A combined vascular surgical and clinical genetics approach to diffuse aneurysmal disease

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ABSTRACT

We report two patients who presented with extensive aneurysmal disease, in association with minimal external physical signs. Patient 1 remained genetically undiagnosed despite multiple structural, biochemical and genetic investigations. He made a good recovery following surgery for popliteal and left axillary artery aneurysms. Patient 2 was diagnosed with vascular type Ehlers–Danlos syndrome, associated with a high degree of tissue and blood vessel fragility, and is being managed conservatively. Early multidisciplinary assessment of such patients facilitates accurate diagnosis and management.

KEYWORDS


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The presence of multiple arterial aneurysms is relatively rarely described, and has been previously reported in association with autoimmune vasculitis, infection and a small number of heritable disorders of connective tissue (HDCTs).1 Vascular type Ehlers–Danlos syndrome (EDS) carries a high risk of morbidity and mortality associated with operative and intravascular procedures.2 For this reason, the identification of individuals with a potential underlying genetic diagnosis is important for surgical planning. Both patients we present had no prior genetic diagnosis. We outline the differential diagnoses for patients with multiple aneurysms and discuss relevant HDCTs.

Case 1

A 54-year-old Sri Lankan man presented with painful, pulsatile, bilateral axillary masses. He had last visited a tuberculosis (TB) endemic area 15 years previously and had a prior diagnosis of latent TB, with a positive Mantoux test (22mm) 18 months before his presentation. There was no history of claudication or rest pain. Popliteal and left axillary artery aneurysms. Patient 2 was diagnosed with vascular type Ehlers–Danlos syndrome, associated with a high degree of tissue and blood vessel fragility, and is being managed conservatively. Early multidisciplinary assessment of such patients facilitates accurate diagnosis and management.

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He underwent successful bilateral femoropopliteal bypass surgery and some months later, left subclavian-to-axillary bypass grafting.

Genetic assessment revealed no relevant family history; the proband was the third of nine siblings of unrelated parents. His skin appeared of normal thickness and integrity, and there was no skin thinning or acrogeria. There was mild bitemporal narrowing, with no other dysmorphism. There was no pectus deformity or generalised large or small joint hypermobility (Beighton score 0/9). The uvula and palate were normal.

Skin biopsy showed a mildly abnormal ratio of elastin to collagen. Ultrastructural studies revealed normal collagen fibril morphology and packing, with dilated endoplasmic reticulum of unknown significance. Collagen protein analysis from cultured skin fibroblasts showed a normal ratio of procollagen (III) and intracellular collagen (III). Popliteal artery histology revealed focal destruction of the muscular arterial wall, with chronic inflammation and thrombus. These findings are not typical of a primary vasculitis or known HDCT. Molecular genetic testing (sequencing and multiplex ligation dependent probe amplification) of COL3A1, TGFBR1 and TGFBR2 were normal/negative.

Case 2
A 36-year-old woman presented with primary infertility. Pelvic ultrasonography revealed a uterus didelphys, an atrophic right kidney and a dilated distal aorta. Magnetic resonance angiography (MRA) revealed saccular aneurysms of her aortic bifurcation and splenic artery (Fig 2).

Genetic assessment revealed was no relevant family history and her parents were unrelated. There was no prior history of ligament or tendon injury, unusual scars or severe ecchymosis although there was mild and lifelong easy bruising. The patient was non-dysmorphic, with a mild degree of skin thinning at the arms. Sequencing of the COL3A1 gene revealed a mutation: c.1340G>A, p.(Gly447Asp). This confirmed the diagnosis of vascular type EDS. The combination of renal and uterine abnormality also raised the possibility of a small chromosome abnormality. Array comparative genomic hybridisation (Agilent [Santa Clara, CA, US] 8 x 60kb 60-mer oligo array, International Standards for Cytogenomic Arrays design 024612) showed a 188kb deletion at 16p12.1, of unknown clinical significance. (Parental samples were not available.) The patient was managed conservatively and referred onward for consideration of celiprolol therapy.

Discussion
Multiple aneurysms are reported commonly in patients presenting with a popliteal aneurysm and are more prevalent in male patients. In 571 patients with a unilateral popliteal aneurysm from the national Swedish registry, 28.1% had aortic aneurysms. While atheromatous disease is the most common pathological correlate, other causes include infection and trauma. In younger patients, the differential diagnoses include Behçet’s disease and/or vasculitis.
Vascular EDS (Online Mendelian Inheritance in Man® (OMIM) database #130050) is caused by a mutation of the COL3A1 procollagen (III) gene on chromosome 2 with autosomal dominant inheritance. Mutations resulting in glycine substitution disrupt type III collagen synthesis and excretion to the extracellular matrix, causing abnormal structural integrity to connective tissues, particularly blood vessels, colon and skin. In the largest cohort of cases to date, the median age of death was 48 years. In 25% of cases, a major complication was present by the age of 20 years, and by age 40, this proportion increased to 80%. The majority of deaths were due to arterial dissection or rupture. Peripartum death due to uterine or vessel rupture occurred in 12 of 81 women.

Vascular EDS is one of six major types of EDS using the most recently described classification. Features of vascular EDS are variable. They include severe arterial and tissue fragility, with arteries prone to aneurysm formation, dissection and rupture both spontaneously and during surgery. Diagnosis is indicated by the presence of two or more major criteria (Table 1). Nonsense mutations result in a milder external phenotype. However, they are still associated with a significant risk of vascular and hollow organ complications. Individuals displaying minor criteria may warrant further investigation for this and alternative diagnoses while those with major features require confirmation by genetic testing.

Evidence for effective prophylactic and therapeutic interventions specific to this group of patients is limited owing to the rarity of the disease. A single randomised clinical trial of celiprolol versus non-treatment showed benefit in the prevention of complications and dissection in vascular EDS patients. The study has been criticised because of the small number of patients included, some of whom did not have a genetically confirmed diagnosis. Nevertheless, the treatment benefits were significant, with reduction in arterial and hollow organ rupture.

Other HDCTs associated with multiple aneurysms include LDS (OMIM #609192) resulting from mutations in the TGFBR1/TGFBR2 and SMAD1 genes. These mutations cause abnormal cell signalling, which affects the development of vascular structures and musculoskeletal tissues. LDS patients may have aggressive aneurysm formation and arterial tortuosity beyond the aortic root, most commonly in the head, neck and thoracic aorta, a feature that is also associated with the Marfan syndrome. Facial dysmorphism affects up to 75% of individuals, with a cleft palate and bifid uvula forming major criteria for clinical diagnosis. Hypertelorism (wide spaced eyes), craniosynostosis, blue sclerae, micrognathia or retrognathia and strabismus are reported. Skin may be translucent, with visible veins, a history of easy bruising and poor wound healing.

ATS (OMIM #208050) is an autosomal recessive disorder affecting the integrity of large and medium sized arteries as a result of elastic fibre disruption in the tunica media. Cases usually present in the paediatric age group, with adult cases reported occasionally. A review of 55 cases reported prominent features including elongation, dilation and stenoses of large and medium sized arteries. Elsewhere, abdominal hernias, joint instability, facial dysmorphism (facial elongation, micrognathia and beaked nose) and skin laxity are present.

PXEx (OMIM #264800) results in mineralisation and subsequent fragmentation of elastic fibres, affecting the retina, dermis and medium sized arteries. The pattern of inheritance is autosomal recessive with a variable mutation in the ABCA6 gene on chromosome 16. Clinical features include skin laxity and papular lesions affecting the flexures and skin creases. Visual impairment is caused by retinal haemorrhage subsequent to retinal mineralisation. Patients can also suffer from angina, claudication and rest pain. A review from 2015 identified peripheral arterial disease as a major component.

Conclusions

These two cases illustrate the potential complexity with which patients with multiple aneurysmal disease present. A multidisciplinary vascular surgical and genetic assessment provides the optimal environment to treat this population. Many patients with different HDCTs have overlapping clinical and histological features, and in many individuals, the genetic cause remains unknown. In these situations, exclusion of...
vascular EDS is recommended if at all possible as vascular surgical intervention could be more harmful than beneficial. Infective and inflammatory aetiologies may also be relevant, particularly in the absence of risk factors for atherosclerosis. Securing a genetic diagnosis is important, not only for preventing excess morbidity and mortality but also for effective medical management and for counselling of family members.

References