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Tørring, Pernille Mathiesen; Lauridsen, Mathilde Faurholdt; I Dali, Christine; Andersen, Poul Erik; Ousager, Lilian Bomme; Brusgaard, Klaus; Kjeldsen, Anette Drøhse

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CASE REPORT

Familial cerebral abscesses caused by hereditary hemorrhagic telangiectasia

Pernille Mathiesen Tørring[1], Mathilde Faurholdt Lauridsen[1], Christine i Dali[2], Poul Erik Andersen[3], Lillian Bomme Ousager[1], Klaus Brusgaard[1] & Anette Kjeldsen[4,5]

[1]Department of Clinical Genetics, Odense University Hospital, Sdr. Boulevard 29, DK-5000 Odense C, Denmark
[2]Department of Clinical Genetics, Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen OE, Denmark
[3]Department of Interventional Radiology, Odense University Hospital, Sdr. Boulevard 29, DK-5000 Odense C, Denmark
[4]Department of Otorhinolaryngology, Odense University Hospital, Sdr. Boulevard 29, DK-5000 Odense C, Denmark
[5]Department of Clinical Research, University of Southern Denmark, Odense, Denmark

Correspondence
Anette Kjeldsen, Professor, Department of Otorhinolaryngology, Odense University Hospital, Sdr Boulevard 29, DK-5000 Odense C, Denmark. Tel: +45 65 41 13 50;
E-mail: anette.kjeldsen@rsyd.dk

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Key Clinical Message

In case of a cerebral abscess without known cause, Pulmonary arteriovenous malformations (PAVM) screening should be performed. If PAVM(s) is identified, Hereditary hemorrhagic telangiectasia (HHT) is very likely and should always be considered. This case shows the benefit of familial screening for HHT and PAVM.

Keywords

Cerebral abscess, endoglin, hereditary hemorrhagic telangiectasia, Osler-Weber-Rendu, pulmonary arteriovenous malformation.

Background

Hereditary hemorrhagic telangiectasia (HHT), also known as Osler-Weber-Rendu disease, is an autosomal dominant hereditary disorder characterized by a variety of clinical manifestations due to the presence of multiple mucocutaneous telangiectases and arteriovenous malformations (AVMs) in internal organs, most commonly lungs, liver, and cerebrum. The most frequent clinical manifestation is spontaneous and recurrent epistaxis, affecting more than 95% of all HHT patients. Pulmonary arteriovenous malformations (PAVMs) are observed in about one-third of all HHT patients [1] and can cause cerebral abscess or stroke due to paradoxical embolism [1, 2]. The prevalence of cerebral abscess among HHT patients with PAVM is reported to be 7.8% [3], which is nearly 400 times the rate seen in the general population [4]. Thus, HHT patients should be screened for PAVMs, and patients with PAVMs are recommended treatment by embolization, whenever possible [5, 6]. Cerebral AVMs are present in at least 10% of HHT patients and hepatic AVMs are common, but rarely symptomatic [7, 8].

In Denmark, the reported prevalence is approximately 1/6500 [9], roughly comparable to that of other European, U.S., and Japanese populations.

Genetically HHT is a heterogeneous disorder caused by mutations in at least three known genes: Endoglin (*ENG)*, activin A receptor type II-like 1 (*ACVRL1)*, and SMA- and MAD-related protein 4 (*SMAD4)*. HHT1 is caused by mutations in *ENG* (OMIM 131195 [Online Mendelian Inheritance in Man, http://www.omim.org/entry/131195?search=eng&highlight=eng]) and HHT2 by mutations in *ACVRL1* (OMIM 601284 [Online Mendelian Inheritance in Man, http://www.omim.org/entry/601284?search=acvrl1&highlight=acvrl1]). A phenotype consisting of HHT and juvenile polyposis syndrome is caused by mutations in the *SMAD4* gene (OMIM 600993 [Online Mendelian Inheritance in Man, http://www.omim.org/entry/600993?search=smad4&highlight=smad4]).

Hereditary hemorrhagic telangiectasia is a clinical diagnosis, according to the Curaçao criteria [10]. In

approximately 85% of the HHT patients, a mutation in either *ENG* or *ACVRL1* [11] can be identified at mutation analysis. Only around 2% of HHT patients have mutations in *SMAD4* [12, 13].

Despite identification of the genes causing HHT, the mechanisms for the pathogenesis of HHT and for the development of telangiectases and AVMs remain obscure.

Case Presentation

A 16-year-old patient (III-1, Fig. 1) was referred to the national HHT Center, Odense University Hospital for embolization of a large PAVM, which was detected by chance after a traffic accident (case story published in Danish [14]). He had a history of spontaneous epistaxis once a month. CT of Thorax showed two PAVMs localized in the right lung, which were embolized, increasing the SaO2 from 88% to 98% and the PaO2 from 7.5–13.3 kPa.

Sequencing of *ENG* identified a mutation (c.1483delC, p.Leu495Trpfs*23 (NM_001114753.2)) in the coding region of exon 11. The frameshift mutation was not previously reported but considered pathogenic as it inserts a premature stop codon.

This index patient (proband) had a family history of cerebral abscesses.

The father of the proband (II-1, Fig. 1) had daily epistaxis lasting 2–4 min, and cerebral abscess at the age of 39, which lead to a three-month-long hospitalization and cerebral abscess sequelae, including a minor visual field defect and fatigue. Typical telangiectases were detected in the nasal and oral cavity and on the facial skin. CT thorax revealed a PAVM, which was embolized. He was analyzed for the *ENG* mutation previously identified in the son and carried this mutation.

The paternal aunt (II-4, Fig. 1) had a cerebral abscess at the age of 31 years, which lead to 2 months absent from work and long-term sequela, including fatigue. She had epistaxis on a daily basis, blue and clubbed nails, cyanotic lips, progressive dyspnea and telangiectases in the nasal cavity, on the lips and tongue. CT thorax revealed two large PAVMs situated bilaterally, which were embolized. She was also analyzed for the familial *ENG* mutation and was a carrier.

Two of the cousins (III-3 and III-4, Fig. 1) both carried the familial *ENG* mutation. III-4 had epistaxis, typical telangiectases in the nasal mucosa, and three small PAVMs identified by CT thorax. One PAVM was embolized, and the other two were too small to undergo embolization. III-3 did not, at the age of 19 years, have any symptoms of HHT, and transthoracic contrast echocardiography was normal, revealing no indication of a PAVM. Cerebral MRI, which was performed as he also had epilepsy, showed a cavernous hemangioma. III-3 and III-4 both carried the familial *ENG* mutation.

The brother of the proband (III-2, Fig. 1), the paternal uncle (II-5, Fig. 1), and a cousin (III-9, Fig. 1) did not

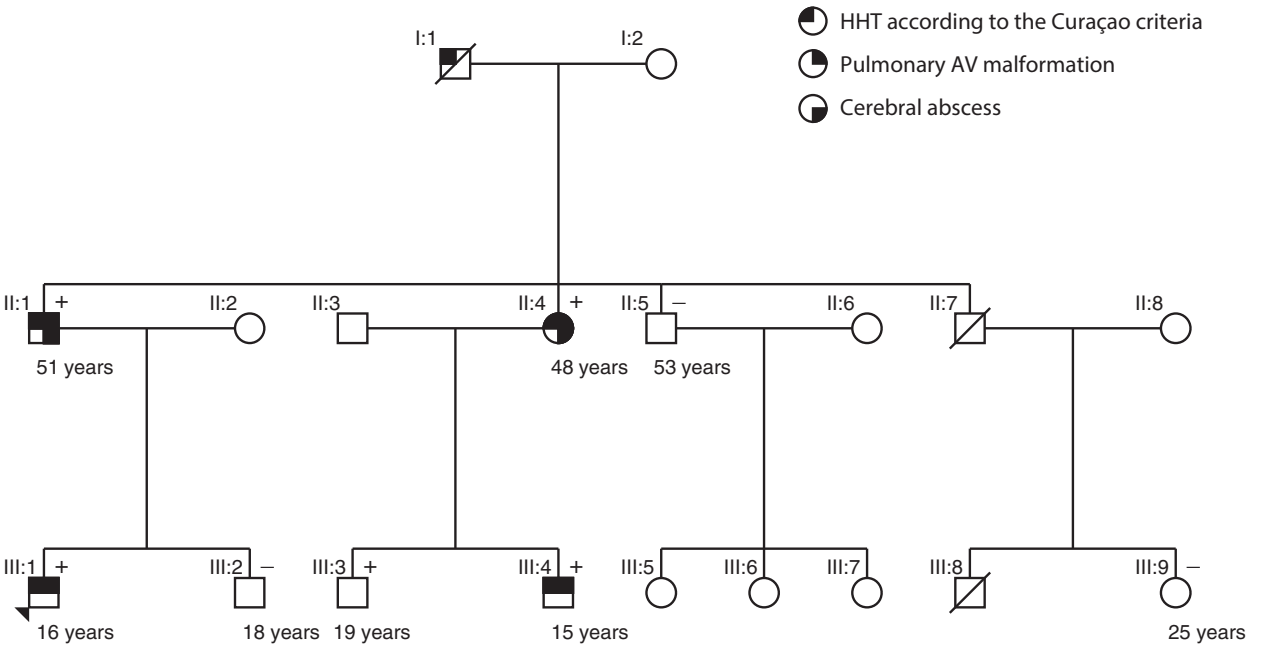

Figure 1. Pedigree of the family. Arrow marks the proband; +, mutation positive; and –, mutation negative. Age is indicated for all tested family members.

carry the familial mutation. None of them showed clinical signs of HHT.

Outcome and Follow-up

All at-risk family members were offered genetic testing for the familial *ENG* mutation, and subsequently clinical evaluation of HHT manifestations with PAVM screening and embolization, when relevant.

Discussion

Cerebral abscess is a serious condition and is fatal in 10% of the cases [15]. PAVMs, associated with HHT, are known to cause cerebral abscesses. We present a rare family with two cases of cerebral abscesses occurring in first-degree relatives.

In this family, the PAVMs and the secondary diagnosis of HHT were not realized until our proband was involved in a traffic accident and accidentally diagnosed with PAVM and successively HHT. Afterward, his family underwent genetic testing and PAVM screening, in which it was realized that his father and paternal aunt both had experienced a cerebral abscess secondary to PAVMs. Both survived the potential fatal cerebral abscess; nevertheless, they both experienced some sequelae. In the rest of the family, additional PAVMs was diagnosed in two family members, possibly preventing further cases of cerebral abscesses – or strokes.

The prevalence of cerebral abscess among HHT patients with PAVM is reported to be 7.8%, which is nearly 400 times the rate seen in the general population [3, 4]. In patients with cerebral abscess without known cause, PAVM screening should be performed, and in case of identified PAVM(s), HHT is the most likely diagnosis and should always be considered [16].

Surveillance in HHT families includes PAVM screening, with the intention to embolize these to prevent cerebral complications, to raise the oxygenation, and to prevent rupture of the PAVMs [8]. Genetic counseling should be offered to HHT patients and first-degree relatives to HHT patients in order to ensure HHT and PAVM screening of relevant family members.

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Conflict of Interest

No competing financial interests exist. All authors declare that they do not have any conflict of interest.

Authorship

PMT, MFL, CID, PEA, LBO, KB, and AK: made contribution to the acquisition of the clinical and genetic data. LBO and AK: provided a detailed review of the contents and structure of the manuscript. PMT: drafted the manuscript. All authors have read and approved the final manuscript.

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