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REVIEW

Neurological involvement in hereditary hemorrhagic telangiectasia

Paul-Emile Labeyrie[a,b], Patrick Courthéoux[a], Emmanuel Babin[c], Emmanuel Bergot[e], Emmanuel Touzé[d], Jean-Pierre Pelage[a,*]

[a] *Department of diagnostic imaging and interventional radiology, medical center, Caen university, avenue de la Côte-de-Nacre, 14033 Caen cedex 9, France*
[b] *Inserm U919 Serine protease and pathophysiology of the neurovascular unit, university Caen—Basse-Normandie, GIP Cyceron, boulevard Becquerel, 14058 Caen, France*
[c] *Ear, nose and throat department, medical center, Caen university, avenue de la Côte-de-Nacre, 14033 Caen cedex 9, France*
[d] *Neurology department, medical center, Caen university, avenue de la Côte-de-Nacre, 14033 Caen cedex 9, France*
[e] *Pulmonology departement, medical center, Caen university, avenue de la Côte-de-Nacre, 14033 Caen cedex 9, France*

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Summary Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant disorder characterized by epistaxis, telangiectases, and multi-organ vascular dysplasia. Head and neck localizations of HHT are recurrent, frequent associated with serious complications. The aim of this study was to describe the clinical and imaging patterns of neurological involvement in HHT and to discuss the role of interventional radiology in the management of HHT patients. Based on a multidisciplinary experience of twenty years at our center, we report here the different aspects of neurological involvement of HHT. Depending on the genetic type of the disease, vascular abnormalities may affect different organs. The knowledge of neurological involvement according to specific localization of HHT makes detection easier. As cerebral or spinal arteriovenous fistula may be present in patients with epistaxis or pulmonary arteriovenous malformations (PAVMs), radiologists should be able to detect high-risk lesions and prevent related complications. Finally, we review indications and techniques of embolization for hemorrhagic

Abbreviations: HHT, hereditary hemorrhagic telangiectasia; PAVM, pulmonary arteriovenous malformation; ENG, endoglin gene; ALK1, activin gene; MRI, magnetic resonance imaging; DWI, diffusion weighted imaging; ADC, apparent diffusion coefficient; CAVM, cerebral arteriovenous malformation; SAVM, spinal arteriovenous malformation; TOF, time-of-flight imaging sequence; SPA, sphenopalatine artery; IMA, internal maxillary artery; ICA, internal carotid artery; ECA, external carotid artery; T1W, TI CE, T1 spin echo and T1 fast spin echo contrast-enhanced weighted sequence; T2W T2*W, T2 spin echo and T2 gradient echo-weighted sequence; CT, computed tomography; FLAIR, fluid attenuated inversion recovery sequence; STIR, short TI inversion recovery sequence; PSA, posterior spinal artery; ASA, anterior spinal artery.

* Corresponding author.
E-mail address: Pelage-jp@chu-caen.fr (J.-P. Pelage).

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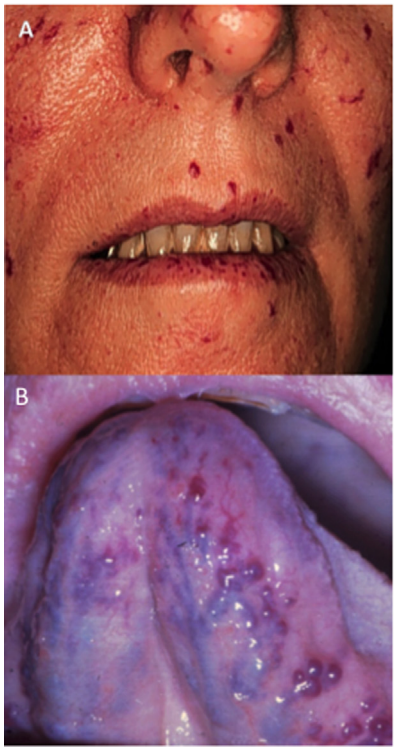
lesions and emphasize that endovascular therapies are very effective and safe in experienced hands. Head and neck imaging is commonly used for the diagnosis of HHT. Imaging plays also a key role for patient evaluation before treatment as pluridisciplinary management is needed.

Introduction

Hereditary hemorrhagic telangiectasia (HHT), also known as Rendu-Osler-Weber disease, is a gene-related disorder that leads to abnormal blood vessel genesis in the superficial soft tissues and often in lungs, liver and brain [1—3]. It is an autosomal dominant multi-organ condition, with an estimated prevalence of at least 1/5000 [2,4,5]. Clinically it is characterized by the presence of multiple small mucocutaneous telangiectasia, localized mainly in the skin or mucous membranes (Fig. 1A) [1], as well as in the gastrointestinal tract [1—5]. Caused by a lack of capillary transition between arteries and veins it leads to abnormal vessel formation and shunting. Abnormal vessels may cause recurrent episodes of bleeding from affected sites [4,5]. Acute complications, chronic disorders and social disability may be reported in affected patients. Epistaxis, which is the most common symptom in HHT patients, may affect their quality-of-life [5—7]. Other manifestations of the disease are related to the presence of pulmonary arteriovenous malformations (PAVMs) and, less often, brain, or visceral involvement [1,2,5]. At the molecular level, the two main types of the disease, HHT1 and HHT2, are caused respectively by mutations in *ENG* gene on chromosome 9 coding for endoglin for HHT1 and mutations in *ACVRL1* gene on chromosome 12 (coding for activin receptor-like kinase 1 (ALK1)) for HHT2 [3,4]. Theses two types of the disease account for most clinical cases but mutations in *MADH4* gene on chromosome 5 (encoding SMAD4), which cause juvenile polyposis/HHT overlap syndrome, have been recently described, and a new type HHT3 has been reported [3]. HHT1 is associated with a higher risk of pulmonary and brain involvements. HHT2 is associated with a high rate of liver involvement [4].

The positive diagnosis of HHT is based on clinical symptoms according to the Curaçao criteria (Fig. 1B) [3,6,7]. Genetic testing may confirm the diagnosis of HHT in patients with minor symptoms who otherwise would have been labeled ''possible HHT'' and allows family screening [6,7]. Therefore, it is strongly recommended for clinicians to refer specific patients for genetic testing of HHT: patients



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The Curaçao Criteria

The HHT diagnosis is	
Definite	if 3 criteria are present
Possible or suspected	if 2 criteria are present
Unlikely	if fewer than 2 criteria are present
Criteria	
1. Epistaxis	spontaneous, recurrent nose bleeds
2. Telangiectases	multiples, at characteristic sites . lips . oral cavity . fingers . nose
3. Visceral lesions	such as .gastrointestinal telangiectasia (with or without bleeding) .pulmonary AVM .Hepatic AVM .Cerebral AVM .spinal AVM
4. Family history	a first degree relative with HHT according to these criteria.

Figure 1 Clinical finding of hereditary hemorrhagic telangiectasia. A. Representative images of common cutaneous facial telangiectasia as a cause of social disability. B. Mucous telangiectasia of the tongue, visible as multiple small bulged vessels on superficial vascularization. The bright red color of the blood inside them indicates the presence of unsaturated blood shunting from the arterial territories. C. Clinical score of curacao is used by all reference centers in the world for HHT positive diagnosis.