ORIGINAL ARTICLE

Anesthetic management of a child with Loeys-Dietz syndrome undergoing complete aortic arch replacement

Manejo anestésico en una niña con síndrome de Loeys-Dietz sometida a recambio completo de arco aórtico

*Unai Olabarrieta-Zarain[1], Leire Martínez-Santos[1], Alex Alberdi-Enríquez[1], Ane Guereca-Gala[1], Blanca Bravo-Sevilla[1], and Alberto Martínez-Ruiz[1,2]**

[1]Servicio de Anestesiología, Reanimación y Terapia de Dolor, Hospital Universitario de Cruces, Osakidetza; [2]Facultad de Medicina, Universidad País Vasco, EHU/UPV. Vizcaya, España

Abstract

Loeys-Dietz syndrome (LDS) is a connective tissue disease related to β-transforming growth factor mutations, which causes aneurysms formation, vascular tortuosity and skeletal manifestations. The prognosis is very poor, and mortality occurs at the age of 27 in patients without surgical treatment. Despite being diagnosed in childhood, is not usual surgical aortic replacement in children. We report a case of 12 years old child with LDS and multiple aneurysms in thoracic aorta, undergoing complete aortic arch replacement and our proposal for the anesthetic management, due to surgical complexity and implications in pediatric population.

Keywords: *Loeys Dietz Syndrome. Aortic arch surgery. Marfan like syndrome. Cervical subluxation. Brain injury neuroprotection.*

Resumen

El síndrome de Loeys-Dietz (SDL) es una enfermedad del tejido conectivo debida a mutaciones del factor de crecimiento transformador beta que provocan formación de aneurismas, malformaciones vasculares y esqueléticas. Tiene mal pronóstico y el fallecimiento sobreviene de media a los 27 años sin tratamiento quirúrgico. A pesar de diagnosticarse en la infancia, es infrecuente la cirugía en niños. Presentamos el caso de una niña de 12 años con SDL y aneurisma múltiple en aorta torácica, programada para recambio completo de arco aórtico, proponiendo estrategias para el manejo anestésico, dada la complejidad y las implicaciones de esta cirugía en la población pediátrica.

Palabras clave: *Síndrome de Loeys-Dietz. Cirugía de arco aórtico. Síndromes marfanoides. Subluxación cervical. Neuroprotección cerebral.*

Introduction

Loeys-Dietz syndrome (LDS) is an autosomal dominant genetic connective tissue disorder caused by mutations in the transforming growth factor beta (TGF-β) gene that was first described back in 2005. It is a rare entity whose incidence rate is 1 for every 100 000 inhabitants. LDS is related to 6 different mutations of TGF-β. Type 1 and 2 (TGFBR1 and TGFBR2 genes), which have an earlier and more severe onset, are the most common mutations (25% and 60%, respectively). Types 3 (SMAD3), 4 (TGFB2), and 5 (TGFB3) are less severe, with frequencies ranging from 10% up to 25%.

***Correspondence:**
Alberto Martínez-Ruiz
E-mail: Alberto.martinezruiz@osakidetza.eus

Date of reception: 25-10-2021
Date of acceptance: 07-01-2022
DOI: 10.24875/CIRUE.M22000568

Cir Cir (Eng). 2023;91(4):558-562
Contents available at PubMed
www.cirugiaycirujanos.com

Variant 6 (SMAD2), recently described, accounts for < 5% of the cases reported (table 1)[1,2]. It predisposes to early development of aortic aneurysms and vascular malformations, with greater aggressiveness compared to other Marfan-like syndromes.

The most serious clinical aspect is cardiovascular involvement, more common in types 1, 2, and 3. Thoracic aortic aneurysms are typical, with rapid growth and risk of rupture at smaller diameters vs other syndromes (3.9 cm vs 5 cm in Marfan syndrome). Unlike Marfan syndrome, the entire thoracic aorta is involved in LDS. In LDS types 1 and 2, up to 95% of the patients have a dilated aortic root, which leads, in most patients, to aortic regurgitation, mitral valve prolapse, and pulmonary artery elongation. A total of 50% of the patients exhibit aneurysms which are distal to the aortic root, and most have vascular tortuosity in the head and neck[2]. Aortic dissections, even in 3-month-old infants, abdominal, iliac, and popliteal aneurysms in up to 20% of the patients, and cerebral vascular malformations have been reported too. Additionally, in LDS type 3, up to 24% of the patients develop atrial fibrillation and left ventricular hypertrophy, and less frequently, patent ductus arteriosus and septal defects, among other disorders[3].

Craniofacial and skeletal abnormalities are also a common finding. Cleft palate and hypertelorism are most common, present in virtually all patients with the types 1 and 2 variants, allowing for early diagnosis. Craniosynostosis is also common in severe forms. Less frequently, retrognathia, dental malocclusion, and bifid uvula have been reported. In LDS type 3, craniofacial abnormalities are mild or absent. In LDS types 1 and 2, arachnodactyly has been reported in 33% of the patients. Also, ligamentous hyperlaxity, clubfoot, cervical subluxations, dorsal kyphosis, and bone fractures. Joint abnormalities and early-onset arthrosis are common findings in LDS type 3[3].

Less commonly reported findings are immunological, and allergic disorders, bronchial hyperreactivity, restrictive lung disease, sleep apnea-hypopnea syndrome, atrophic skin, retinal detachment, and blue scleral among others.

Early diagnosis is essential due to the aggressive course of the disease. It is based on clinical suspicion, family history, presence of a dilated aortic root, or type A dissection, and confirmed by genetic testing. Differential diagnosis with Marfan syndrome and other syndromes such as Ehler Danlos, Shprintzen-Goldberg, and Turner is required too. *Cutis laxa* and Noonan syndrome, as well as non-familial causes of aortic dilatation and dissection, valvular heart diseases, or fibromuscular dysplasia also need to be ruled out.

Table 1. LDS classification based on the clinical spectrum

LDS variant	Genetic disorder	Frequency	Predominant clinical signs
LDS, type 1	*TGFBR1*	25%	TAA, TAD, hypertelorism, cleft palate, craniosynostosis, AA
LDS, type 2	*TGFBR2*	60%	TAA, TAD, hypertelorism, cleft palate
LDS, type 3	*SMAD 3*	10% to 25%	TAA, premature arthrosis, AF, LVH
LDS, type 4	*TGFB2*	5% to 10%	Tortuosity and cerebral vascular malformations. Skeletal abnormalities

AA: abdominal aneurysm; AF: atrial fibrillation; LDS: Loeys-Dietz syndrome; LVH: left ventricular hypertrophy; TAA: thoracic aortic aneurysm; TAD: thoracic aortic dissection. *Adapted from Meester et al., 2017[1] and MacCarrick et al., 2014[2].*

Treatment is essential to increase survival. Angiotensin-converting enzyme inhibitors (ACEIs), and/or beta-blockers are advised for hemodynamic control and early surgical intervention.

Prognosis is grim and mortality rate is high. The main causes of death are rupture, aortic dissection, and cerebral hemorrhage.

Case report

A 12-year-old girl weighing 33 kg with LDS type 2 and multiple aneurysmal dilatations in the thoracic aorta was scheduled for aneurysm resection in the ascending aorta and replacement of the valve and complete aortic arch.

The patient's past medical history included a normal pregnancy and eutocic delivery. The patient presented with a dysmorphic phenotype with clubfoot, joint hyperlaxity, arachnodactyly, camptodactyly, and bifid uvula. At the age of 8, genetic testing confirmed the presence of heterozygosity for the pathogenic variant *de novo* c.1639 G > C in the TGFBR2 gene. Associated findings included dilated aortic root, patent ductus arteriosus, patent foramen ovale, and tortuosity in the thoracoabdominal aorta, both internal carotid arteries, and the right vertebral artery. Atenolol and losartan were prescribed, and the surgical intervention involved aortic root replacement. Over the past year, there was rapid aneurysmal growth distal to the prosthesis (47 mm diameter), with damage to the brachiocephalic trunk and moderate-to-severe aortic regurgitation. Both the arch

and the descending aorta were normal. A new surgical procedure was scheduled for aortic valve repair and aortic arch replacement.

Anesthesia evaluation found the patient asymptomatic. Airway examination revealed the presence of a high-arched palate and Mallampati I/IV with a bifid uvula, but without any other craniofacial malformations. Both the lab test results, and the electrocardiogram were normal. Cervical x-ray revealed the presence of atlanto-axial subluxation with a 9 mm distance between C1 and the odontoid. The patient was classified as ASA III, losartan discontinuation was advised 24 hours before the procedure, and the patient remained on atenolol.

During pre-anesthesia, a peripheral 18 G IV line was established in the right forearm, and midazolam (2.5 mg IV) was administered. In the operating room, non-invasive blood pressure, electrocardiogram, oxygen saturation, bispectral index (BIS), and regional oxygen saturation (NIRS) were monitored. Before induction, lidocaine (1 mg/kg) and tranexamic acid (50 mg/kg) were administered. General anesthesia was induced with propofol (4 mg/kg), fentanyl (5 μg/kg), and cisatracurium (0.2 mg/kg). Endotracheal intubation was performed with the head in a neutral position, avoiding cervical hyperextension and mandibular subluxation. A size 6.5 endotracheal tube was placed using an Airtraq® device (Prodol Meditec, Vizcaya, Spain). Another peripheral 18 G line, a central internal jugular line, and a femoral artery line were established. A transesophageal echocardiography (TEE) probe was inserted. For maintenance, a balanced technique with sevoflurane (CAM 0.8-1), cisatracurium (0.1 mg/kg/h), and fentanyl (2-4 μg/kg/h) was used. After sternotomy, 2 new aneurysms in the aortic arch and descending aorta, not diagnosed preoperatively, were identified, which required complete thoracic aortic repair.

The surgical team decided to proceed with peripheral cannulation for extracorporeal circulation (ECC), with cannulas placed in the right axillary artery and ipsilateral femoral vein. During the first part of ECC, after an unsuccessful attempt to repair the aortic valve, the valve was replaced, and the ascending aortic aneurysm was resected. Subsequently, under deep hypothermia (22 ºC), in total circulatory arrest (TCA) and antegrade selective cerebral perfusion (SCP), the aortic arch was replaced. Neuroprotective measures were implemented with sodium thiopental (5 mg/kg), methylprednisolone (30 mg/kg), magnesium sulfate (25 mg/kg), local ice helmet, and insulin infusion. A hybrid device with a covered stent distal to the left subclavian artery was deployed in the descending aorta, with reimplantation of both supra-aortic trunks. Thirty out of 153 minutes went by in hypothermia and SCP. After ECC was restarted, the device was anastomosed to the proximal aorta. The total ECC time was 200 minutes, with 136 minutes of aortic clamping. ECC termination was uneventful after confirming adequate contractility, valvular function, and volume status through TEE. Vasoplegia and profuse bleeding both require noradrenaline (0.1 to 0.3 μg/kg/min), fluid therapy, blood and plasma transfusion, and fibrinogen (2 g).

After a 6-hour procedure, the intubated child was transferred to the intensive care unit, where she remained for 8 days before being discharged from our center 1 week later.

Discussion

LDS type 2 is more aggressive than other connective tissue disorders such as Marfan syndrome. The mean age of death is 27 years in unoperated patients vs 50 years for the Marfan syndrome[2-5]. Replacement of the aortic root is advised for diameters ≥ 99th percentile, or aortic annulus > 1.8 cm² in children[2]. Its recent description and the rarity of aortic arch surgery in the pediatric population limit experience regarding management. Some authors suggest adopting aspects of Marfan patients' management. However, there are particularities addressed in this article.

Management is challenging, and complications are frequent and severe. Risk factors include severity of vasculopathy, duration and invasiveness of surgery, difficult airway, adrenergic discharge from laryngoscopy, ECC with hypothermia, interruption of cerebral blood flow (CBF), and hemorrhage, among others.

- We suggest paying special attention to allergy history, airway assessment, and drug adjustment in the pre-anesthetic evaluation, which is mandatory. The high incidence of immunological disorders triggers many allergies, which should be noted. ACEIs and beta-blockers may delay surgical indication in diameters of 2 cm to 2.2 cm. Beta-blockers will be maintained by discontinuing ACEI/angiotensin receptor blockers (ARB) II 24 hours prior to avoid refractory hypotension. Transverse atlanto-axial ligament hyperlaxity causes cervical subluxation and instability. Cervical flexion-extension x-rays will be requested to avoid neurological injury during ventilation and

orotracheal intubation (OTI). A distance between the atlas and odontoid > 5 mm is diagnostic vs 3 mm in adults[6]. Airway examination will reveal those craniofacial anomalies impeding ventilation and OTI. In our case, a high-arched palate and bifid uvula did not cause any problems in the previous surgery. The Mallampati grade is only valid for older children.

- We suggest monitoring with invasive blood pressure (BP), TEE, NIRS, and EEG or BIS. In addition to the standard recommendations of the American Society of Anesthesiologists (ASA), invasive BP and central venous pressure should be monitored. Wilkey et al.[7] advocate for invasive arterial monitoring prior to anesthetic induction. TEE is advised for all patients, and a pulmonary artery catheter is recommended in the presence of pulmonary hypertension. Neurological complications are common following ECC, TCA, embolization, aortic clamping, and interruption of CBF. Keenan and Hughes[8] recommend combined monitoring of NIRS and electroencephalography in aortic arch surgery to detect ischemia. In some cases, somatosensory evoked potentials or jugular venous saturation may be useful. Due to the complexity of EEG, BIS has been proposed to determine anesthetic depth and electrical silence during TCA, and NIRS to detect changes in regional cerebral oxygen saturation (pre-induction baseline of 60% to 70%). According to Svyates et al., the degree and duration of desaturation are predictive of postoperative neurological complications. Levels < 55% kept for > 5 minutes are associated with neurological impairment.
- We propose induction with lidocaine. Anesthetic induction should be gentle with strict hemodynamic control, as arterial hypertension could trigger aortic ruptures. Adequate premedication is necessary. A midazolam-type anxiolytic associated with an opioid and a drug minimizing adrenergic discharge, such as esmolol, urapidil, or lidocaine, as in our case, are advised. The appropriate anesthetic depth and relaxation prior to OTI are advised. According to Postaci et al.[9], short-acting opioids at high doses such as remifentanil 0.5-1 μg/kg as a bolus for induction in pediatrics may be useful; however, the advantage of using this over other drugs has not been demonstrated. Therefore, in our case, we opted for fentanyl as a valid alternative, considering our limited experience with the IV bolus administration of remifentanil in children.
- We propose intubation with a fiberoptic bronchoscope or videolaryngoscope. Cervical subluxation increases the risk of neurological injury during OTI. Airway structures are very close to the cervical spine in children, causing displacement during positioning, manipulation, mandibular traction, and insertion of ventilation and OTI devices. Therefore, it seems reasonable to avoid aggressive maneuvers, as no ventilation devices is risk-free. Naola et al.[10] recommend a neutral head position and avoiding cervical hyperextension or the "sniffing" position, which would cause maximum extension and atlantoaxial instability. In this case, we intubated with Airtraq® (Prodol Meditec, Vizcaya, Spain), as the use of videolaryngoscopes for OTI is prioritized, as they require less force to expose the airway. However, direct laryngoscopy may be safe in experienced hands.
- We propose the use of moderate hypothermia (22°C) with antegrade SCP and pharmacological neuroprotection. There is no evidence on the superiority of one maintenance technique over the other. We prefer balanced techniques in the pediatric population. Complete replacement of the aortic arch requires interruption of CBF. The balance between oxygen supply and demand to the brain should be guaranteed, avoiding factors that worsen neurological damage. Among protective measures, deep hypothermia allows prolonged interruption of CBF, reducing the cerebral metabolic rate (CMR) by 50% for every 6° to 10°C. However, it causes longer ECC, edema, coagulopathy, and organ dysfunction[11]. In our case, we opted for moderate hypothermia (22°C) with antegrade SCP, as there are fewer complications, and pharmacological neuroprotection. Corticosteroids have been proposed to reduce ischemic brain damage, inflammation, and reperfusion ischemia; barbiturates reduce CMR and protect vs focal ischemia; mannitol and furosemide reduce cerebral edema, and calcium channel blockers, magnesium sulfate, and lidocaine block calcium channels[12]. Local cooling with ice may be effective and, although controversial, we used it due to its low rate of complications. Hyperglycemia should be avoided, as it worsens cerebral ischemia; levels > 180 mg/dL are harmful, and > 250 mg/dL are associated with poor neurological outcomes.

Insulin infusion therapy is protective. The impact of anesthetics is varied; halogenated ones increase CBF and reduce CMR, while propofol, etomidate, and benzodiazepines decrease CBF and CMR alike. Relaxants reduce CMR.

- We propose the use of tranexamic acid. Post-ECC hemorrhage is common and particularly severe in children. Hypothermia inhibits platelet function, and prolonged ECC dilutes coagulation factors. Thrombin consumption triggers hypofibrinogenemia, thrombocytopenia, and hyperfibrinolysis, a situation similar to disseminated intravascular coagulation (DIC). Bleeding is often profuse due to multiple vascular sutures. Prophylactic use of antifibrinolytics is advised. We use tranexamic acid for its proven efficacy over others[12].

In conclusion, LDS is a serious condition. It poses an anesthetic challenge in the pediatric population due to 3 factors: potentially difficult airway due to craniofacial malformations, high rate of intraoperative and postoperative neurological complications, and difficult hemodynamic management due to the risk of aneurysmal rupture before surgical control. Additionally, aortic arch surgery is uncommon in children, and experience is limited. It is essential to develop a plan considering all these variables for the appropriate anesthetic management of these patients.

Funding

None declared.

Conflicts of interest

None declared.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

References

1. Meester JAN, Verstraeten A, Schepers D, Alaerts M, van Laer L, Loeys BL. Differences in manifestations of Marfan Syndrome, Ehler Danlos syndrome and Loeys Dietz syndrome. Ann Cardiothorac Sur. 2017;6:592-94.
2. MacCarrick MS, Black III JH, Bowdin S, El-Hamamsy I, Frischmeyer-Guerrerio PA, Guerrerio AL, et al. Loeys–Dietz syndrome: a primer for diagnosis and management. Genet Med. 2014;16(8):576-87.
3. Loeys BL, Dietz HC. Loeys-Dietz Syndrome. Gene reviews® [Internet]. Seattle (WA): University of Washington; 1993-2023 [actualización marzo 2018]. Disponible en: https://pubmed.ncbi.nlm.nih.gov/20301312.
4. Aftab M, Cikach FS, Zhu Y, Idrees JJ, Rigelsky CM, Kalahasti V, et al. Loeys-Dietz syndrome: Intermediate-term outcomes of medically and surgically managed patients. J Thorac Cardiovasc Surg. 2019;157(2):439-50.e5.
5. Mühlstädt K, De Backer J, von Kodolitsch Y, Kutsche K, Muiño Mosquera L, Brickwedel J, et al. Case-matched comparison of cardiovascular outcome in Loeys-Dietz syndrome versus Marfan syndrome. J Clin Med. 2019;8:2079.
6. Ghanem I, El Hage S, Rachkidi R, Kharrat K, Dagher F, Kreichati G. Pediatric cervical spine inestability. J Child Orthop. 2008;2:71-84.
7. Wilkey BJ, Weitzel NS. Anesthetic considerations for surgery on the aortic arch. Semin Cardiothorac Vasc Anesth. 2016;20(4):265-72.
8. Keenan JE, Benrashid E, Kale E, Nicoara A, Husain AM, Hughes GC. Neurophysiological intraoperative monitoring during aortic arch surgery. Semin Cardiothorac Vasc Anesth. 2016;20:298-302.
9. Aytac I, Postaci A. Anaesthesia recommendations for patients with Loeys-Dietz syndrome. Prog Asp in Pediatric and Neonat. 2018;1(4).
10. Austin N, Krishnamoorthy V, Dagal A. Airway management in cervical spine injury. Int J Crit Ill INJ Sci. 2014;4(1):50-6.
11. Svyatets M, Tolani K, Zhang M, Tulman G, Charchaflieh J. Perioperative management of deep hypothermyc circulatory arrest. J Cardiothorac Vasc Anesth. 2010;24(4):644-55.
12. Gregory SH, Yalamuri S, Bisawi M, Swaminathan M. Management of ascending aortic dissection. Cardiovascular and Thoracic Anesthesiology. 2018;127(6):1302-13.