Surgical Experience in a Patient With Loeys-Dietz Syndrome Type I

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Loeys-Dietz syndrome is a recently described genetic disorder with aortic and vascular involvement. Here, we present the medical history and surgical management of a patient with Loeys-Dietz syndrome type I caused by a mutation in M253I in the TGFBR1 gene who received complete aortic replacement and various peripheral vascular surgeries over the course of 25 years.


Loeys-Dietz syndrome (LDS) is a recently identified genetic syndrome with aortic and systemic involvement first described in 2005 [1]. The syndrome is caused by heterozygous mutations in the transforming growth factor beta receptor 1 or 2 (TGFBR 1/2) genes, a family of signal receptors that is responsible for multiple cellular processes, including extracellular matrix maintenance and tissue development [2]. The syndrome demonstrates autosomal dominant inheritance with variable phenotypic expression. The average life expectancy of LDS patients is 26 years.

There are two subtypes of LDS [3]. The typical clinical manifestation of LDS I includes the triad of arterial tortuosity and aneurysms, hypertelorism, and a bifid uvula or cleft palate. Patients with LDS I usually undergo cardiovascular surgery and die at a young age. Patients with LDS II display the facial stigmata of vascular Ehlers-Danlos syndrome and require cardiovascular surgery later compared with LDS I patients.

Here, we present a patient diagnosed with LDS I who received various complex cardiovascular operations. At the time of the writing of this document, the patient is 63 years old and in good general and medical condition. Considering that most patients die in their 20s, this person is one of the oldest LDS patients alive based on our research.

In 1988, a 38-year-old Caucasian man (height 198 cm, marfanoid habitus) was admitted to our institution because of aortic dissection type Stanford A. He received composite replacement of the ascending aorta and the aortic valve using a mechanical valved conduit (29 mm). By 1992, the descending aorta had enlarged to 80 mm. He underwent aortic replacement from the left subclavian artery to the T9 vertebral level using a 30-mm polyester prosthesis (Hemashield; Maquet, San Jose, CA) with insertion of a distal elephant trunk (70 mm) using left heart bypass. In October 1992, he showed aneurysms of the abdominal aorta and the right iliac artery. He underwent replacement of the infrarenal abdominal aorta to the left iliac artery and the right femoral artery using a polyester prosthesis (Uni-Graft; Braun, Melsungen, Germany) measuring 20 × 10 × 10 mm. In November 1992, the thoracoabdominal aorta had enlarged to 70 mm. We implanted a 20-mm polyester prosthesis (Uni-Graft) anastomosed to the elephant trunk of the previously implanted prosthesis of the descending aorta and the previously implanted infrarenal aortic prosthesis using a clamp-and-sew technique without cardiopulmonary bypass. In mid-December 1992, a dehiscence between the anastomosis of the thoracoabdominal and infrarenal prosthesis necessitated resection of the distal part of the thoracoabdominal prosthesis, followed by interposition of a short segment of a 20-mm polyester prosthesis (Uni-Graft).

In 1997, the distal aortic arch had enlarged to 60 mm. Using deep hypothermic circulatory arrest, we replaced the complete aortic arch from the previously implanted composite graft to the descending aorta using a 30-mm woven prosthesis (Hemashield). The left subclavian artery had to be ligated. A subclavian steal syndrome then developed. In early March 1998, the patient underwent implantation of a carotid-subclavian bypass using a 6-mm enhanced polytetrafluoroethylene prosthesis (Impra; C. R. Bard, Haverhill, PA). By 2007, the subclavian artery measured 40 mm at the origin of the aortic arch and showed an outlet stenosis of the carotid-subclavian bypass. The patient received a new carotid-subclavian bypass using an 8-mm polyester prosthesis (Uni-Graft) with distal end-to-end anastomosis and ligation of the retrograde supplying arteries to the proximal subclavian aneurysm. In 2013, the left common iliac artery had enlarged to 35 mm and the right femoral artery measured 32 mm (Fig 1). The left aortoiliac branch of the previously implanted abdominal prosthesis was extended to the left external iliac artery using a 10-mm polyester prosthesis (Uni-Graft) with reinsertion of the left internal iliac artery. The right aortofemoral branch was extended to the femoral bifurcation with a 10-mm polyester prosthesis (Uni-Graft).

In 1988, the patient had been diagnosed clinically with Marfan syndrome. He fulfilled the criteria of the Gent nosology [4] and also had a bifid uvula. He had a positive family history for aortic disease. Despite showing clinical signs of Marfan syndrome, however, genetic analysis in December 2000 was negative for the syndrome. After Loeys and Dietz [1] described a new vascular syndrome caused by mutations in TGFBR 1/2, the patient underwent genetic testing again. He was diagnosed to be a heterozygous carrier of the mutation M253I (759G>A) in the fourth exon of the TGFBR1 gene, indicating a positive diagnosis for LDS I.
At the time of writing this report, the patient is 63 years old and in good general condition. He is still working. The most recent routine computed tomography scan showed no aortic pathologies requiring surgery. However, peripheral vascular aneurysms were emerging. The innominate artery (24 mm) shows a residual dissection. Despite ligation in 1997 and further surgical revision in 2007, the patient had an aneurysm of the left subclavian artery (56 × 63 mm). He underwent interventional treatment in 2013, and the left occipital artery was identified as the supplying vessel of the subclavian aneurysm. However, embolization was not possible, leaving the aneurysm untreated. Surgical options are extrathoracic ligation of the feeding artery by neurosurgical intervention or a high-risk thoracic reoperation.

Comment

Loeys-Dietz syndrome represents a potentially life-threatening cardiovascular disease caused by mutations in the genes encoding the TGFBR 1 and 2. Based on our knowledge, the M253I (759G>A) mutation in the fourth exon of the TGFBR 1 gene has not been described in the literature before and is caused by the replacement of the amino acid methionine in position 253 with isoleucin, resulting in a missense mutation of the TGFBR 1 gene. The recent discovery of LDS is of great importance for affected patients’ diagnostic and therapeutic management. As LDS typically shows a more aggressive course than MFS, patients with arteriopathic disease should receive correct genetic testing and subsequent clinical treatment. Further, screening family members is of great importance. Although LDS is a potentially deadly disorder [3], it is possible to extend the life of affected patients while maintaining an adequate quality of life through frequent diagnostic monitoring and well-timed surgical intervention, as shown here.

The prognosis for LDS is poor because of its sudden early onset (usually acute dissection) in previously undiagnosed patients. Survivors and patients who receive early diagnoses require frequent follow-up examinations, as a lack of follow-up monitoring may also lead to a poor prognosis. For patients who receive frequent monitoring, the life expectancy can be extended but is still limited by the sum of the risks of all operations that they receive over time.

Our patient received total aortic replacement over time and peripheral vascular aneurysms began to develop. This course is typical for LDS, whereas MFS patients usually only have pathologies of the aorta but not the peripheral vascular system. Our patient was 38 years old when he had type A aortic dissection, which is relatively late for LDS I. Whether it was due to a less aggressive form caused by this patient’s newly described mutation cannot be determined. The patient’s persistent subclavian artery aneurysm may be linked to the nature of LDS. The time and the extent of surgical intervention in LDS patients remain debatable as the therapeutic options range from conservative operations to more radical ones. As LDS is more aggressive than MFS, and in addition might lead to a pronounced collateral perfusion of excluded/ligated peripheral arteries, one could argue in favor of a more radical approach including complete treatment.

![Fig 1. (A) Three-dimensional reconstruction of the complete aorta and certain branches. (B) Recurrent subclavian artery aneurysm in sagittal plane. (C) Aneurysm of the right femoral artery in axial plane.](image_url)
resection of aneurysmal arteries and early, extended aortic replacement. For the same reasons, we believe that LDS patients should not be treated by thoracic endovascular aneurysm repair.

References