Cardiology in the Young

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Isolated aortic dilation without osteoarthritis: a case of *SMAD3* mutation

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Brief Report

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Abstract

Aneurysm–osteoarthritis syndrome is a recently discovered inherited autosomal dominant connective tissue disease caused by *SMAD3* mutations. Aneurysm–osteoarthritis syndrome is responsible for 2% of familial thoracic aortic aneurysms and dissections and is characterised by aneurysms, dissections, and tortuosity throughout the arterial tree in combination with osteoarthritis. Early-onset osteoarthritis is present in almost all patients. We present the case of a non-syndromic young boy with *SMAD3* mutation isolated from the dilated aortic root and ascending aorta without osteoarthritis.

The *SMAD3* gene provides instructions for making a protein involved in transmitting chemical signals from the cell surface to the nucleus. This signalling pathway, called the transforming growth factor-β, allows the environment outside the cell to affect cell function, including how the cell produces other proteins. Pathologies such as Loeys-Dietz syndrome, thoracic aortic aneurysms, and dissections and aneurysms–osteoarthritis syndrome associated with the gene mutation *SMAD3* cause aneurysmal dilation of large vessels, especially aortic root dilation. Despite similarities with Marfan syndrome at present, conducting a genetic panel and the use of imaging tests can diagnose patients with such precision, as well as detect asymptomatic family, and thus help in planning their treatment

Case report

An 11-year-old boy was referred to the cardiology department because of chest pain with a history of dilation of the aortic root. There was a family history of death due to aneurysmal rupture of the aorta. In the physical examination, the patient presented with good general condition, normal phenotype, and no chest deformities; the patient's weight was 54 kg, height was 160 cm, and body surface area was 1.55 m^2. Echocardiography revealed normal cardiac structure, adequate contractility (FE 66%), normal chamber dimension (left ventricular internal dimension-diastole of 50 mm (z-score +0.48), left ventricular internal dimension-systole of 31 mm (z-score +0.85), interventricular septum thickness at end-diastole of 8 mm (z-score +0.48), and left ventricular posterior wall dimensions-diastole of 9 mm (z-score +1.6)),[1] but moderate to severe dilation of the aortic root and ascending aorta (aortic annulus: 26 mm (z-score +2.2), sinuses: 41 mm (z-score +3.7), sino-tubular junction: 34 mm (z-score +3.6), ascending aorta: 26 mm (z-score +0.68), and abdominal aorta: 15 mm (z-score +0.6)),[1] with mild aortic valve insufficiency (Fig 1).

A cardiac magnetic resonance revealed a common origin of the innominate artery and left carotid artery with severe dilation of the aorta: aortic roots, 46 × 36 mm (z-score +9.7); ST Junction, 31 × 35 mm (z-score +6); ascending aorta, 24 × 24 mm (z-score +1.9); transverse aorta, 19 × 19 mm (z-score +0.6); aortic–isthmus, 21 × 21 mm (z-score +3.6); and descending aorta, 17 × 15 mm (z-score +0.9) (Fig 2).[2,3]

In subsequent echocardiograms, progressive dilation of the aortic root and ascending aorta was documented in a period of 1 year (aortic annulus: 31 mm (z-score +3.85) 5 mm/year, sinuses: 47 mm (z-score +5.06) 6 mm/year, ST junction: 36 mm (z-score +4.17), 2 mm/year).[1] An angiotensin II receptor antagonist was initiated to reduce the rate of aortic dilatation and to limit aortic wall stress for surgical repair.[4] The patient was scheduled for a valve sparring aortic root replacement but ended up with a prosthetic valve (27 mm) Cardomedics implantation supported by a Dacron tube (30 mm) Sorin (Ref 330968; valve conduit of Palex Medical, Barcelona, Spain) with coronary artery reimplantation according to the Bentall technique.[5] The patient had an uneventful postoperative course and was discharged on anti-coagulation. Results of genetic tests (DNA extraction and aortic pathology check by Sanger sequencing) revealed a mutation of pathogenic effect on *SMAD3* (Alteration c.733 G > C (p. Gly245Arg) heterozygous for the gene *SMAD3*).[6,7]

The asymptomatic patient at the bone system level, but based on the genetic results, is evaluated by traumatology and rheumatology, which rule out osteopathy. Cerebral

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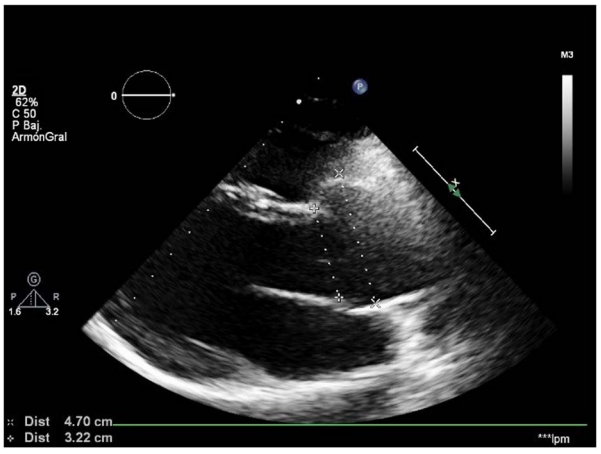


Figure 1. Echocardiogram, long paraesternal axis, dilatation of the aortic root. cm = centimeters; Dist = distance.

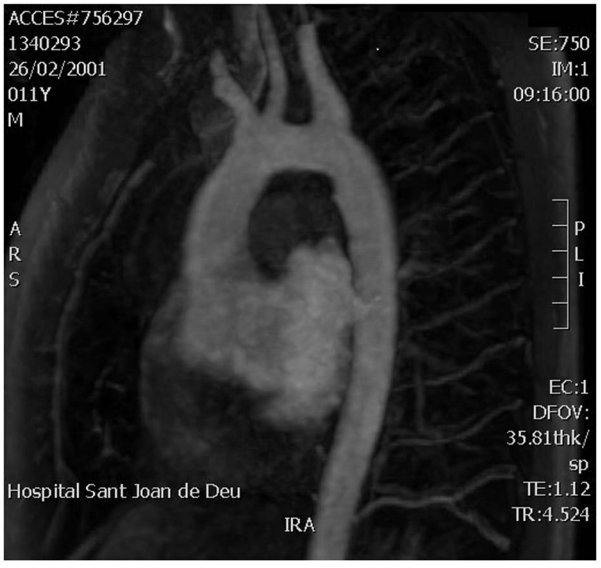


Figure 2. Cardiac magnetic resonance, sagittal plane, severe dilatation of the aortic root.

angiotomography was performed to evaluate aneurysmal formations, observing a discrete increase in the tortuosity of both internal carotids, especially at the level of the sigmoid sinuses.

Discussion

There is a broad spectrum of pathogenic genetic mutations associated with dilation of the aortic root and ascending aorta; in this case report, a mutation in the *SMAD3* gene was observed. *SMAD3* mutations have been associated with familial dilatation of the thoracic aorta and other connective tissue diseases such as Loeys-Dietz Syndrome, a rare disease of autosomal dominant character, previously described as Syndrome Furlong in 1987 and in 2005 under its current name. Loeys-Dietz syndrome is characterised by vascular findings (cerebral, thoracic, and abdominal artery aneurysms and/or dissections) and skeletal manifestations (pectus excavatum or carinatum, scoliosis, joint laxity, arachnodactyly, clubfoot).[8]

Aneurysm–osteoarthritis syndrome is a recently delineated autosomal dominant disorder disease characterised by thoracic aortic aneurysms and dissections, the presence of arterial aneurysms and tortuosity, mild craniofacial, skeletal, and skin abnormalities, and early-onset osteoarthritis associated with gene *SMAD3* mutations.[7] Despite different genes involved, clinical features of aneurysm–osteoarthritis syndrome significantly overlap with other multisystem disorders such as Loeys-Dietz syndrome, which is caused by mutations in transforming growth factor-β receptor type I (Loeys-Dietz syndrome type 1) and transforming growth factor-β receptor type II (Loeys-Dietz syndrome type 2). According to a new classification, aneurysm–osteoarthritis syndrome is now called Loeys-Dietz syndrome type 3.[9] Both are aggressive diseases that are associated with significant mortality and a high risk of aortic rupture and dissection of the aorta with light dilations. In contrast with Marfan syndrome, cerebrovascular abnormalities are more frequent.[8]

SMAD3 gene mutations should be investigated in patients with aneurysmal dilation of the aorta of unknown origin. Although connective tissue abnormalities and large arterial dilation (intracranial, iliac artery, splenic) are commonly associated, isolated aortic dilations can be seen as a form of presentation of the *SMAD3* mutation. Complementary tests such as echocardiography, tomography, and magnetic resonance are recommended as initial studies, and routine follow-up studies should be done to monitor the rate of progression of the dilation (considered significant an increase of 5 mm/year). The presence of the associated clinical features seems to be age dependent; aneurysms and dissections occur primarily in adolescence and adulthood.[4,7]

Medical treatment with angiotensin II receptor antagonist is indicated at an early stage. The antagonist losartan has shown promising results in patients with Marfan syndrome. A combination of losartan with β blockers can be also beneficial. Currently, randomised studies are analysing the utility of angiotensin II antagonists in patients with aneurysms–osteoarthritis syndrome and carriers of mutation in the gene *SMAD3*.[4,10]

Because aneurysm–osteoarthritis syndrome patient's dissections can occur in relatively small aortic diameters, early surgical intervention is indicated elective to reduce the risk of mortality. As the data are limited and the rate of progression is unknown, it is advisable to follow the same surgical recommendations that apply for Loeys-Dietz syndrome. Preservation of the valve and replacement of the aortic root reimplantation as the technique is the intervention of choice.[4,9,10]

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Conflicts of Interest. None.

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