Hereditary haemorrhagic telangiectasia with pulmonary arteriovenous malformations: a treatable cause of thromboembolic cerebral events

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ABSTRACT

Hereditary haemorrhagic telangiectasia (HHT) or Osler-Weber-Rendu syndrome is associated with mucocutaneous telangiectases and iron deficiency anaemia caused by epistaxis or blood loss from the gastrointestinal tract. We describe a 41-year-old Chinese man who presented with amaurosis fugax secondary to emboli from pulmonary arteriovenous malformations associated with HHT. He was diagnosed with the disorder in adolescence but follow-up in the outpatient setting was incomplete. Early screening and regular follow-up of patients with HHT are important to minimise the risk of development of serious sequelae, such as thromboembolic strokes and cerebral abscesses. Appropriate management demands a knowledge of the risks and benefits of asymptomatic screening and treatment in the rapidly-evolving evidence base for this disease.

Keywords: amaurosis fugax, arteriovenous malformations, hereditary haemorrhagic telangiectasia, Osler-Weber-Rendu syndrome

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INTRODUCTION

Hereditary haemorrhagic telangiectasia (HHT) is an uncommon autosomal-dominant multi-system disorder of vascular dysplasias. It occurs across a wide ethnic and geographical distribution, with an incidence varying from 1:2,000 to 1:10,000 in the Western population. It has been estimated that half a million people worldwide have HHT[1]. Currently, the diagnosis of HHT is based on family history and the presence of arteriovenous malformations (AVMs), which may consist of cutaneous or mucocutaneous telangiectases or large visceral AVMs. Prior to the diagnostic criteria proposed by Plauchu et al[2] and Shovlin et al[3], HHT has been frequently misdiagnosed or undiagnosed.

HHT is typically identified by a combination of telangiectases, recurrent epistaxis and a positive family history. HHT results from the AVMs that lack capillaries. It is a disease of variable age-related penetrance and has a wide spectrum of presentations, e.g. patients may be asymptomatic or have multiorgan involvement. The symptoms vary greatly, even between relatives, and the severity of epistaxis or skin telangiectases do not seem to be related to the likelihood of having internal organ AVMs. Untreated pulmonary AVMs (PAVMs) are a common cause of thromboembolic strokes and cerebral abscesses in families with HHT.

CASE REPORT

A 41-year-old Chinese man was admitted after experiencing complete visual loss of the left eye on waking one morning. His vision returned in a bottom-to-top visual field manner, and he regained full vision in three minutes after the blindness was realised. He did not experience any pain or redness in the eye, headaches, vomiting or other neurological symptoms. There were no associated cardiovascular or respiratory symptoms, particularly palpitations and dyspnoea. Prior to this event, he had been well. He also did not experience any neurological symptoms previously.

As a teenager, he was wrongly treated for pulmonary tuberculosis based on chest radiograph findings of right upper zone shadowing. After review by a respiratory physician, the diagnosis of tuberculosis was refuted, and HHT with PAVMs was suspected. A few years later, pulmonary angiography confirmed the presence of PAVMs. There was no intervention carried out for the PAVMs at that time and he was followed up in the outpatient clinic intermittently for a few years. Subsequently, he was lost to outpatient review because he had gone abroad for work purposes in his job as an executive. The patient's father gave a history of frequent but mild epistaxis and was diagnosed to have HHT two years ago. There was no other family history of note.

On physical examination, he had multiple telangiectasia on the palate but none on the skin. He had finger clubbing and was mildly cyanotic. Examination of the respiratory and neurological

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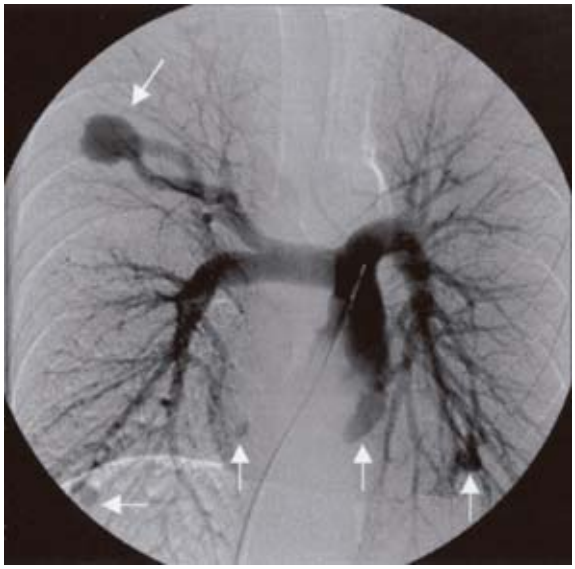

Fig. 1 Preliminary pulmonary angiogram done prior to embolisation shows multiple pulmonary arteriovenous malformations (arrows).

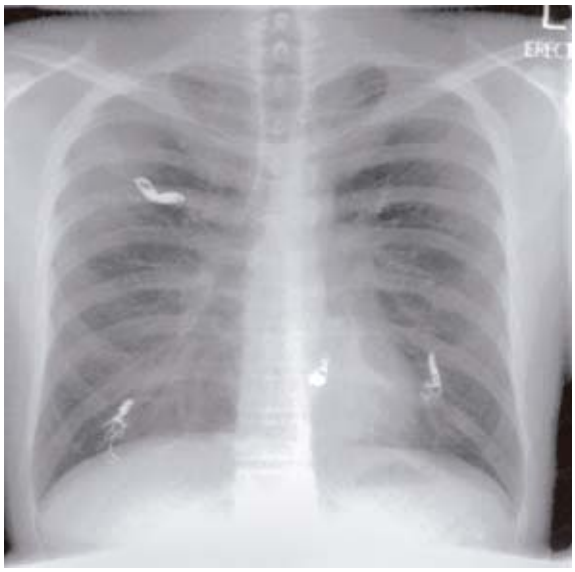

Fig. 2 Post-embolisation chest radiograph shows Nester embolic coils deposited in the feeding arteries via the right femoral vein route.

system was normal. Systematic review was unremarkable. Laboratory tests showed a serum haemoglobin level of 18.1g/dL. Arterial blood gases on room air showed mild hypoxaemia (pO2 of 70.6mmHg). Electrocardiography (ECG) showed a sinus rhythm. Chest radiograph on admission showed a faint 1.5cm soft tissue density in the right upper zone with no scarring or mediastinal nodal mass. Computed tomography (CT) of the chest and liver revealed five PAVMs but no hepatic AVMs. Magnetic resonance (MR) imaging with magnetic resonance angiography (MRA) of the brain was normal. Ultrasonography of the carotid arteries and transthoracic echocardiogram did not reveal any abnormality. The ophthalmological review was normal. Assessment by the otolaryngologists revealed no other cause for the epistaxis apart from intranasal mucosa telangiectases which required no intervention.

It was concluded that the amaurosis fugax was caused by embolic phenomenon from the PAVMs. Transcatheter embolisation (embolotherapy) was recommended. Pre-embolisation pulmonary angiography revealed the five PAVMs (Fig. 1). All but one of the PAVMs were embolised, using Nester platinum coils (Fig. 2). The remaining PAVM, the smallest-sized one, was inaccessible. Arterial blood gas analysis prior to discharge from hospital showed a marked improvement in blood oxygenation (pO_2 of 84.4mmHg). He was well when recently reviewed in the outpatient clinic.

DISCUSSION

The patient did not have tuberculosis and was eventually appropriately diagnosed to have HHT. However, he was not followed up for more than 20 years until this presentation of amaurosis fugax. In retrospect, our patient satisfies the criteria proposed by Plauchu et al[2] and Shovlin et al[3] which states that the clinical diagnoses of HHT is considered definite if $\geq$3 of the following four findings are present; suspected, if two of the findings are present; and unlikely, if fewer than two findings are present. The findings considered are: epistaxis, especially if they are spontaneous, recurrent and nocturnal in nature; multiple mucocutaneous telangiectases; one or more visceral AVMs found in the lung, brain, liver, spinal cord or gastrointestinal tract; and a first degree relative with HHT.

HHT is a heterogeneous condition and at least two genes are associated. Diagnostic laboratory-based genetic testing for mutations in endoglin (ENG) and activin receptor-like kinase type 1 (ALK-1), which are associated with HHT, is currently available only on a limited basis. The precise mechanisms by which these mutations lead to vascular abnormalities in HHT are unclear. AVMs have thin walls and tortuous paths and can, therefore, bleed or rupture easily with minimal trauma or rise in intravascular pressure. The most common manifestations of HHT are epistaxis and telangiectases. Epistaxis is usually the earliest symptom, with the mean age of onset being 12 years old. However, many patients do not have epistaxis severe enough to cause anaemia or to seek medical attention.

Large AVMs larger than 1cm in diameter, which may occur in the lung, brain, liver, gastrointestinal tract or spinal cord, result from blood shunting through the abnormal vessels and bypassing the capillary bed. Shunting of thrombotic and septic emboli through

PAVMs, thereby bypassing the filtering capabilities of the lungs, may lead to embolic neurological phenomenon such as cerebral abscess, embolic stroke or a transient ischaemic attack (TIA), as seen in our patient. Haitjema et al[4] found that PAVMs occured in about 33% and cerebral AVMs in about 11% of cases. Serious neurological events, including TIA, stroke and cerebral abscess, occurred in up to 40% of HHT patients with PAVMs and near-normal oxygen tension. It was also noted that PAVMs may enlarge with time[5].

Our patient had HHT with untreated PAVMs for at least 25 years, but fortunately did not develop cerebral abscesses or any lasting neurological deficits. He did not have any cerebral or hepatic AVMs. PAVMs larger than 3mm in diameter require treatment, and transcatheter embolisation (embolotherapy) with Nester platinum coils by an experienced interventional radiologist has been shown to be safe and effective[6]. Embolotherapy not only significantly reduces the likelihood of the development of cerebral complications, but also pulmonary haemorrhage[7]. Cerebral AVMs larger than 1cm in diameter are usually treated with embolotherapy, neurovascular surgery, and/or stereotactic radiosurgery[8].

Our patient will be followed-up with regular arterial blood gas analyses. Regular screening for underlying PAVMs, possibly initially undetectable because of its small size, with methods such as shunt fraction measurements is of paramount importance as they may grow larger with time. Lee et al[9] have shown that contrast transthoracic echocardiography is a very sensitive method of screening for PAVMs and can detect those which are smaller than 3mm in diameter. However, this sensitive and technically-advanced method of screening or surveillance for PAVMs may cause anxiety for patients because very small PAVMs, although detected, may not be amenable to transcatheter embolisation.

Our patient does not need repeat imaging studies for cerebral AVMs as there is currently little evidence in the literature that they grow. Significant epistaxis may be controlled with laser ablation, and gastrointestinal bleeds with endoscopic application of heater probes or laser. Air humidification and nasal lubricants may help to decrease the frequency of epistaxis. Other measures include patient education about HHT. The patient has been informed to avoid anticoagulants and anti-inflammatory agents which interfere with blood haemostasis. The need for antibiotic prophylaxis for procedures was reinforced. Genetic counselling, which provides the patients and their families with information on the nature, inheritance and implications of HHT to enable them to make informed medical and personal decisions, will be offered, particularly as the patient is planning to have children.

In conclusion, this report serves to remind clinicians about HHT and the possibility of underlying AVMs, which may not always manifest clinically in the first instance. If untreated, the consequences are serious and can prove to be a medico-legal pitfall. This case also illustrates the importance of patient education, including genetic counselling, for hereditary conditions and appropriate screening with regular follow-up for patients with HHT.

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