Unusual association of diseases/symptoms

Type IV Ehlers-Danlos syndrome presenting as recurrent, bilateral carotid dissections

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Summary

Vascular (type IV) Ehlers-Danlos is an autosomally dominant inherited condition that results from a defect in type III collagen production. It can result in vascular complications such as rupture and dissection, as well as gastrointestinal and uterine rupture. We present the case of a 17-year-old girl who presented with transient neurological signs and pulsatile tinnitus secondary to carotid dissection 1 year after suffering from a stroke caused also by a carotid dissection on the contralateral side. We managed acutely and investigated for an underlying connective tissue disorder. Genetic analysis of COL3A1 was performed and a heterozygous missense, non-conservative mutation of c.970G>A was detected. This replication mutation has previously been associated with type IV Ehlers-Danlos syndrome.

BACKGROUND

The presentation of a recurrent and contralateral carotid dissection in a young patient prompted a discussion about our standard practice of screening young stroke patients for a primary cause. The other signs on examination prompted the possibility of a connective tissue disorder such as Ehlers-Danlos syndrome (EDS). The subsequent genetic analysis confirmed our suspicions. We feel that the case nicely illustrates the process we went through, from a clinical suspicion to confirmation.

CASE PRESENTATION

We present the case of a 17-year-old girl who presented to Leighton Hospital in February 2012 with a history of expressive dysphasia, dysarthria and right-sided paraesthesia associated with painless, pulsatile tinnitus that occurred suddenly while cycling. Her symptoms lasted 45 min and resolved spontaneously prior to hospital arrival. Neurological and cardiovascular examinations were normal in the accident and emergency department.

Her medical history included a history of mitral valve prolapse diagnosed as a child and there was also a history of recurrent patellar dislocation. Significantly she had been admitted 1 year previously with left-sided facial weakness and headache. MRI at the time revealed a right-sided mid-frontal lobe cerebral ischaemic lesion (figure 1). Time-of-flight angiography revealed reduced flow and calibre through the right extracranial internal carotid artery consistent with a right-sided carotid artery dissection (figure 2). She was started on warfarin for 6 months and her symptoms resolved with no residual neurological deficit. A further MRI was performed on her second admission which revealed a new left-sided, distal, extra-cranial internal carotid artery dissection (figure 3). On this occasion no corresponding, acute ischaemic lesion was detected intracerebrally.

On further questioning, it was noted in her family history that her paternal grandmother had a history of

hypermobile joints. There was no other family history of vascular rupture, dissection or sudden death.

She was not on any regular medications including the oral contraceptives. She had no known drug allergies. She was a non-smoker, did not consume alcohol and was studying in college full-time.

Further examination revealed hypermobile joints with a Brighton score of 8 of 9, but there was no evidence of hyperelastic or translucent skin. She was noted to have lobeless ears but no other distinguishing facial features.

INVESTIGATIONS

She had an echocardiogram, which showed trivial mitral regurgitation without an obvious valve prolapse. They were unable to exclude a potentially aneurysmal brachiocephalic artery on the scan and proceeded to CT angiogram of the aortic arch and its branches. The CT angiogram showed normal anatomy and dimensions of the aortic branches and no dissection flaps. Both extracranial internal carotid arteries were noted to have an irregular outline and reduced calibres consistent with the known dissections.

No aneurysmal vessels were found on ultrasound of the aorta or bilateral leg Doppler ultrasound.

Routine blood tests were normal.

OUTCOME AND FOLLOW-UP

The unusual presentation of recurring carotid dissections in multiple vessels prompted a rheumatology referral and a potential diagnosis of vascular EDS was suggested. She was investigated for connective tissue conditions as well as vasculitic disorders. An autoimmune profile, including antinuclear antibody and anti-neutrophil cytoplasmic antibodies, was negative. Erythrocyte sedimentation rate was not significantly raised enough to consider vasculitis as a causative factor.

Genetic analysis of COL3A1 was performed and this highlighted a heterozygous missense, non-conservative mutation of c.970G>A. This replication mutation has

Figure 1 Left T2-weighted; middle diffusion-weighted images; right apparent diffusion coefficient images: MRI sequences illustrating abnormal high signal intensity on the in the right mid-frontal lobe on T2-weighted and diffusion-weighted imaging consistent with acute ischaemic infarction. Apparent diffusion coefficient excludes artefact such as T2 shine. MRI performed in January 2011.

previously been associated with type IV EDS.¹ This defect results in structurally abnormal type III collagen production by fibroblasts.²

DISCUSSION

EDS is a collection of related, inheritable disorders of collagen production. There are six recognised major subtypes, of which type IV EDS is one of the less common forms.³ It is an autosomally dominant inherited disorder of the COL3A1 gene resulting in abnormal collagen production; however, as high as 50% of cases are the result of de novo mutations.⁴ It is typically associated with hypermobile joints, typical facies (thin nose and lips, large eyes, small chin and lobeless ears) and thin, translucent skin. The condition can result in significant vascular rupture and neurovascular complications such as occurred in this case.⁵ There is no curative treatment available.³

There are two reported cases in the literature of type IV EDS presenting as simultaneous bilateral carotid dissection.^{6,7} This case represents the first case of type IV EDS

presenting with bilateral carotid dissections, separated temporally in the literature.

Recurrent carotid dissection is an uncommon presentation, especially with involvement on the contralateral side to the initial insult. It should prompt further investigation to exclude an underlying, connective tissue disorder such as EDS. While rare it should be considered in the differential diagnosis of young patients presenting with arterial dissection or stroke.⁸

While there was no family history of vascular rupture, dissection or connective tissue disease, a thorough family history may prompt this differential diagnosis earlier, thus allowing for confirmatory evidence to be obtained. Furthermore, prompt diagnosis can allow for future planning and management of potential complications earlier in the disease course. It can also allow for appropriate counselling of the diseases natural course. The risk of uterine rupture in pregnancy is of particular importance in a female patient of reproductive age, such as in this report.⁹

Figure 2 Time-of-flight angiography showing restricted flow and reduced calibre of the right internal carotid artery (black arrows). Scan performed in January 2011.

Figure 3 Time-of-flight angiography showing near absent flow of the distal, extracranial left internal carotid artery (white arrow). MRI performed in February 2012.

Given the autosomal-dominant inheritance of the condition it is vital to confirm the diagnosis, thus allowing genetic counselling for relatives and for future family planning to take place. The diagnosis is of significant relevance to first-degree relatives and referral for genetic counselling is essential, as is routine surveillance of the patient.

Learning points

- ▶ Bilateral and recurrent vascular dissection is an unusual presentation and should prompt further investigation for an underlying disease process.
- ▶ A differential diagnosis with recurrent vascular dissection should include vasculitis and connective tissue disorders such as Ehlers-Danlos syndrome (EDS).
- ▶ Prompt diagnosis of type IV (vascular) EDS is essential for genetic counselling and family planning.
- ▶ Prompt diagnosis can also allow for future planning due to the natural disease course of potential gastrointestinal, vascular and uterine rupture.

Competing interests None.

Patient consent Obtained.

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