RESIDENT & FELLOW SECTION

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Clinical Reasoning: Sudden-onset pulsatile headache in a previously healthy young man

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SECTION 1

A previously healthy 41-year-old man presented to the local hospital with a sudden-onset right-sided pulsatile headache, accompanied by vertigo, unstable gait, nausea, and vomiting. On admission, he additionally presented with left central facial paralysis, left-sided hemiparesis, and NIH Stroke Scale score of 2. The patient denied history of hypertension, diabetes, or any other high-risk factors for cerebral vascular diseases (CVD). Diffusion-weighted imaging (DWI) revealed multiple acute focal infarctions in the right frontoparietal lobe consistent with decreased blood supply through the right carotid artery (figure e-1A1 at Neurology.org).

Question for consideration:

1. What are the most common causes for stroke in young adults without high-risk factors for CVD?

GO TO SECTION 2

Supplemental data at Neurology.org

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SECTION 2

Ischemic stroke in young adults is different from old stroke with respect to the high prevalence of unusual risk factors and etiology among young patients with stroke.[1] The top 10 rare causes that have been linked chiefly to stroke in young patients are migraine, illicit drug use, patent foramen ovale, oral contraceptives, pregnancy, arterial dissection, reversible cerebral vasoconstriction, inflammatory arteritis, cardiomyopathy, and coagulation factors.[1]

Routine blood test, ECG, heart and carotid ultrasonography, and transcranial Doppler were unremarkable. Further digital subtraction angiography (DSA) revealed a complex pattern of brain blood supply (figure e-2, A and C): (1) irregularity of contrast filling indicating artery dissection formation in the C1 segment of the right internal carotid artery (RICA) with visible active thrombosis and diminished forward flow; (2) Dissection at C1 level of the left internal carotid artery (LICA) without luminal restriction with normal flow (3); intracranial supply of internal carotid artery (ICA) partially compensated by lateral circulation from normal vertebral arteries (VA).

Cerebral artery dissection (CAD) is one of the most frequent causes of stroke in young adults, and is usually related to trauma, massage, or other neck injuries. Spontaneous cerebral artery dissections occur primarily in middle-aged patients with a higher frequency in men. Pain is most frequently the initial symptom. Ischemic manifestations are common, with a reported frequency of 50%–95%.[2] The most common mechanism of ischemia is thromboembolism. Ischemic symptoms can be exacerbated by hemodynamic insufficiency. In our case, however, although dissections occurred on both sides, ischemia mainly resulted from acute severe stenosis of RICA. Recently, high-resolution magnetic resonance (HR-MR) scan has become an alternative noninvasive approach to diagnose occlusive dissection and determine the extent of CAD.

The patient was transferred to our hospital. HR-MR scan revealed unstable plaques in the upper segment of RICA, with multiple ulcers and a dissecting aneurysm about 18 mm long extending distally without reaching past the petrous. Intramural hematomas appear as hyperintensities in the false arterial lumen and the real arterial lumen was greatly compromised. A small round area of low signal in the false lumen was connected to the real lumen, indicating that both false and real lumens had blood flow (figure e-1B1). LICA dissected about 7 mm in the distal C1 segment, with small intimal flap inside (figure e-1C1).

Questions for consideration:

1. What are the most common risk factors for CAD?
2. As multiple concurrent dissections of carotid artery have only rarely been described, how can we explain spontaneous bilateral ICA dissections in such a young man?

GO TO SECTION 3

SECTION 3

Risk factors for CAD include both genetic and environmental factors. Patients often describe a history of trauma, such as a traffic accident or sports injury involving sudden neck movements and stretching, or even simply coughing, vomiting, or sneezing. Considering the lack of antecedent trauma in our patient and spontaneous bilateral ICA dissection in such a young man, special attention should be paid to heritable disorders.

A mutation analysis was performed by sequencing of all coding exons, including intron/exon boundaries of the 31 pathogenic genes of aortic disease. Altogether, 156 known or novel variations were detected by semiconductor sequencing. Filtered based on their status in dbSNP, 1000 genome project, and HGMD database, 2 novel missense variations of *COL5A1* (figure 1), c.1402G >A (p.Glu468Lys), and c.4241G >C (p.Gly1414Ala) were predicted with a probable damaging effect on protein type V collagen, and consequently the fragility of blood vessels. His parents had died more than 1 decade earlier of sudden-onset uncertain cerebral vascular diseases. Sequencing of these 2 sites for his sister and children showed wild-type in his sister and the older son (19 years old) and heterozygous mutations in the younger son (9 years old).

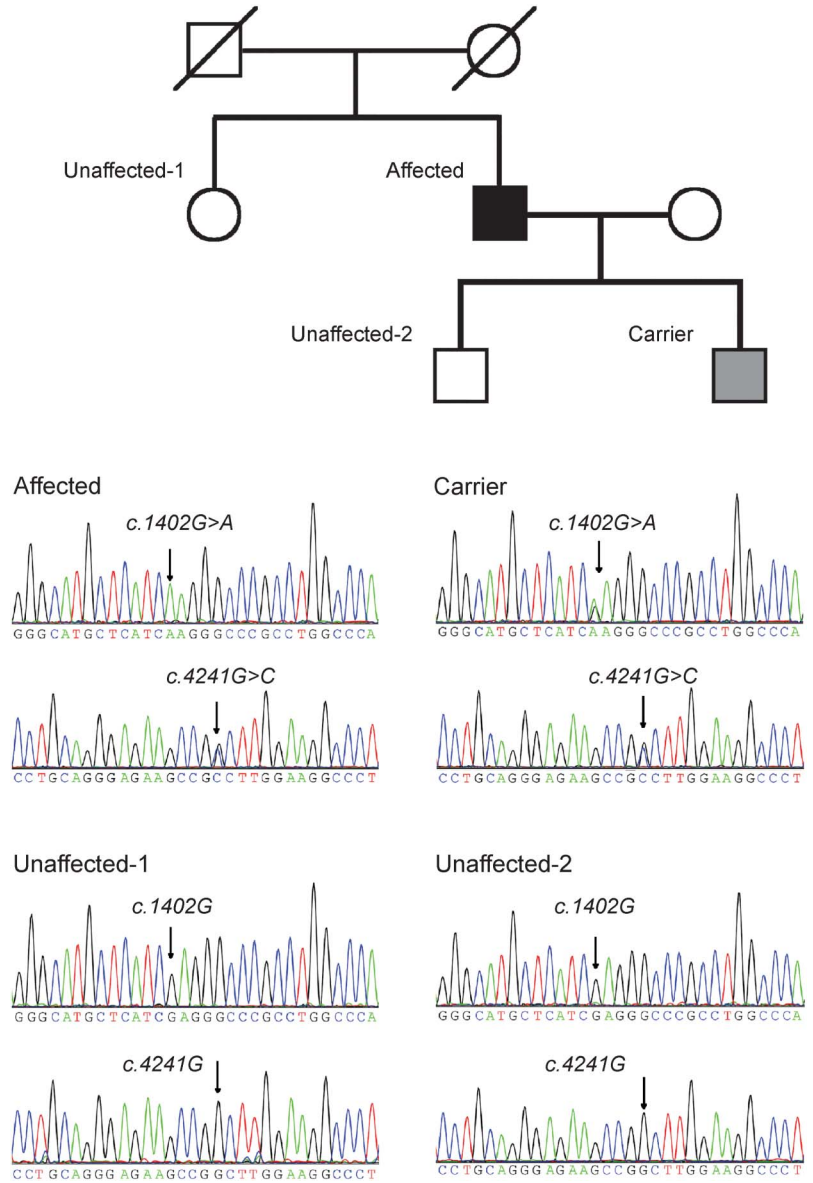
Mutations in *COL5A1* have been reported in Ehlers-Danlos syndrome, which can result in artery dissection, aneurysm, or ruptures. *COL5A1* mutations may decrease aortic stiffness and breaking strength, based on data from mice haploinsufficient for orthologous Col5a1.[3] The 2 mutations of *COL5A1* we found here are likely to be the genetic cause of our patient's multiple dissections. The patient's parents died of unknown disorders, with sudden-onset conceivably stroke attacks. His sister and older son are wild-type for these 2 sites (probably reverse mutation), and so far remain healthy with no signs of artery dissection. His younger son, however, inherited both mutations, and intense attention should be paid to the possibility of artery dissection in the future.

Question for consideration:

1. What is the next step in management?

GO TO SECTION 4

Figure 1 Sequence analysis of *COL5A1*



The patient (Affected) has 2 missense mutations, homozygous c.1402G >A (p.Glu468Lys) mutation and heterozygous c.4241G >C (p.Gly1414Ala) mutation. His sister (Unaffected-1) and the older son (Unaffected-2) are wild-type. His younger son (Carrier) has heterozygous mutations for these 2 sites.

SECTION 4

Medical management is the primary treatment approach for CAD, and anticoagulation with IV heparin followed by oral warfarin has been recommended for all patients with acute dissections,[4] with antiplatelets being the other first-line treatment.[5] Anticoagulant therapy was initiated at the time of CAD diagnosis. The patient had repeated gingival bleeding. Anticoagulant was discontinued and dual antiplatelet therapy (aspirin 100 mg/d and clopidogrel 75 mg/d) was administrated instead, accompanied with statin treatment. Neurologic deficits gradually improved and fully resolved at discharge. The patient was sent home neurologically intact on dual antiplatelet and statin therapy.

At a 3-month follow-up, DSA of all vessels was performed, revealing persistent dissection of both ICAs and incomplete recanalization of ICAs (figure e-2, B and D). Antegrade flow was relatively greater than diagnosis, with adequate blood supply to the brain. There were no new signs of right-sided ischemia on DWI (figure e-1A2). HR-MR scan further illustrated that unstable plaques in the RICA had shrunk and the intramural hematomas had almost disappeared. The real arterial lumen was greatly enlarged as visible on black-blood sequence (figure e-1B2). LICA remained roughly the same as at diagnosis (figure e-1C2).

Endovascular treatment was recommended for this complicated situation that had inadequately responded to medical therapy, but the patient refused it for financial reasons. The patient continued on antiplatelet and statin therapy, and 6 months after diagnosis, he has continued to do well clinically.

DISCUSSION We present a case of simultaneous ischemia due to spontaneous bilateral carotid artery dissection with mutations in *COL5A1* and good outcome in an adult man. This case highlights that (1) cerebral ischemic stroke in young adults without high-risk factors for vascular diseases should raise the suspicion of artery dissection; and (2) in the setting of spontaneous multiple vessel dissection without appreciable traumatic triggers, special attention should be paid to possibilities of gene mutation.

Though no randomized trials are available for medical treatment in CAD,[4,5] antithrombosis should be initiated promptly to prevent further thromboembolic events.[6] In most patients with multiple CADs, complete recanalization occurs in 78% of the dissected vessels and therefore medical treatment is sufficient.[7] Though our patient recovered from cerebral ischemia clinically, false lumen remained in both sides and recanalization was delayed indefinitely. Endovascular treatment would be reasonable in case of expanding pseudoaneurysm in our patient. However, with only medical intervention, he has remained neurologically intact at latest follow-up. Duration of treatment remained controversial (typically continued for 3–6 months)[2,4] and should be determined individually on long-term monitoring.

Our clinical observation implies that the 2 *COL5A1* mutations we describe might cause disorganized arterial vessel architecture resulting in artery dissection. While this is speculation lacking histologic support, the mutations might also explain delayed recanalization of our patient.

AUTHOR CONTRIBUTIONS

Dr. Qin: study concept and design, acquisition of data, drafting the manuscript. Dr. Pan: analysis and interpretation, critical revision of the manuscript for important intellectual content. Dr. Tian: critical revision of the manuscript for important intellectual content, study supervision, obtaining funding.

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DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

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