in angiogenesis that determine telangiectasies and AVM.

Studies in vivo on animals showed that endothelial expression of endoglin and *Alk1* is required for development of vascular smooth muscle cells and for communication between the endothelium and the mesenchyme (6). The *ALK1* is important for the arterial identification because plays a role in the regulation of *Efnb2* that is a molecular marker of the arteries. It is not yet well know the mechanism in base to which *Efnb2* and *ALK1* enter on relationship, but this interaction determines the clinical variations of HHT1

and HHT2 (7). Nevertheless the existence of family group with HHT symptoms but without these genes mutations suggests that another gene not yet identified may be the cause of HHT (8). Recent studies on the mice showed that the increased plasma levels of vascular endothelial growth factor (VEGF) in HHT patients (9) determine abnormal microvessels in *Eng* heterozygous (10).

Sadick et al. reported that VEGF expression is increased not only in the plasma but also in the nasal mucosa of HHT patients (11).

The basis of the clinical symptoms in HHT is the irregular vessel formation. Telangiectases in the nasal mucosa and nosebleeds are the most common and the earliest symptom of HHT. The 95% of affected present recurrent epistaxis, with a mean age of first event at about 12 years and mean frequency of 18 episodes per month. Severe nosebleeds may cause chronic anaemia, but infrequent nosebleeds require no treatment. Generally the nosebleed frequency and severity increase with age, but there are some patients that not refer particular change in nosebleeds.

In a similar percentage of patients there are multiple telangiectases of the hands, face and oral cavity usually after epistaxis (12-13).

The patients affected by HHT, can present gastrointestinal telangiectases, more frequently in the stomach and upper duodenum; 25% of the patients affected over 60 years have gastrointestinal bleeding often associated to melena or anaemia. The slow bleeding is persistent and may worsen with age (14). Thrombosis or embolus are complications of AVM as result of blood shunting and may enlarge over time (15); pulmonary AVM occur in approximately 30% of individuals with HHT (16, 17) About 30-40% of patients with pulmonary AVM can have central nervous system troubles with thrombotic and embolic events such as stroke, brain abscess or transient ischemic attacks, due to blood shunting. Pregnant women with untreated pulmonary AVM are at high risk of pulmonary hemorrhage (18). Central nervous system AVM can be congenital.

In the 10% of patients with HHT19, (20) are present cerebral AVM and they may present at any age as seizure, headache, stroke and intracranial hemorrhage 21, 22). In 1% of HHT patients are present spinal AVM that can cause subarachnoid hemorrhage, progressive myelopathy, radicular pain or sphincter disturbance (23). It is possible to find hepatic shunts with as high-output heart failure, portal hypertension, biliary disease and portosystemic encephalopathy (24-27). A recent study identified by computed tomography hepatic vascular abnormalities in 78% of consecutive HHT patients (26), even if they remain asymptomatic in some cases.

## DIAGNOSIS

The first diagnosis of HHT is still based on the presence of clinical signs and family history (28). For the molecular diagnosis it is necessary to sequence the entire coding regions of the ALK1 and ENG genes, even if it is possible to have diagnosis of HHT in approximately 70% of case, because there are novel sequence variants of uncertain clinical significance. The genetic test is positive not in the 100% of all patients with clinical diagnosis of HHT, but it is also possible to find different mutations in the same family group (11). Future studies will show us the reason of this discrepancy.

## MANAGEMENT

The main procedure for the patients with HHT is the symptomatic treatment for oral and nasal bleeding, and the prevention of possible complications such as hemorrhage, internal AVM in the lung and brain. The first procedure for HHT diagnosis is a careful clinical examination appraising the presence of telangiectasia in the nasal and oral cavity; for a systemic evaluation is very important the contrast echocardiography to screen for intrapulmonary shunts29, computed tomography, resonance imaging of the brain, auscultation and ultrasound exams for a hepatic assessment.

To reduce risk of embolic events, pulmonary AVM with a feeder vessel of over 3 mm should be treated using transcatheter embolization16; these lesions need to be followed15 because they may grow in size during the time. All the surgical procedures for the

intrapulmonary shunt, cerebral and hepatic AVM are very dangerous for the high risk of hemorrhage, neurological deficits, or death; for these reasons there are no surgical protocols for HHT lesions and for each patient any action must be valued considering this risk. Gastrointestinal bleeding is treated with iron therapy, ethinyl estradiol /norethindrone, danazol and aminocaproic acid or by endoscopic application, and most recently by the laser (30).

The anemia can be controlled by oral or parenteral iron therapy or by blood transfusion. The best management for the mild epistaxis is the daily application of nasal lubricants; the use of laser for the treatment of moderate nosebleeds is desirable (30, 31), but for the severe form of epistaxis is possible to use split thickness skin grafts (32).

The skin manifestation of HHT usually not require treatment, but if they bleed or for aesthetic reasons, they can be ablated by laser. The patients should not assume all the drugs that interfere with the coagulation, such as the FANS.

## CONCLUSIONS

It is commonly accepted that pulmonary AVM (33, 34), are more frequent in HHT1 and hepatic disorder more common in HHT2 (*35-37),* but most manifestations, such as the oral manifestations have been seen in both subtypes. There are patients with HHT2 and pulmonary AVM and patients with HHT1 and liver manifestations, there are not correspondence between the genetic diagnosis and clinical behavior (36-38).

The oneness and the peculiar characteristics of this pathology make its manifestations difficult to manage both for the difference of the anatomical districts where they manifest, both for the risk in therapy; for these reasons it is important to make a complete screening of the patients with the purpose to plan the best therapeutic treatment.

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