



Aortic Emergency in Loeys-Dietz Syndrome: Clinical Findings and Molecular Characterization in a Child

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Abstract

Loeys-Dietz syndrome, a rare autosomal dominant disorder showing the involvement of cutaneous, cardiovascular, craniofacial, and skeletal systems, presents early in life with rapidly progressive aortic aneurysmal disease. Aortic emergency in young children is an extremely rare occurrence. We present clinical findings and molecular characterization of a 5-year-old Loeys-Dietz syndrome patient whose diagnosis was missed and consequently underwent urgent aortic repair due to aortic rupture. Pediatricians and surgeons should be educated about this rare disorder, to ensure early proper diagnoses resulting in a timely and efficient management strategy before emergence of aortic rupture.

Abbreviations

LDS: Loeys-Dietz Syndrome; TGF: Transforming Growth Factor; TGFBR2: TGF Beta-Receptor Type II; VEDS: Vascular Ehlers-Danlos Syndrome; MFS: Marfan Syndrome

Introduction

Loeys-Dietz syndrome (LDS) is a rare autosomal dominant disorder showing the involvement of cutaneous, cardiovascular, craniofacial, and skeletal systems [1]. In particular, LDS patients show arterial tortuosity with widespread vascular aneurysm and dissection, and have a high risk of aortic dissection or rupture at an early age and at aortic diameters that ordinarily are not predictive of these events [1,2]. LDS is due to mutations in the transforming growth factor (TGF) beta-receptor type I (TGFBR1) and type II (TGFBR2) genes, and has been subdivided in LDS type I (LDSI) and type II (LDSII) on the basis of the presence or the absence of cranio-facial involvement, respectively [1,2]. Furthermore, LDSII patients display at least two of the major signs of vascular Ehlers-Danlos syndrome (vEDS) [2].

Case Presentation

Clinical findings

A 5-year-old boy was referred to emergency room for back pain between the scapulae, hoarseness, and dyspnea. He was born at term after uncomplicated pregnancy from non-consanguineous parents. At the age of 4 years he was diagnosed as thoracic aortic aneurysm and Marfan syndrome (MFS). Clinical follow-up was recommended with consideration of the young age and the insufficient aortic size. At the age of 5 years he showed: height 122 cm, arm span 118 cm, upper: lower segment ratio 0.85. A physical examination revealed bifid uvula, muscular hypotrophy, hypoplastic alae nasi, microretrognathia, high-arched palate, joint hypermobility (Beighton score 8/9), and velvety texture skin. Echocardiography demonstrated a large pseudo-aneurysm (73 x 54 mm) at the aortic isthmus and severe depression of the pulmonary trunk. Therefore, a CT imaging was made rapidly, which clarified disruption of aortic isthmus vessel wall, formation of a large pseudo aneurysm (diameter 77 mm), and depression of the pulmonary trunk and left pulmonary artery (Figure 1). Those findings led to the diagnosis of LDSII. An urgent aortic operation was performed. The patient recovered rapidly and was discharged on the ninth postoperative day. Histopathological examination of the aortic wall showed diffuse degeneration and elastin fragmentation in the media.

Molecular characterization

Sequencing analysis of genomic DNA disclosed in exon 4 of the TGFBR2 gene the c.1067G>C missense mutation, leading to the substitution of a glycine with a cytosine in position 356 of the amino acid sequence (p.Arg356Pro variation). This novel missense mutation was not detected in the patient's parents, suggesting that it arose as a de novo event. The Arg356Pro variation, located

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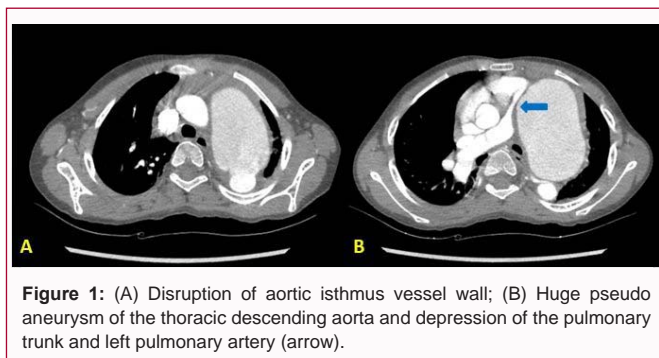


Figure 1: (A) Disruption of aortic isthmus vessel wall; (B) Huge pseudo aneurysm of the thoracic descending aorta and depression of the pulmonary trunk and left pulmonary artery (arrow).

in the highly conserved serine-threonine kinase domain of TGFBR2, was identified only in the patient with LDS but not in 20 MFS patients. In addition, the Arg356Pro mutation was absent in the 50 healthy controls. In silico prediction algorithms, polymorphism phenotyping v2 (PolyPhen-2), characterized the p.Arg356Pro substitution as damaging and affecting protein function. Furthermore, the TGFBR2 gene c. 1067 G>C missense mutation was validated by Sanger sequencing (Figure 2).

Discussion

LDS was first described in 2005 as autosomal dominant with widespread systemic involvement. The disease is characterized by the triad of the following: 1) arterial tortuosity, aneurysms, or dissections, 2) hypertelorism, and 3) bifid uvula or cleft palate [1,2]. The patient showed suggestive signs (i.e., marfanoid habitus without fulfilled Ghent criteria for MFS, facial, skeletal, cutaneous and cardiovascular involvement) consistent with LDSII phenotype. In particular, the patient resembled vEDS for skin presentation and joint involvement, that generally is less evident in vEDS than in other EDS types and in LDS patients [2]. However, the straight involvement of the thoracic aorta of Patient 2 is more suggestive of an LDS rather than a vEDS phenotype, since in vEDS the medium-sized arteries are more frequently affected than aorta and great vessels [3].

In the TGFBRs-related disorders no genotype-phenotype correlation has been drawn, and the prediction of the clinical effects of different TGFBRs mutations remains difficult to envisage [1,4]. All the clinical entities caused by mutations in TGFBRs genes should be considered a phenotypic continuum of the same disease, ranging from isolated thoracic aneurysm to syndromic vascular rupture, and LDS should be considered a complex syndrome characterized by full penetrance, pleiotropic effects, and high incidence of de novo events. On the other hand, LDS shows marked overlapping signs with other genetically triggered disorders, due to different gene defects and characterized by vascular fragility, such as MFS, vEDS, and arterial tortuosity syndrome [2,5]. The differential diagnosis between these genetically triggered aortic diseases is important because the progression and prognosis of aortic and branch vessel disease is significantly different. Although the TGFBRs-related disorders share genetic mutations in the same signaling pathway, previous studies have reported that vascular disease in LDS seems to be more widespread and aggressive than it is in MFS. For these reasons, earlier surgical intervention should be considered for young LDS patients with smaller aortic diameter as opposed to the general population

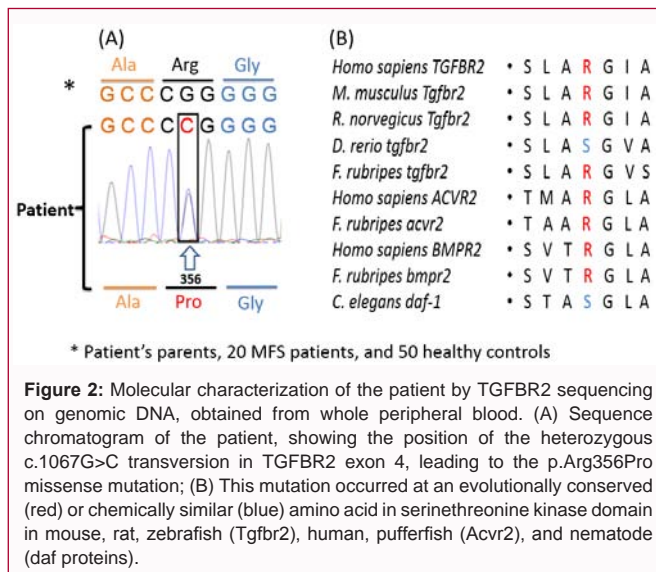


Figure 2: Molecular characterization of the patient by TGFBR2 sequencing on genomic DNA, obtained from whole peripheral blood. (A) Sequence chromatogram of the patient, showing the position of the heterozygous c.1067G>C transversion in TGFBR2 exon 4, leading to the p.Arg356Pro missense mutation; (B) This mutation occurred at an evolutionarily conserved (red) or chemically similar (blue) amino acid in serine/threonine kinase domain in mouse, rat, zebrafish (*Tgfr2*), human, pufferfish (*Acvr2*), and nematode (*daf* proteins).

and even Marfan patients. One of our most important findings is the evidence for the aggressive nature of the aortic pathology in LDS. Fatal aortic catastrophes occurred in the 5-year-old patient, a clinical scenario that is extremely rare in Marfan syndrome. This finding indicates that not only should surgical intervention be considered earlier, but these patients require strict, aggressive, lifelong surveillance of the entire arterial tree to identify problems that are generally amenable to surgical intervention.

Conclusion

We present a 5-year-old patient with LDS who was only correctly diagnosed after aortic emergency, and report an Arg356Pro mutation in the TGFBR2 gene. Pediatricians and surgeons should be aware of this rare disorder, to ensure early proper diagnoses resulting in a timely and efficient management strategy before emergence of aortic rupture.

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