Small Head with Big Vessels

A 46-year-old gentleman with normal intellectual and cognitive function presented to the emergency department with acute left-sided chest pain and palpitations. He was of normal stature, although joint hyperextensibility and microcephaly were noted on examination. Upon further history acquisition, a positive maternal family history of vascular disorder was obtained. Computed tomography (CT) aortogram was performed and showed intramural haematoma of the ascending aorta, along with the presence of dural ectasia (Fig. 1). He subsequently underwent emergency aortic repair. During the postoperative period, he developed facial twitching and neuroimaging studies of the brain were performed (Fig. 2). What is the most likely diagnosis?

A. Marfan syndrome
B. Loeys-Dietz syndrome
C. Shprintzen-Goldberg syndrome
D. Ehlers-Danlos syndrome
E. Arterial tortuosity syndrome

Findings and Diagnosis

CT aortogram showed dural ectasia and intramural haematoma of the ascending aorta (Fig. 1). CT angiogram of the brain showed an aneurysm of the azygos anterior cerebral artery (ACA) as well as ectatic and tortuous proximal basilar and distal left cervical internal cerebral arteries (Figs. 2A-C). The 3-dimensional (3-D) CT images shown in Figures 2D to 2F of the skull demonstrate severe microcephaly and pancraniosynostosis.

Discussion

Loeys-Dietz syndrome (LDS) is a rare autosomal dominant connective tissue disease with an estimated prevalence of less than 1 in 100,000 persons.[1] It was first described in 2005 by Loeys et al[2] and is characterised by the triad of: 1) arterial tortuosity, aneurysms, or dissections, 2) hypertelorism, and 3) bifid uvula or cleft palate. To date, 4 genetic aetiologies of LDS have been identified: 1) *transforming growth factor β receptor I (TGFBR1)* gene, 2) *transforming growth factor β receptor II (TGFBR2)* gene, 3) *mothers against decapentaplegic homolog 3 (SMAD3)* gene, and 4) *transforming growth factor β 2 ligand (TGFB2)* gene. These genetic aetiologies form the basis of the 4 different subtypes of LDS, as detailed in Figure 3.[2-5] All 4 types of LDS have been associated with thoracic aortic aneurysm and/or dissection. Aortic root dilatation is seen in up to 98% of patients with LDS.[3] Loeys et al suggested that cardiovascular outcome of patients with LDS may be predicted by a "craniofacial severity index", based on 4 clinical indices: hypertelorism, cleft palate, craniosynostosis and uvula anomalies. A higher score (from 0 to 11) indicates a more severe malformation and poorer cardiovascular outcome.[3] LDS is often misdiagnosed as other multisystem connective tissue disorders with vascular manifestations such as Marfan syndrome, Shprintzen-Goldberg syndrome (Marfanoid craniosynostosis syndrome), vascular Ehlers-

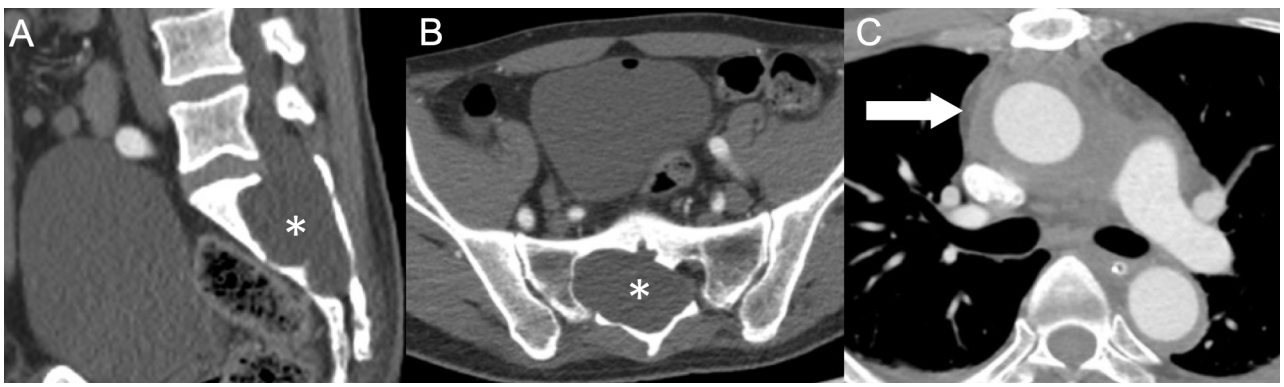

Fig. 1. Computed tomography (CT) aortogram showed dural ectasia (*in A and B) and intramural haematoma of the ascending aorta (arrow in C).

Answer: B

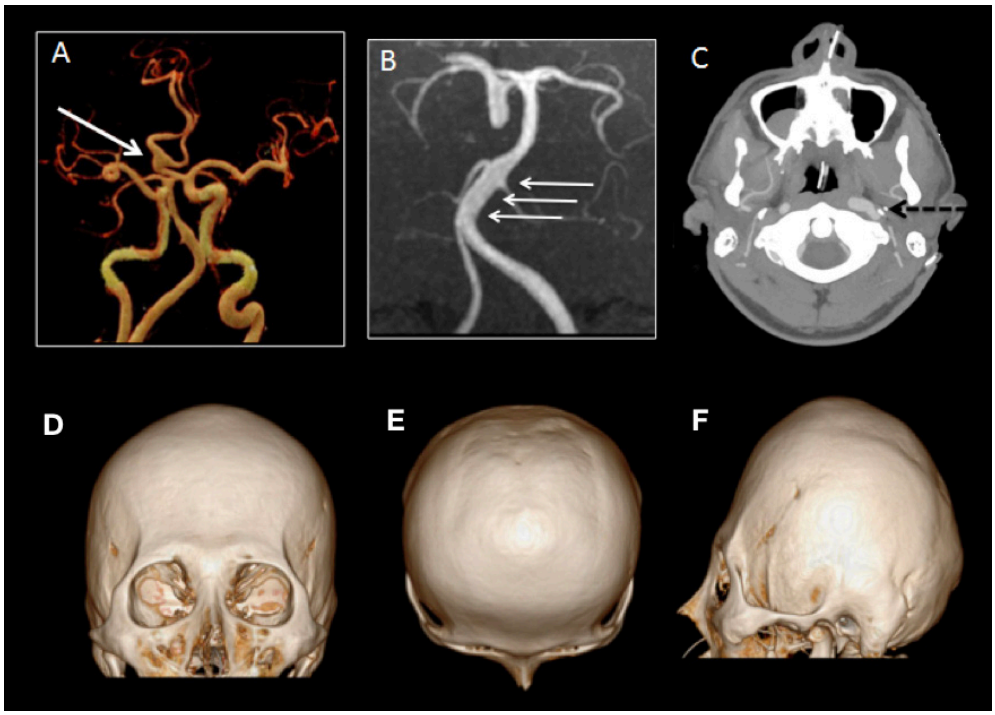

Fig. 2. Computed tomography (CT) angiogram of the brain showed an aneurysm of the azygos anterior cerebral artery (ACA) (arrow in A) as well as ectatic and tortuous proximal basilar (arrows in B) and distal left internal cerebral arteries (arrow in C). D to F depict 3-dimensional (3-D) CT images of the cranial vault, demonstrating severe microcephaly and pancraniosynostosis.

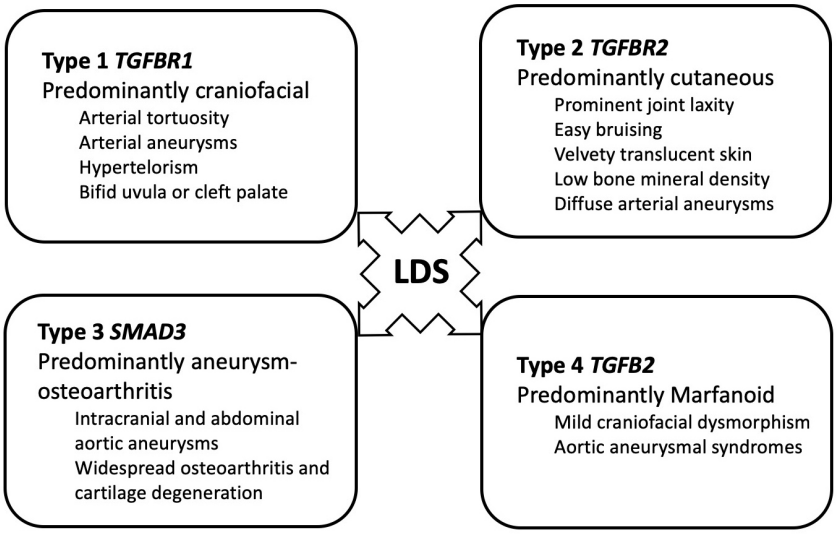

Fig. 3. Diagram showing Loeys-Dietz syndrome (LDS) subtypes and phenotypes.

Danlos syndrome and arterial tortuosity syndrome. These disorders have a common feature of which aneurysms are formed at a young age and have a propensity for dissection. Apart from the acute manifestations of aortic dissection, patients with thoracic aortic aneurysm may occasionally present with paradoxical orthodeoxia or left vocal cord palsy due to compression upon the left recurrent laryngeal nerve (Ortner's syndrome).[6,7]

Marfan syndrome is an autosomal dominant disorder due to mutations involving the *FBN1* gene. LDS is often misdiagnosed as Marfan syndrome as both entities can share some common features. However, vascular manifestations in Marfan syndrome are often isolated to the aorta, in contradistinction to LDS which usually has arterial involvement other than aorta, such as in our described patient.[1] In addition, ocular manifestations such as ectopia lentis are more common in Marfan syndrome compared to LDS.[8] The current diagnosis of Marfan syndrome relies on the clinical criteria of the 2010 Revised Ghent Nosology.[9] In the presence of family history, aortic root aneurysm and ectopia lentis are 2 cardinal criteria of diagnosis.

Shprintzen-Goldberg syndrome (SGS) is an extremely rare autosomal dominant connective tissue disease which can also present with aortic aneurysm and craniosynostosis. The aneurysm seen with SGS is commonly restricted to the aortic root and less severe than those seen in LDS and Marfan syndrome. SGS is also not associated with arterial tortuosity, a feature commonly seen in patients with LDS.[1] Developmental delay and intellectual disability are commonly seen in patients with SGS.[10] To the best of our knowledge, these have never been reported in association with LDS before. Hence, the diagnosis of SGS is highly unlikely in our patient who has normal intellect and cognition.

Vascular Ehlers-Danlos syndrome (EDS) or EDS Type 4 is an autosomal dominant disorder characterised by increased bruising, arterial and bowel wall fragility due to defective collagen synthesis. The most common genetic aetiology of EDS Type 4 involves pathogenic variants of *COL3A1* gene. Clinical diagnostic criteria established in Villefranche in 1997[11] are useful to guide genetic testing in patients with clinical features suggestive of EDS. Vascular manifestations of EDS Type 4 are often similar to LDS and Marfan syndrome. Easy bruising, a feature classically described in patients with EDS, may also be present in LDS. Individuals with vascular EDS tend to have short stature, in contrast to the tall stature in patients with Marfan syndrome. Also, craniosynostosis is extremely rare in vascular EDS. Hence, the presence of craniosynostosis in our patient is an extremely useful clinical clue, rendering the diagnosis of EDS Type 4 as less likely compared to LDS.

Arterial tortuosity syndrome (ATS) is a connective tissue disorder characterised by elongated and tortuous large and medium-sized arteries with a propensity for aneurysm formation, dissection and ischaemic events. Arterial tortuosity is also a feature of LDS. ATS is caused by mutations involving the *SLC2A10* gene which is involved in the synthesis of GLUT10. GLUT10 is a regulatory protein of the transforming growth factor-beta (TGF-β) signalling pathway. ATS is inherited in an autosomal recessive manner, unlike the rest of the prior described connective tissue diseases (including LDS), which are generally inherited in an autosomal dominant manner. Congenital diaphragmatic abnormalities including diaphragmatic hernia are frequently reported in association with ATS. The family history elicited from our patient suggested an autosomal dominant disease, making the diagnosis of ATS less likely.[12]

A pragmatic approach to inherited connective tissue diseases with vascular manifestations is crucial to facilitate the diagnostic process and this is only possible with adequate clinical information, as delineated in Figure 4. Timely diagnosis allows for rapid intervention and this is crucial in the prevention of life-threatening complications.

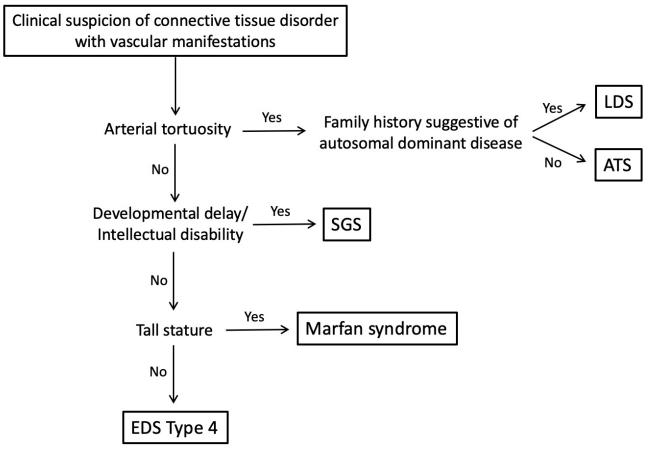

Fig. 4. Diagnostic approach to inherited connective tissue diseases with vascular manifestations. ATS: Arterial tortuosity syndrome; EDS: Ehlers-Danlos syndrome; LDS: Loeys-Dietz syndrome; SGS: Shprintzen-Goldberg syndrome.

Conclusion

Although rare, cognisance of the clinical features of LDS is important in expediting the diagnosis and enabling effective patient management. A pragmatic approach to inherited connective tissue disorders with vascular manifestations as suggested by the authors would facilitate the diagnostic process.

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