Juvenile stroke in combined syndrome of Hereditary Hemorrhagic Telangiectasia and Juvenile Polyposis.

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Running title: Stroke due to PAMVs in HHT-JP.

Key words: Pulmonary arteriovenous malformations, juvenile stroke, Hereditary Hemorrhagic Telangiectasia-Juvenile Polyposis syndrome.

Abstract

We report on a case of juvenile stroke associated to pulmonary arteriovenous malformations causing a relevant right-to-left shunt, clearly documented through contrast-enhanced transcranial Doppler and pulmonary angiography, in a patient affected by the overlap syndrome of Hereditary Hemorrhagic Telangiectasia- Juvenile Polyposis. The pathophysiological mechanism of this altogether rare event is nevertheless exemplary. Associated clinical features together with diagnostic and therapeutical issues are discussed.

Introduction

In 2004 a new condition called "Hereditary Hemorrhagic Telangiectasia- Juvenile Polyposis" (HHT-JP) was described, in which symptoms of the autosomal dominant diseases HHT (Osler-Rendu disease) and JP, overlap, both genetically and clinically. In this syndrome, juvenile polyps and anaemia are the predominant clinical features and, although affected patients display symptoms of both diseases, and a high prevalence of visceral arteriovenous malformations (AVMs) has been reported [1]. Stroke secondary to pulmonary AVMs (PAVMs) is one of the possible neurological manifestations of HHT [2]. Interestingly, the underlying pathophysiological mechanism of stroke in this rare disease is exemplary of strokes due to paradoxical embolism [3].

To our knowledge, only 2 patients with HHT-JP syndrome presenting with stroke have been reported, but no details of the related clinical picture can be found in the literature [1]. We therefore report on a case of juvenile stroke associated to PAVMs as the clinical presentation of HHT-JP overlap syndrome.

Case Report

A 28-year-old man was admitted to our Hospital because of acute onset of confusion, dysphasia and sensory disturbance in his right hand. Brain imaging showed left thalamic ischemia (Figure 1A)

with normal MR angiography. On clinical examination the patient had multiple lip and tongue telangiectases (Figure 1B), and digital clubbing (Figure 1C). Pulse oximetry in supine and standing position was 98% (heart rate 56/min) and 95% (heart rate 65/min), respectively. The patient suffered from migraine with aura, recurrent, spontaneous epistaxis, and "intestinal polyposis", diagnosed at 18 after lower gastrointestinal bleeding due to multiple polyps of the sigma (Fig D). Several subjects on the paternal side of the family were affected by colorectal cancer and/or gastrointestinal (GI) polyposis, as well as recurrent epistaxis, lip and nose telangiectases and recurrent brain haemorrhages. On admission, full evaluation for juvenile stroke, including standard and coagulation blood tests, extra and intra-cranial vascular imaging, standard and 24-hours ECG recording, did not reveal abnormalities, apart from severe anemia (6.6 g/L). Trans-thoracic echocardiogram did not reveal any inter-atrial septal abnormalities, while contrast enhanced transcranial Doppler (ce-TCD) revealed a large, permanent right-to-left shunt (RLS). Transesophageal echocardiogram suggested a possible extra-cardiac source of the RLS. Chest CT confirmed the presence of a 3 cm diameter pulmonary arteriovenous malformation (PAVM) within the right inferior pulmonary lobe (Figure 2A, 2B). The patient underwent percutaneous embolization of the PAVM, with a good result documented by both arteriography and ce-TCD evaluation (Figure 2C, 2D). Colonoscopy revealed over 10 benign colorectal polyps and a bulky, pedunculated polyp with signs of severe dysplasia on histologic examination. Two years later, a repeated ce-TCD showed marked increase of the residual RLS, leading to the discovery of a second PAVM in the left inferior pulmonary lobe, which was successfully treated.

The patient had 4/4 of the Curaçao diagnostic criteria for HHT [4] (spontaneous and recurrent epistaxis, multiple mucocutaneous telangiectasias, visceral AVM, and a first-degree relative with HHT) and JP, fulfilling the clinical diagnosis of the rare HHT-JP overlap syndrome, an autosomal dominant disorder due to mutations in the *SMAD4* gene [1]. Genetic analyses of the whole family through Illumina HumanCytoSNP-12 arrays with parametric linkage analysis indicated a linkage

(LOD 3,3) on chromosome 18 between the markers RS4940257 and RS570046, in a region containing the *SMAD4* gene. However, sequencing of *SMAD4* gene coding regions, exon-intron boundaries, 5'-UTR and promoters A and C regions, did not reveal any detectable mutations [5]. Amplification of the corresponding genomic regions by general PCR methods and Sanger sequencing was performed (ABI PRISM 3.1 Big Dye terminator chemistry, Life Technologies). Sequencing data analysis by Lasergene software v10.1 (DNASTAR) did not reveal any anomalies, and no chromosomal imbalances were found in the *SMAD4* region when checking for copy number variation.

Discussion

JP and HHT are both autosomal dominant conditions, the first predisposing to bleeding and malignancy of the GI tract, the latter presenting with a range of clinical manifestations, from haemorrhages to stroke and to cardiac, hepatic, pulmonary manifestations [1,2]. The co-occurrence of the two diseases in the same patient has been reported, usually due to SMADH4 gene mutations [1]; both HHT and JP underlie an involvement of the TGF β signaling pathway [1]. The present case displays the full-blown spectra of either phenotypes, presenting both severe intestinal polyposis, and high-risk visceral AVMs in the form of multiple PAVMs associated with paradoxical embolism. PAVMs are likely the pathological substrate underlying not only the patient's brain ischemia, but even migraine with aura and digital clubbing [6]. Nevertheless, in this case the clinical diagnosis of HHT-JP was mad only after the patients' stroke, although AVMs had been clinically evident since childhood with massive epistaxis. From a genetical point of view, although parametric linkage analysis of the whole family indicated a linkage in a region containing the *SMAD4* gene, *SMAD4* gene sequencing did not reveal any detectable mutations, and no chromosomal imbalances were found in the *SMAD4* region. This suggests that the disease-causing mutation in this family is probably a deep intronic change that alters splicing leading to a loss of function, as all of the other known HHT-JP mutations to date [5]. About 2% of HHT patients have a causative mutation in SMAD4 gene, but in up to 20% of patients with a clinical HHT diagnosis,

there is no evidence of any mutation. Hence, failure to detect a causative mutation does not rule out the disease, and patients with a clinical diagnosis of HHT should be screened for high risk AVMs ad monitored accordingly [7]. Additionally, it is generally accepted that all patients with SMAD4 mutations are potentially affected by the combined syndrome of JP–HHT, and hence they should be thoroughly screened for the manifestations of both diseases, including high risk AVMs. Overlooking signs of JP in HHT patients or of HHT in JP patients with potentially lifethreatening consequences for the patients [5].

Ce-TCD proved to be very sensitive not only in PAVM detection in the screening phase, but even after percutaneous embolization, in the follow-up phase of the residual RLS (Figure 2A, 2B). A negative test after embolization was not expected anyway, given that contrast echocardiography remains positive in 90% of patients after the procedure [8], but there was a substantial reduction of the shunt entity, consistent with a good radiological result. Although trans-thoracic echocardiography is considered the gold standard for PAVM screening in HHT patients, ce-TCD should be considered as an alternative routine assessment, since it proved to have 100% sensitivity in detecting RLS due to PAMV in HHT [9].

Disclosure

The Authors have no conflict of interests.

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Figure Legends

Figure 1: (1A) Left thalamic ischemic lesion; (1B) Small telangiectasia on the patient's lower lip; (1C) Digital clubbing; (1D) Benign polyp of the descending colon.

Figure 2: Right inferior pulmonary lobe arteriovenous malformation on contrast enhanced (ce) chest CT (2A), and the corresponding right-to-left shunt as assessed by ce-TCD (2B); the same pulmonary arteriovenous malformation after embolisation on pulmonary angiography (2C); ce-TCD after embolisation shows dramatic reduction of the right-to-left shunt (2D).