CASE REPORT

Brain abscess as an initial presentation in a patient of hereditary haemorrhagic telangiectasia caused by a novel *ENG* mutation

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SUMMARY

Hereditary haemorrhagic telangiectasia (HHT) is a rare inherited autosomal-dominant vascular dysplasia involving multiple organs. Brain abscess is an uncommon and potential fatal complication. We report a case of HHT caused by a novel *ENG* mutation who initially presented as brain abscess. The patient, with a family history of epistaxis, presented with fever, headache and right-sided haemiparesis. Upon examination, brain MRI showed a contrast-enhanced abscess on the left fronto-parietal region. Open brain drainage was performed and pus culture yielded *Actinomyces meyeri*. The chest image revealed multiple pulmonary arterio-venous fistulas. HHT was diagnosed according to Curacao criteria. Genetic analysis revealed a novel duplication on exon 6 of *ENG* gene, which segregates with symptomatic subjects in her family. Clinicians should be cautiously aware of HHT as a differential diagnosis if patients presented with an unknown entry source of intracerebral infections.

BACKGROUND

Hereditary haemorrhagic telangiectasia (HHT), also called as Rendu–Osler–Weber syndrome, is a rare autosomal-dominant hereditary disease with a prevalence rate suggested to be 1 in 50 000–100 000.[1] Although this disease has been reported in all races, it is rare in Asian populations.[1 2] Mutations in two genes have been shown to be associated with HHT, including genes encoding endoglin (*ENG*) and activin A receptor type II-like 1 (*ACVRL1*).[3 4] Both gene products related to the function of transforming growth factor-related angiogenesis.[4 5] HHT usually manifested with nose bleeding, telangiectasia over mucosa or skin, and multiple recurrent arterio-venous malformations (AVMs), especially in the gastrointestinal tract, liver, lung or brain.[6 7] Most of the HHT patients lived without major bleeding episodes except recurrent epistaxis. However, brain abscess is a rare and potentially fatal complication.[8–11] Here we report a HHT patient who initially presented with brain abscess and confirmed to have a novel gene mutation of *ENG*.

CASE PRESENTATION

A 39-year-old lady without a systemic disease before had a history of recurrent nose bleeding since she was a teenager. She presented to the neurology clinic with progression of right-side limbs weakness for several days. Upon admission, the patient was alert and oriented. Her physical examination was unremarkable except for mild fever. There were no obvious skin telangiectasia lesions. There was no neck stiffness and the fundoscopy was normal. Neurological examination revealed right central-type facial palsy, slurred speech and right limbs weakness. During hospitalizstion, there were several episodes of fever along with intermittent headache.

Tracking back her family history, her mother, grandmother, uncle and one of her aunts had been diagnosed with lung AVMs. Besides, there was a strong family history of epistaxis over most of her family members (figure 1). The son of the proband, who is 21 years old now, has frequent nosebleeds since he was in elementary school. The images of the brain and lung did not reveal any evidence of AVMs.

INVESTIGATIONS

All her biochemical data and cell count of the blood sampling were within normal limits, including elevated whole blood count and C reactive protein. The patient did not have immuocompromised status. MRI of the brain revealed a 2 cm hypodense lesion with perifocal oedema and contrast enhancement on the left fronto-parietal region. Based on clinical history, a brain abscess was strongly suspected and she received open craniotomy with abscess drainage on the third day after admission. Culture of the pus drained yielded *Actinomyces meyeri*, while blood cultures were sterile. Cardiac and abdominal ultrasonography showed no site of potential microbial entry. Chest x-ray and MRI revealed multiple well-defined small nodules at bilateral lungs, which were pulmonary arterio-venous fistulas (AVFs) (figure 2). In addition, some tiny vascular tufts were also noted over the right lobe of liver, suggesting intrahepatic AVMs.

According to the clinical presentation of our index patient and radiological evidences of multiple AVMs in lung and liver associated with a strong family history of vascular dysplasia, she was clinically diagnosed as definite HHT according to Curacao criteria.[12] After getting the informed consent forms, DNA was extracted from 6 ml of peripheral venous blood from the subject and her family members, using standard protocols. All exons with intron—exon boundaries of *ENG* gene and *ACVRL1* gene were amplified by PCR using the primers reported in the GDB database (Human Genome Database) and were sequenced by TagMan

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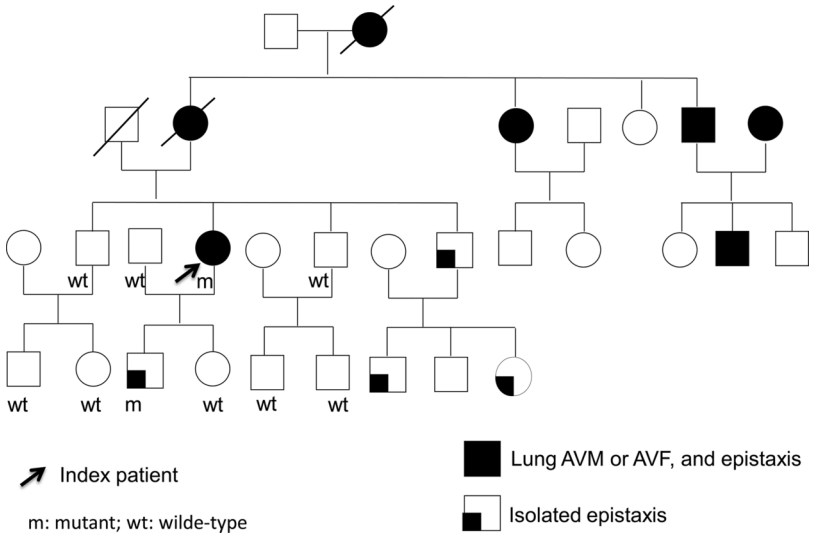

Figure 1 Family pedigree of our index patient. The proband we described is marked with an arrow. M denotes mutated alleles and wt denotes normal alleles.

ABI 3730 (Applied Biosystems Inc). Each mutation was confirmed at least by a second reverse sequence. Base variants, deletions or duplications are labelled according to the longest mRNA transcript (GenBank accession number NM_001114753.1). The genetic analysis of the index patient shows normal findings of *ACVRL1* gene but a novel duplication on exon 6 of *ENG* gene, 975–988 dupl CGGACGGTGACGG, segregating symptomatic subjects in her family (figures 1 and 3).

DIFFERENTIAL DIAGNOSIS

A clinically diagnosed HHT patient, presented with brain abscess as an initial presentation, was confirmed by genetic analysis to have a novel *ENG* gene mutation.

TREATMENT

The patient was treated with ceftriaxone and metronidazole intravenously for 5 weeks. The treatment course was uneventful and she was discharged 5 weeks after admission.

OUTCOME AND FOLLOW-UP

She remained independent with only mild right foot weakness after follow-up for 10 years. All the family members were suggested to be aware of frequent nosebleeds, which are a common sign of HHT. The affected carriers receive long-term follow-up and regular image studies.

DISCUSSION

We report a family with clinically and genetically confirmed HHT, in whom the proband presented initial cerebral symptoms as brain abscess. We identified a novel *ENG* mutation contributing to the clinical phenotypes of this family.

HHT is a rare disease marked by a familial pattern of telangiectasia on mucocutaneous surfaces and larger AVMs in other organ systems.[2 6] As compared with the incidence of brain abscess in normal population that is 1.3/100 000,[13] previous studies have shown that brain abscess is estimated to occur in 1% of patients with HHT and carries as high as 40% death rate.[9] Many reported cases are associated with pulmonary AVMs or AVFs. Several possible mechanisms of brain abscess formation

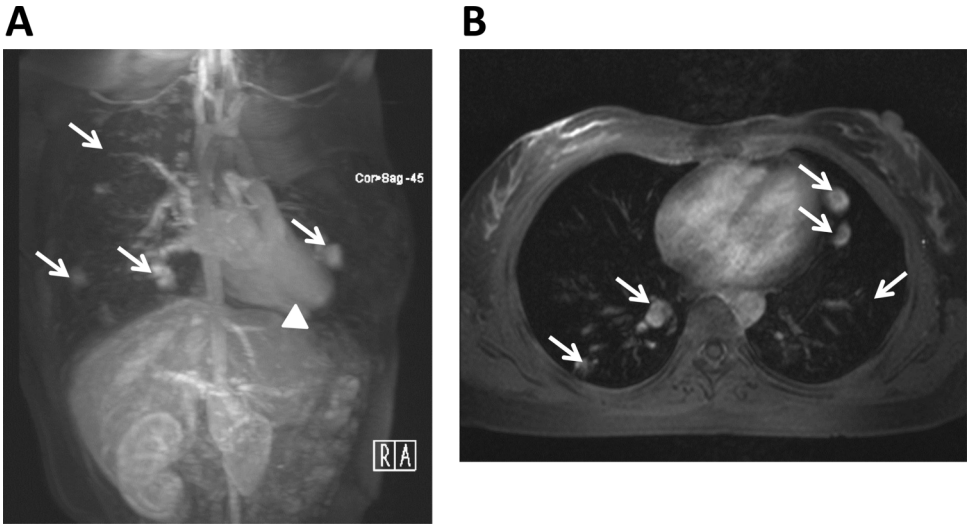

Figure 2 MRI findings of our index patient. MR angiography of the lung and liver shows prominent pulmonary arteries, pulmonary arterio-venous malformations AVMs and AVFs (arrows) with multiple aberrant collateral vessels in both sagittal (A) and coronal (B) views, and abnormal dilation of the hepatic artery (arrowhead) in the liver (A). AVM, arterio-venous malformations; AVF, arterio-venous fistulas.

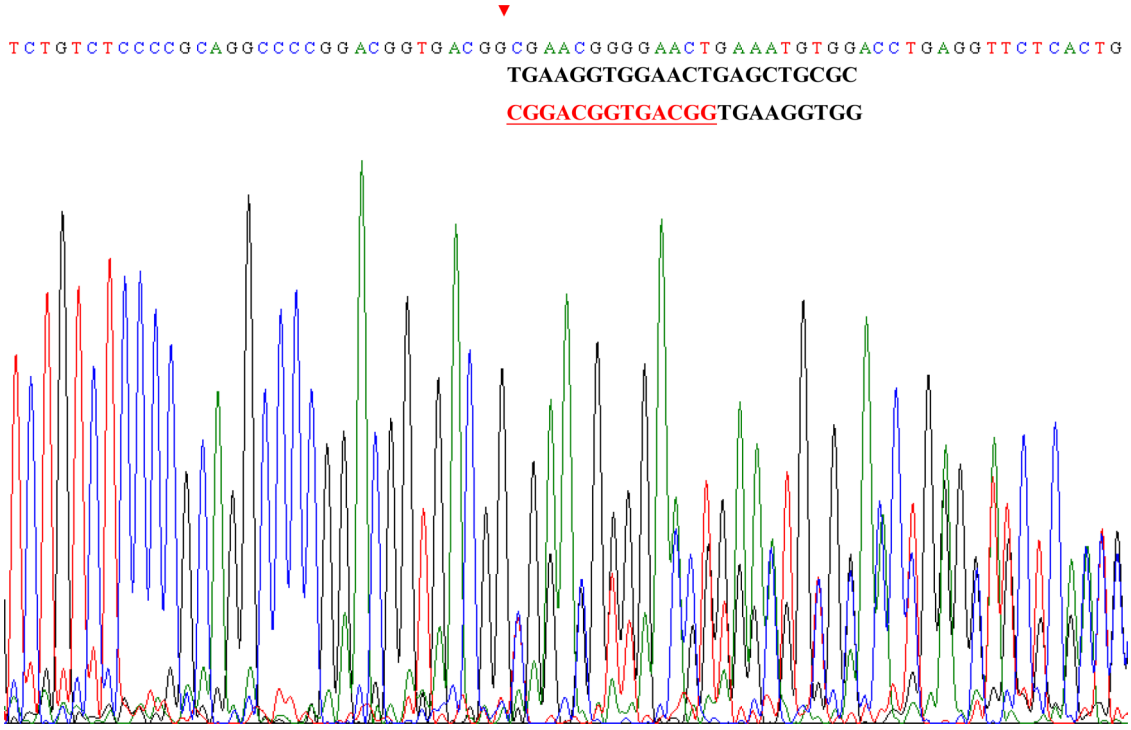

Figure 3 Genetic findings in the index patient with *ENG* mutation. Chromatograms of direct sequencing of the *ENG* genomic sequence of our patient. The start position of the genetic duplication identified in this study is indicated by red arrowheads and the duplicated nucleotides are marked in underlined red characters.

in patients with HHT have been proposed. Pulmonary vascular malformations make the pulmonary artery flow into the venous return directly and skip the capillary circulation. This would not only lead to blood acidosis in artery circulation, but also allow micro-metre-level particles like bacteria break through the capillary bed barrier, resulting in the catastrophic cerebral abscess.[8 14] In addition, secondary bacterial seeding of an ischaemic portion of the brain after paradoxical sterile emboli also contributes to the brain abscess formation.[15]

A meyeri is an infrequent causative agent of brain abscess. It is usually an oral saprophyte pathogen that particularly affects periodontal lesions and carious teeth.[16] It is rarely present as a pathogen of central nervous system infection. Rarely if ever as a cause of brain abscess, it has been associated with previous dentogingival disease, chronic alcoholism or immunodeficiency.[16] Given that our patient did not have drinking history or was not under immunocompromised state, we speculated the possible entry focus of our patient was dentogingival infection, albeit there was no preceding dental surgery.

In the recent decade, dysfunction of transforming growth factor-β owing to mutations of *ENG* and *ACVRL-1* genes which represented HHT-1 and HHT-2, respectively, delineated the pathophysiology of HHT.[3 4] Patients carrying *ENG* mutations are more frequently from Northern Europe and the Americas, while Mediterranean populations have a majority of *ACVRL1* mutations.[17–19] As compared with the mutations of *ACVRL1* gene clustered in exons 3, 7, 8, *ENG* mutations are almost evenly distributed in the various exons coding for the extracellular domain of endoglin protein.[19] In line with these previous studies, the present index patient has a genetic duplication on the exon six of *ENG* gene, which is on the extracellular domain of endoglin protein. In addition to point mutations, frameshift mutations and duplication of *ENG* gene were frequently reported in patients with HHT.[19]

In conclusion, this case clearly demonstrates that brain abscess could be the first symptom of HHT, a potentially devastating disease. HHT should be considered in patients with intracranial infection without an obvious entry source of infection. Screening family members of patients with HHT by means of chest radiography and neuroimages has been recommended. Genetic testing could be provided as a diagnostic tool for susceptible family members with only mild symptoms and genetic counselling is recommended for those who know the disease runs in their families.

Learning points

- Hereditary haemorrhagic telangiectasia (HHT) should be considered in patients with an intracranial infection without an obvious entry source of infection.
- Screening family members of patients with HHT by means of chest radiography and neuroimages are suggested.
- Genetic testing could be provided as a diagnostic tool for susceptible family members with only mild symptoms of epistaxis.

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Competing interests None.

Patient consent Obtained.

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