AGGRESSIVE AORTIC DISEASE WITH MARFAN-LIKE PHENOTYPE IN MALAYSIAN PATIENTS WITH LOEYS-DIETZ SYNDROME

Muzhirah Haniffa¹, Geetha Kandavello², Jeya Bawani Sivabalakrishnan³

ABSTRACT

Loeys-Dietz Syndrome (LDS, pronounced LOH-eez-DEETS) is a connective tissue disorder that was first described in 2005. In the past, many patients were misdiagnosed clinically as Marfan Syndrome (MFS) due to their overlapping phenotype. Distinguishing craniofacial features of LDS include hypertelorism, bifid uvula, cleft palate and absence of lens dislocation. Unlike MFS, aortic root dilatation with or without arterial tortuosity elsewhere are almost always present. Patient 1 was a 7-year-old boy, diagnosed with MFS at 4 years of age. Echocardiogram showed aortic root dilatation with no lens dislocation on eye assessment. He was initially started on β-blocker by the cardiologist, losartan was added on subsequently due to the increasing size of his aortic root diameter. Patient 2 was a 14-year-old boy, followed up for severe aortic root dilatation. He had a stormy neonatal period; diagnosed with tracheobronchomalacia, multiple joint dislocation, feeding intolerance, scoliosis and squint. He was followed up for many years as possible MFS. Genetic testing performed showed mutation at TGFBR2 gene, confirming a diagnosis of LDS in both patients. In addition to these families, another 6 families under our aortopathy clinic follow up have had their diagnosis of LDS confirmed molecularly. LDS is increasingly being described in patients with a more severe aortic disease and Marfan-like phenotype. The difference in disease severity highlights the importance of genetic testing in patients with suspected aortopathy, enabling timely implementation of therapeutic strategies.

Keywords: Marfanoid habitus, Aortic root dilatation, Genetic counseling

DOI: 10.51407/mjpch.v29i2.242

Introduction

Loeys-Dietz Syndrome (LDS) is a multisystemic, dominantly inherited aortic aneurysm syndrome. The disease prevalence is unknown though with more availability of genetic testing the number of patients diagnosed has increased significantly in recent years. The condition occurs in all ethnic groups [1]. Typical clinical triad includes hypertelorism, bifid uvula or cleft palate and aortic aneurysm with tortuosity [2]. Compared to Marfan Syndrome (MFS), aortic dissection occurs at a smaller aortic diameter and arterial aneurysms may be seen throughout the arterial tree. Its diagnosis is established by the identification of a pathogenic variant in TGFBR1, TGFBR2, SMAD2, SMAD3, TGFB2 or TGFB3 genes [3].

These genes play a role in the cell signalling pathway called the transforming growth factor beta (TGF-β) pathway, which direct the functions of the body's cells during growth and development. This pathway also regulates the formation of the extracellular matrix, an intricate lattice of proteins and other molecules that forms in the spaces between cells and is important for tissue strength and repair. Mutations in these genes result in the production of a protein with reduced function. Even though the protein is less active, signalling within the TGF-β pathway is increased throughout the body. The overactive TGF-β pathway disrupts the development of the extracellular...
matrix and various body systems, leading to the signs and symptoms of Loeys-Dietz syndrome [4].

**Case History**

Patient 1 was a 7-year-old boy, followed up since infancy for left-sided hydronephrosis with duplex collecting system. He was diagnosed with Marfan Syndrome at 4 years of age in view of his suggestive clinical features and echocardiogram findings which showed aortic root dilatation. There was no lens dislocation on eye assessment. During an admission for acute gastroenteritis at 7 years old, splenomegaly was detected during physical examination. Ultrasound and CT scan findings were suspicious of splenic abscess and hence antibiotics were commenced; this diagnosis was revised a month later as the repeat abdominal scan finding was more consistent with a benign vascular enlargement. His follow up echocardiogram showed increasing aortic root size and hence losartan was further added to his existing atenolol. Parents gave a history of poor adherence to medical therapy. Clinically he was thin and had reduced subcutaneous tissue. He had hypertelorism, downslanting palpebral fissures, bifid uvula, pectus carinatum and scoliosis. In view of this, his primary diagnosis was revised to Loeys-Dietz Syndrome. As per recommendation, MRI brain, thorax, abdomen and pelvis were arranged but patient defaulted. He succumbed at 8 years old from aortic dissection with concurrent covid-19 infection.

Patient 2 was a 10-year-old boy. He was delivered at 36 weeks and had a stormy neonatal period; he was diagnosed with tracheobronchomalacia requiring prolonged ventilation, dislocated hip and knee joints, feeding intolerance, scoliosis, inguinal hernia and squint. He was followed up for many years as possible MFS. He had aortic valve repair and ascending aortic replacement when he was 13 years old. His aortic root measurement at the time was 5.3cm. He remained well for the next 5 years. At 18 years old, he developed another aneurysm just distal to the operation site. Genetic testing performed showed mutation at TGFBR2 gene, confirming a diagnosis of LDS in patient 1 and 2.
Discussion
Patients with Marfan-like phenotype and a negative FBN1 testing were previously classified as Marfan Syndrome 2 (MFS2). At the time of the report in 2004, other discriminating features of LDS had not yet been described [5]. The term Marfan Syndrome type 2 became obsolete upon the description of this syndrome by Bart and Loeys in 2005 [6]. This is the second commonest aortopathy condition after MFS [6].

Genetic testing was not routinely performed in our patients followed up at the aortopathy clinic. Not until 4 years ago, genetic testing was not readily available at a bearable cost. These tests are currently not available locally and all samples are sent overseas for analysis. According to a clinical audit that was performed on our patients that were followed up at the aortopathy clinic from 2003-2021, opportunistic genetic testing was performed on a total of 60 out of 215 families. Eight families with LDS had their diagnosis confirmed molecularly. Clinical diagnosis of LDS was suspected in only half of those 8 patients. All our patients with LDS presented with aortic root dilatation except for one patient, who was still asymptomatic at 2 years old. She was clinically suspected to have Ehlers-Danlos Syndrome. Genetic testing was performed via whole exome sequencing which picked up a mutation at TGFBR2 gene. None of these patients had lens dislocation. Family history was only found in 1 family. Six families had mutations identified at TGFBR2 gene, which is the commonest mutation found in patients with LDS (unpublished data). The information above indicates the difficulties clinically to distinguish between the major aortopathies and that genetic testing provides valuable information.

Causes
To date, LDS is caused by mutations in either of these 6 genes: TGFBR1, TGFBR2, SMAD2, SMAD3, TGFB2 or TGFB3 genes. There is no well-described genotype-phenotype correlation and there is significant intrafamilial variability in the severity of their disease [5].

Inheritance
LDS is inherited in an autosomal dominant manner. About 75% cases of LDS syndrome are de novo in origin, unlike MFS [6]. Our families received detailed genetic counselling encompassing the natural history of the disorder, its inheritance pattern and recurrence risk depending on the parental status. Pre- and post-test genetic counselling were performed prior to all genetic analysis.

Management
Specific guidelines are available for LDS patients. In November 2022, new guidelines for the diagnosis and management of aortic disease were published in the Journal of the American College of Cardiology and Circulation [7].

Pressure on the aorta and other arteries can be controlled by medications that work to lessen the strain on the body’s major arteries by reducing heart rate and blood pressure. Angiotensin receptor blockers and beta-blockers are recommended for patients with LDS and they should remain on these medications even after surgical repair of aneurysms [7].
Annual echocardiograms and a baseline CTA or MRA of the head, neck, chest, abdomen and pelvis should be performed to detect and monitor aneurysm formation and/or dissections. The frequency depends on aneurysm size and rate of growth. Individuals with LDS should not go for more than two years without head-to-pelvis imaging. If a person is using MRA imaging for surveillance, every few imaging cycles of a CTA of the head and neck should be considered, as this imaging has better clarity of small arteries in the head and neck [7].

X-rays of the cervical spine in the flexion and extension positions are recommended to assess for vertebral anomalies and/or instability. It is important to assess for cervical spine instability prior to undergoing any surgery, as this may impact intubation procedures [7].

Vascular surgery is a widely recommended treatment option as a preventative surgery for individuals with a rapidly enlarging aorta or artery or has significant family history of arterial dissection. Aortic root replacement is the most common vascular surgery and it is highly successful. Vascular tissue is not typically weak or fragile in individuals with LDS [7].

Exercise restrictions are put in place to slow the rate of aortic and arterial aneurysm growth. It is advised that individuals with LDS avoid competitive sports, especially contact sports, and other exercises or muscle straining activities. A good recommendation for cardiovascular activities is to exercise only to a level where you can hold a conversation while performing the activity [7].

Orthopedic surgery or other interventions such as bracing for scoliosis, orthotics/surgeries for foot deformities or contractures or harnesses for congenital hip dislocation may be required. Typically, surgery for pectus anomalies is pursued for cosmetic purposes and not out of medical necessity [7].

Environmental and food allergies are increased in individuals with LDS. These may present as rhinitis or sinusitis, eczema, or hives. Gastrointestinal complaints include diarrhea, abdominal pain or difficulty gaining weight. Some individuals have severe inflammatory disease of the esophagus or intestines that may need stricter intervention such as medications or feeding tubes to help with caloric intake [7].

**Affected Populations**

Because the condition is relatively recent, some physicians may not be aware of it and may not properly diagnose patients. LDS is not known to be more prevalent in a certain ethnic group or geographic location [7]. To the best of our knowledge, this is the first reported cases of molecularly confirmed LDS from Malaysia.

**How is Loeys-Dietz Syndrome different from Marfan Syndrome?**

In the past, many individuals with LDS were mistakenly diagnosed with Marfan syndrome. It is important to distinguish between Marfan syndrome and LDS because there are a few management differences. Firstly, individuals with LDS are not at risk of having lens dislocation. Secondly, surgery in Marfan Syndrome is considered when the aorta is around 5 cm; however, in LDS individuals, aortic root measurements of 4 cm have shown aortic root dissection (in teens/adults). Therefore, surgery is recommended when the aorta approaches this dimension before a tear occurs [7,8].

**Conclusion**

LDS should be considered as a differential diagnosis for patients with possible Marfan Syndrome who show additional atypical features such as craniosynostosis, bifid uvula, absence of lens dislocation and camptodactyly. The difference in disease severity and timely decision for therapeutic strategies highlights yet again the importance of genetic confirmation in patients with aortopathy. Early diagnosis enables accurate genetic counseling with proper long term monitoring and surveillance in place.

**Acknowledgement**

The authors declare no relationships or financial benefits that may lead to a conflict of interest in this report.

**References**


[7] Loeysdietz.org [Internet]. Available from https://www.loeysdietz.org