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Novel Mutation of the TGF-β 3 Protein (Loeys-Dietz Type 5) Associated With Aortic and Carotid Dissections

Case Report

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Abstract

Objectives

Loeys-Dietz syndrome (LDS) is a rare genetic cause of stroke associated with connective tissue disorders but is not well known among stroke physicians.[1] The main objectives of this case report are to increase awareness of this condition and to improve stroke prevention at follow-up visits.

Methods

A patient with aortic and carotid artery dissection who had undergone 2 major aortic surgeries with mechanical composite graft and treated with full-dose anticoagulation was reevaluated by neurologists due to retinal hypoperfusion symptoms. After musculoskeletal examination, cervical ultrasonography, and computerized tomography angiography, he was referred for whole-genome sequencing.

Results

We found joint hypermobility, skin hyperelasticity, bifid uvula, and combined cervical artery dissections that caused intermittently decreased blood flow in the left ophthalmic artery and an acute asymptomatic embolic stroke. A novel pathogenic variant of LDS type 5 consisting of a heterogeneous nonsense variant c.1044C>A, p.(Cys384*) was found in the TGF-β 3 (TGFB3) gene. Consequently, anticoagulation was intensified, and at 1-year follow-up, the patient's symptoms improved.

Discussion

This novel genetic variant coupled to the patient's phenotype contributes to the knowledge of genetic causes of stroke. Patients with multiple arterial dissections and musculoskeletal features should be offered genetic testing and be carefully evaluated to avoid further cerebrovascular ischemic lesions.

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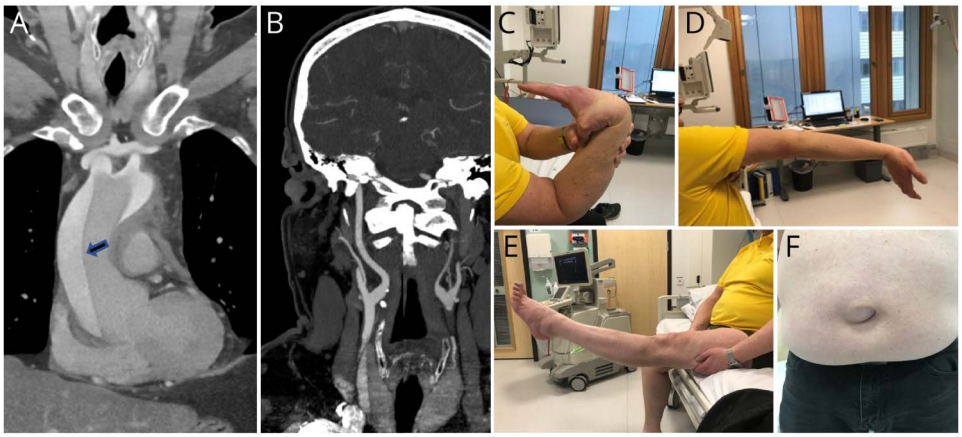
Figure Vascular and Clinical Findings



CT angiography (CTA) showing aortic dissection membrane (black arrow, A). Coronal reconstruction of CTA showing right common carotid artery (CCA) dissection and left CCA occlusive dissection extending to the internal carotid artery (B). Passive apposition of the thumb to the flexor aspect of the forearm (C). Passive hyperextension of the elbow beyond 10° (D). Passive hyperextension of the knee beyond 10° (E). Postoperative umbilical hernia (F).

Case Report

A 54-year-old man with a history of congenital hip luxation underwent acute surgery and supracoronary graft in the ascending aorta in 2018 due to a Stanford type A, Debakey type I aortic dissection. Follow-up CT angiography showed a rapid dilatation of the proximal descending aorta, from 37 to 57 mm (Figure, A).

He was reoperated in 2019 with replacement of the aortic arch using a frozen elephant trunk technique followed by individual reimplantation of the cervical vessels and replacement of the aortic root with a mechanical composite graft and thereafter prescribed oral warfarin.

Postoperative follow-up computerized tomography angiography showed proximal right common carotid artery (CCA) dissection and an occluded left CCA (Figure, B). During several months, the patient experienced dizziness and monocular visual loss induced by head rotation to the left.

Carotid duplex ultrasound at our department confirmed patency of the right CCA (peak systolic velocity/end diastolic velocity = 142/15 cm/s) and right internal carotid artery (ICA, 75/17 cm/s). The left CCA was occluded, and the left ICA had a steal morphology (42/10 cm/s). Lower flow velocities in the left ophthalmic artery were detected with the patient's head turned to the left (28/10 cm/s vs 46/11 cm/s in neutral head position), indicating retinal artery hypoperfusion. Flow velocities in the right ophthalmic artery remained unchanged during head rotation (55/16 cm/s). Brain CT showed an asymptomatic small-sized acute ischemic infarct in the right superior frontal gyrus. Consequently, oral anticoagulation was adjusted to international normalized ratio (INR) target of 2.5–3.5 due to an initial INR of 2.1.

The patient informed us about previous joint dislocations. Physical examination showed skin hyperextensibility and joint hypermobility (Figure, C, D, and E), scoring 6 points on the Beighton scale score. Findings included pectus carinatum, bilateral pes cavus, bifid uvula, and unexpected postoperative umbilical hernia (Figure, F). In addition, one of his daughters had joint hypermobility. His mother had died suddenly at age 74 years of undetermined cardiovascular cause and had joint hypermobility. Whole-genome sequencing analyzing coding, splicing, and structural variants regarding 141 genes involved in connective tissue disorders[2] identified a heterogeneous nonsense variant in the TGFB3 gene (NM_003239.4) c.1044C>A, p.(Cys384*), which is associated with Loeys-Dietz syndrome (LDS) type 5.

Discussion

LDS was first described in 2005 but remains relatively unknown. Since 2005, 5 major subtypes have been identified in relation to the gene mutations found in the transforming growth factor (TGF)-β receptor (types 1 and 2), TGFB 2 and 3 receptor ligands (types 4 and 5), or the small mothers against decapentaplegic homolog proteins 2 and 3, which are downstream transcription factors for cell growth, angiogenesis, apoptosis, and tumor inhibition (type 3).[3] LDS type 5, caused by TGFB3 mutations situated in chromosome 14q24.3, is associated with aortic aneurysms and dissections involving the thoracic and/or abdominal aorta. Other features may include bifid uvula (links.lww.com/NXG/A475), cleft palate, mitral valve disease, skeletal overgrowth, cervical spine instability, and clubfoot deformity, although the phenotype varies largely between patients.[3-5]

The variant found in our patient, c.1044C>4, p.(Cys384*), located in a functional TGF domain, is novel and was found using whole-genome sequencing analyzing 141 genes causing connective tissue disorders. It has not been found, either in the normal population (gnomAD)[6] or in patients. Other pathogenic sequence variants in the TGFB3 gene have been reported in

children and adults and include missense substitutions (c.898C>G, p.(Arg300Gly), c.898C>T, p.(Arg300Trp) and c.899G>A, p.(Arg300Gln), c.1226G>A, p.(Cys409Tyr)), nonsense (p.Tyr365*), frameshift (c.704del, p.Asn235-Metfs*11 and c.1102_1105del, p.(Leu368Thrfs*18)), and splice site (c.754+2T>C) variants. The patient's family members could potentially be mutation carriers and will be offered genetic counseling. A correlation with known mutations of this gene and the clinical features of our patient suggests that this variant is pathologic.

This case report emphasizes the vascular vulnerability of an aberrant TGFB signaling pathway. The multiple dissections predisposed our patient to retinal hypoperfusion. Acute ischemic infarcts have been reported in adults with LDS emphasizing the importance of thorough neuroradiology, ultrasonography, and thoracic radiology to prevent serious neurologic complications.[7] At 1-year follow-up, our patient reported visual symptoms to occur more seldom and did not experience any dizziness recurrence. Cervical ultrasound showed an improvement of the left ICA dissection, which no longer exhibited any steal phenomenon, and flow velocities in the ophthalmic arteries were symmetrical. The patient did not report any new stroke symptoms or hemorrhagic complications with the higher INR target.

In conclusion, this report illustrates the need for early phenotype recognition of LDS, which may overlap with Ehlers-Danlos and Marfan syndromes, highlighting a potential underrecognized genetic cause of ischemic stroke.

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Kristina Lagerstedt-Robinson, MD, PhD	Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden; Department of Clinical Genetics, Karolinska University Hospital, Stockholm, Sweden	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; and analysis or interpretation of data
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