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EDITORIAL

Genetics of Spontaneous Coronary Artery Dissection Gains New Momentum

See Article by Kaadan et al

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Spontaneous coronary artery dissection (SCAD) is a nonatherosclerotic pathogenesis of acute coronary syndrome, characterized by a hematoma within the coronary artery vessel wall. SCAD may cause heart attack, cardiac arrest, and a variety of symptoms, including shortness of breath, chest pain, a rapid heartbeat, sweating, nausea, and fatigue. SCAD can occur at any age, but most patients are otherwise healthy women ≤50 years of age.[1,2]

Novel research methods and social media have contributed to a better recognition of this condition, which was previously considered rare with a prevalence of up to 1.1%.[1,3] Most SCAD events occur in patients with minimal cardiovascular risk factors. Furthermore, characteristic angiographic and intracoronary imaging appearances are not widely recognized, partly because of a common misconception that a visible dual lumen or linear dissection flap will usually be present. Recent series using careful diagnostic criteria that exclude iatrogenic, traumatic, and atherosclerotic dissection suggest that SCAD causes acute coronary syndrome in up to 35% of heart attack in women ≤50 years of age and is the most common cause of pregnancy-associated myocardial infarction.[1]

Risk factors of SCAD include pregnancy, recent delivery, high blood pressure, extreme exercise, and previous SCAD. Frequently associated conditions are fibromuscular dysplasia and inherited connective tissue disorders. Fibromuscular dysplasia in arteries other than the coronary arteries (characterized by alternating stenosis and dilatation resulting in a string-of-beads pattern in angiography) is diagnosed in many patients with SCAD . Only a minority of patients with SCAD present with known inherited connective tissue syndromes, like vascular Ehlers–Danlos syndrome, Marfan syndrome, or Loeys–Dietz syndrome. SCAD has also been associated with polycystic kidney disease, Alport syndrome, takotsubo syndrome, and other conditions.[4] Syndromic SCAD may cluster within families whereas the occurrence of nonsyndromic SCAD is usually sporadic.

Recently, genetic testing with a panel of 22 genes underlying familial thoracic aortic aneurysms and dissections and related disorders was performed in 59 patients from the retrospective Mayo Clinic SCAD registry.[5] The diagnosis of a known inherited connective tissue disorder was confirmed in 3 (5.1%) patients: 2 patients with pathogenic mutations in COL3A1 (collagen type III alpha 1 chain) causing vascular Ehlers–Danlos syndrome and in 1 patient with Marfan syndrome because of a disease-causing FBN1 (Fibrillin 1) mutation. Unfortunately, the description of the observed mutations was incompletely reported.

The current study by Kaadan et al[6] reports on genetic testing in 44 patients from a prospective SCAD registry at the Massachusetts General Hospital. Vari-

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ants of 29 genes were analyzed, with 16 genes tested in >50% of the sample. Pathogenic variants were identified in 6 (13.6%) patients: 3 patients had deleterious variants in COL3A1 (causing vascular Ehlers–Danlos syndrome). A COL3A1 variant in another patient was regarded as variant of uncertain significance, but its pathogenic role was not ruled out. Three further patients carried pathogenic variants associated with polycystic kidney disease, Loeys–Dietz syndrome, and nail-patella syndrome. None of the aforementioned patients with molecular findings had radiographic evidence of fibromuscular dysplasia. Moreover, patients with an identified pathogenic variant were younger than those without such variants.

The findings suggest that pathogenic COL3A1 variants predispose to SCAD at least in a minority (3%–7%) of the patients. Moreover, pathogenic variants in several other connective tissue genes seems to play a role in the pathogenesis of SCAD. Besides the aforementioned pathogenic findings, the authors reported multiple variants of uncertain significance.

Mutations in COL3A1 were also reported in earlier case studies whereas SCAD was recognized as a rare vascular manifestation of several heritable connective tissue disorders.[7,8] The overlap between the genetic findings in patients with cervical artery dissection is striking.[9–11] Interestingly, skin biopsies from the majority of the patients with cervical artery dissection show minor morphological alterations of the connective tissue structure, in absence of clinical signs of a known connective tissue disorder.[12,13]

The current prospective cardiovascular genetics evaluation in SCAD included patients tested at the Massachusetts General Hospital, as well as patients who had already been tested previously at an outside facility. As a consequence, the selection of analyzed genes varied across the study population. Moreover, the selection of analyzed genes was restricted to a set of commercial panels. It remains unclear why no disease-causing mutations could be identified in the majority of the patients with SCAD from the current study, in particular in patients presenting with additional dissection or aneurysms in other arteries—a pattern where one would expect to find a genetic cause more frequently.

Extending the number of genes to be analyzed or even performing a whole exome analysis may be an obvious next step to increase the diagnostic yield of pathogenic findings. Future genetic analysis may also include the study of larger-sized variants, in particular copy number variants, as recently associated with aortic dissection and cervical artery dissection.[14,15] Further studies will also reveal to what extent a common genetic background predisposes to arterial dissections in different arterial beds and which genetic variants are specific for events in particular arterial locations.[16]

The increased recognition of SCAD and the ongoing recruitment of larger study samples may lead to the identification of more patients with familial or recurrent SCAD. Prioritization of patients (young age, familial occurrence, recurrent/multiple SCAD events, and absence of known environmental risk factors) may increase the mutation detection rate. The analysis of familial cases, moreover, will facilitate the identification of disease-causing variants in novel candidate genes.

ARTICLE INFORMATION

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