Neurological manifestations in hereditary hemorrhagic telangiectasia type 1 : a familial case in Japan

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Abstract

Hereditary hemorrhagic telangiectasia (HHT), also known as Rendu-Osler-Weber syndrome, is an autosomal dominant disorder characterized by epistaxis, telangiectasia, and vascular dysplasia. HHT is classified into three types according to the responsible gene: HHT type 1 (HHT1), HHT type 2 (HHT2), and HHT type 3 (HHT3). Pulmonary arteriovenous malformations (PAVMs) are one of the manifestations in HHT. Paradoxical emboli, bypassing the pulmonary capillary system via PAVMs, may give rise to be ischemic cerebral events. An 18-year-old Japanese woman suffered from repeated epistaxis and an embolic stroke associated with severe PAVMs. Although this case had been recognized as sporadic case with PAVMs, we traced the clinical course and performed mutation analysis related to this patient and family members.Younger sister and mother of this case also had recurrent epistaxis and cutaneous telangiectasia, but they didn't have any severe symptoms. We found a de novo mutation in the causative gene of HHT1 in this Japanese family. From clinical findings and results of mutational analysis, we diagnosed this family with HHT1. An appropriate therapy such as embolization or surgical resection must be done for this patient to prevent life-threatening events and to reduce the risk for cerebral abscess and stroke. This report underscores that clinical survey and mutation analysis are very important for this family to detect severe systemic complications.

Key Words: Hereditary hemorrhagic telangiectasia (HHT), HHT type 1 (HHT1), endoglin, pulmonary arteriovenous malformations (PAVMs), cerebroarteriovenous malformations (CAVMs)

Introduction

Hereditary hemorrhagic telangiectasia (HHT) is a disorder that causes vascular malformations and hemorrhage [1, 2]. The disease-causative gene of HHT1 is a transforming growth factor-beta (TGF-beta)-binding protein, endoglin on 9q33-34 [1]. Pulmonary arteriovenous malformations (PAVMs) are found in 15-33% of HHT patients [1, 3, 4]. Patients with HHT1 exhibit a higher incidence of symptomatic PAVMs than patients with HHT2 [5]. Cerebral vascular malformations (CVMs) are found in 5-11% of patients with HHT [4]. CVMs may present with headache, epilepsy, ischemia, or hemorrhage [1]. Paradoxical emboli, bypassing the pulmonary capillary system via PAVMs may give rise to stroke or cerebral abscess [6, 7]. It has been reported that various symptoms are occurred within a family whose members have the same underlying mutation [8, 9]. We report here a Japanese family with

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HHT1 in which clinical forms are different among affected family members.

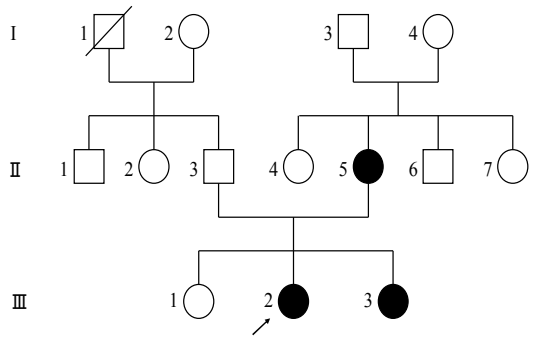

Figure 1. Family pedigree of the proband with hereditary hemorrhagic telangiectasia (HHT). The proband is indicated by the arrow. HHT subjects are indicated by black.

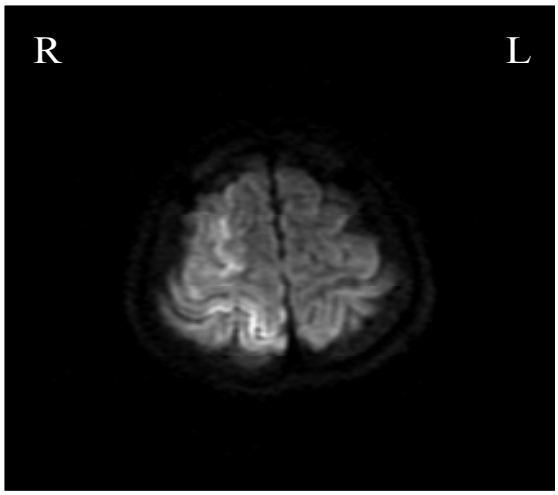

Figure 2. Brain MRI on 5th hospital day of the proband (Ⅲ-2). Diffusion weighted image showed high intensity of right parieto-occipital lesions.

Patients and Methods

An 18-year-old Japanese woman (Ⅲ-2) with a history of epistaxis was found multiple asymptomatic PAVMs at the age of 16 years (Fig 1). She underwent embolization with metal coils for her PAVMs. She was suffered from dyspnea and generalized convulsion November 1, 2004 and was admitted to our hospital. Physical examination revealed sinus tachycardia, cyanosis and telangiectasia of the tongue. Neurological examination revealed left hemispatial agnosia and moderate weakness in the left hand. Her electroencephalogram was normal. Brain magnetic resonance imaging (MRI) revealed abnormal lesions in the right parieto-occipital cortex that suggested a stroke (Fig 2). CVMs were not detected in MR angiography (MRA).

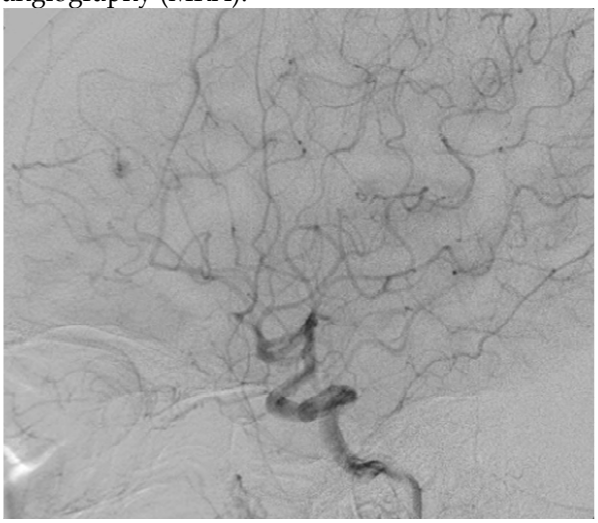

Figure 3. Cerebrovascular angiography (CAG) of her mother (Ⅱ-5). CAG revealed a small CAVM.

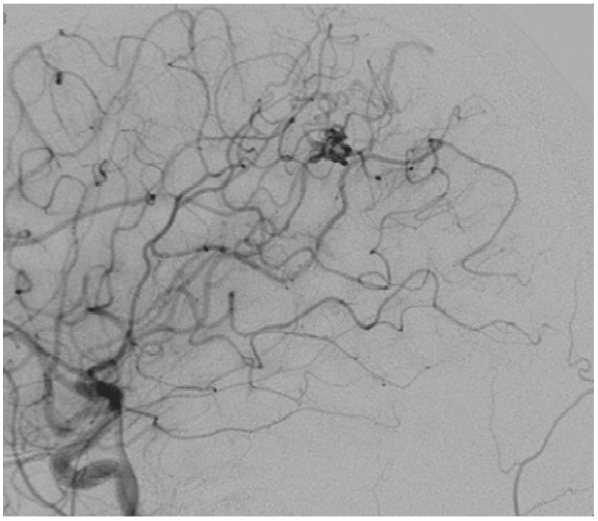

Figure 4. CAG of her younger sister (Ⅲ-3). CAG showed a CAVM of 1.5cm in diameter.

We couldn't find any other embolic sources except for a few recanalized PAVMs. We speculated that the right-to-left shunt from PAVMs was the cause of her brain embolism. Her mother (Ⅱ-5) and younger sister (Ⅲ-3) also had histories of recurrent epistaxis, so we examined the clinical feature of her family members.

We collected peripheral blood from the patient (Ⅲ-2), her parents (Ⅱ-3, Ⅱ-5), her two sisters (Ⅲ-1, Ⅲ-3) and her maternal grandparents (Ⅰ-3, Ⅰ-4) (Fig 1). Informed consent was obtained from the family members. Genomic DNA was isolated from lymphocytes by using insta Gene TM Matrix (Bio-Rad). The 14 exons of endoglin

were amplified by polymerase chain reaction (PCR) using genomic DNA as previously described [10, 11]. The PCR mixture contained 1×ExTaq buffer, 0.2 µg each of forward and reverse primers, 0.25 mM of dNTP mixture, 1 µg of genomic DNA, and 0.25 U of Taq polymerase (TaKaRa Ex Taq, TaKaRa, Sigma, Japan). PCR direct sequencing for each exon was performed using a BigDye TerminatorTM on an ABI310 Genetic Analyze.

Results

he patient (Ⅲ-2), her mother (Ⅱ-5), and younger sister (Ⅲ-3) had not only recuTrrent epistaxis but also cutaneous telangiectasia. Although Ⅲ-2 had a few severe PAVMs, Ⅱ-5 had two small asymptomatic PAVMs and one micro cerebroarteriovenous malformation (CAVM) - right frontal (Spetzler-Martin grade Ⅰ) (Fig 3). On the other hand, Ⅲ-3 had no PAVMs but had two small CAVMs - right medial occipital (Spetzler-Martin grade Ⅰ) and left parietal (Spetzler-Martin grade Ⅱ) (Fig 4). We diagnosed this family with HHT according to the criteria proposed by Shovlin et al [12]. Direct sequencing of endoglin in Ⅲ-2 revealed a substitution of G to A in the 3' exon/intron boundary site (Fig 5). This substitution in the boundary site was also found in Ⅱ-5 and Ⅲ-3. The mutation was not found in her father (Ⅱ-3) or older sister (Ⅲ-1).Neither of her maternal grandparents (Ⅰ-1, Ⅰ-2) had the mutation (data not shown). The mutation therefore arose de novo at the stage of the patient's mother and was transmitted to her children.

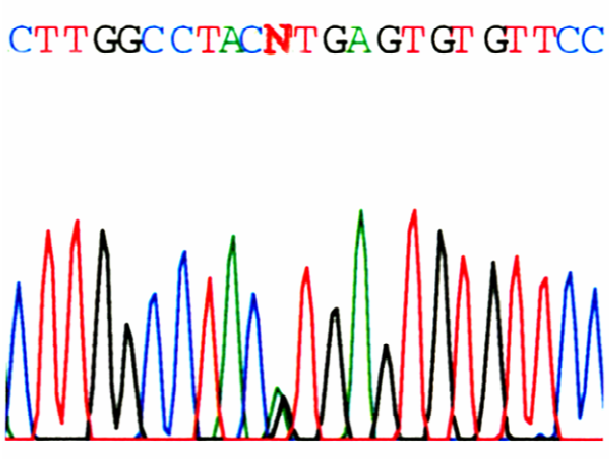

Figure 5. Analysis of genomic DNA in the proband (Ⅲ-2). Exon 3 and the flanking intronic sequence was seen. The profiles depicting sequence of the 3'-exon 3/intron boundary reveal a G-to-A substitution.

Discussion

PAVMs tend to increase in size, often multiple, and they are associated with significant morbidity and mortality [4, 6, 13, 14]. Chest radiography or CT every 1-2 years is recommended for Ⅱ-5 and Ⅲ-2 to exclude the relevant PAVMs [15]. Besides, an appropriate therapy such as embolization or surgical resection must be done for Ⅲ-2 to prevent life-threatening events and to reduce the risk for cerebral abscess and stroke [14, 15].After neurological findings were improved, Ⅲ-2 underwent embolization for a few recanalized PAVMs.It has been assumed that CVMs in HHT are mostly low-grade AVMs (Spetzler-Martin grade Ⅰ or Ⅱ), are frequently multiple, and have a lower risk of bleeding than that associated with sporadic AVMs [16, 17]. In addition, there has been considerable debate about the optimal therapy for asymptomatic CAVMs [16, 18]. We decided to choose a conservative management for Ⅱ-5 and Ⅲ-3 with asymptomatic CAVMs, and they have not shown any symptoms so far.

We diagnosed this family with HHT1 based on results of mutational analysis, and these clinical findings showed a variability among the family members despite having the same disease causing mutation. It is concluded that the mutation analysis should be screened for HHT1 family members, because we can firstly provide an accurate clinical survey in the mutated individuals and, secondly prevent lifethreatening events due to systemic vascular abnormalities..

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