Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/radcr

Case report

Loeys-Dietz syndrome: Case report and review of the literature ☆

David F. Malyuk, MD, Norbert Campeau, MD, John C. Benson, MD*

Department of Neuroradiology, Mayo Clinic, 200 1st St SW, Rochester, MN 55905, USA

ARTICLE INFO

Article history:
Received 30 November 2021
Accepted 13 December 2021

Keywords:
Loeys-Dietz syndrome
Arterial tortuosity
Bifid uvula
Aortic aneurysm
Dissection

ABSTRACT

Loeyz-Dietz syndrome (LDS) is a genetic connective tissue disorder characterized by various clinical manifestations, most notably vasculopathies and skeletal abnormalities. The disease is rare, and has multiple overlapping features with other connective tissue disorders. As such, many radiologists remain unfamiliar with the imaging and clinical findings in LDS. Here, we describe the case of a 14-year-old male without previous diagnosis of LDS who presented with aortic root aneurysm and acute type A aortic dissection. Further workup revealed numerous abnormalities, including marked tortuosity of the cervical arterial system, a bifid uvula, hypertelorism, and a superior mesenteric artery aneurysm. Genetic testing ultimately revealed a mutation in Transforming Growth Factor Beta Receptor 1.

Introduction

Loeys-Dietz syndrome (LDS) is an autosomal dominant connective tissue disorder (CTD) associated with mutations in genes affecting transforming growth factor beta 1 and 2 (TGFBR1 and TGFBR2), as well as decapentaplegic homolog 3 (SMAD3 and TGFB2) [1–3]. Classically, it is characterized by the triad of arterial tortuosity and aneurysms, hypertelorism, and either bifid uvula or cleft palate [1,2]. However, LDS has multiple phenotypic similarities to other CTDs, including Marfan syndrome, Shprintzen-Goldberg syndrome (SGS), and Ehlers-Danlos syndrome. As such, the diagnosis often requires a combination of radiological and clinical findings, family history, and genetic testing [2].

Of the clinical manifestations of LDS, arterial vasculopathies tend to be most severe. Aortic aneurysms often develop at a young age, which are prone to rupture early [2,4,5]. Elsewhere, observed arterial abnormalities include aneurysms, dissections, and tortuosity [1,2,6,3]. Arteries of the head and neck are among the most common sites of systemic arterial involvement [3,7]. Specifically, arterial tortuosity in the head and neck is pervasive and often prominent [8,9]. In addition, intracranial aneurysms are a known neurovascular association [8,10] with intracerebral bleeding being reported as the cause of death in up to 7% of patients with LDS [4].

The rarity of LDS, in addition to its overlapping manifestations with other CTDs, can make this diagnosis particularly challenging for radiologists. In this article, we describe a previously undiagnosed patient who presented with an aortic dis-

☆ Competing Interests: The authors have declared that no competing interests exist.

* Corresponding author. D.F. Malyuk.
E-mail address: malyuk.david@mayo.edu (D.F. Malyuk).

https://doi.org/10.1016/j.radcr.2021.12.024

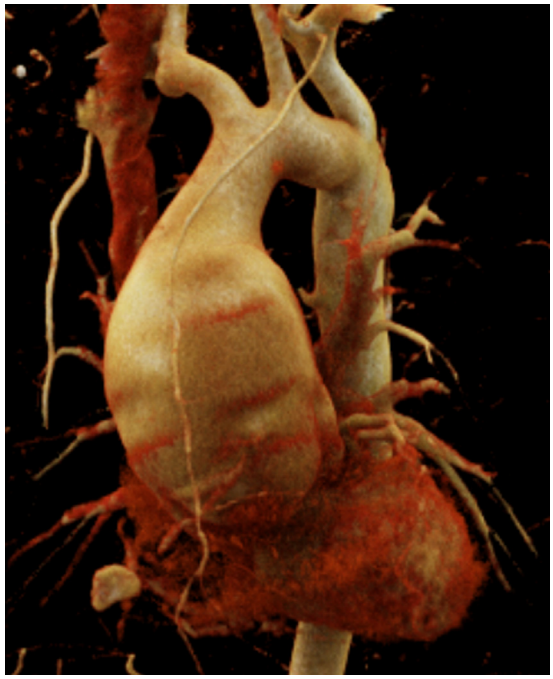

Fig. 1 – Volume rendered computed tomographic angiogram (CTA) demonstrates aortic root and ascending aortic aneurysm, which measured up to 6.8 cm.

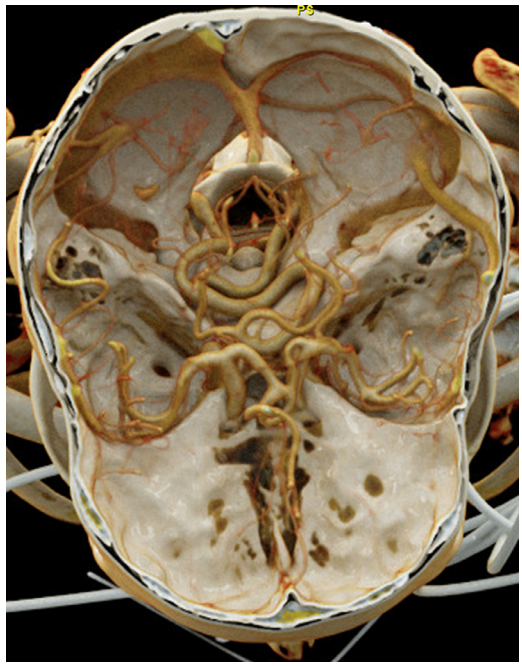

Fig. 3 – Volume rendered computed tomographic angiogram (CTA) demonstrates marked arterial tortuosity involving the intracranial arterial vasculature. Findings are highly unusual for a pediatric patient and should raise suspicion for LDS.

section. The patient's clinical and radiological findings will be reviewed, as will the relevant up-to-date literature on this topic.

Case report

A 14-year-old male without significant past medical history presented to the emergency department with acute onset chest pain and shortness of breath. Computed tomography angiography (CTA) of the chest revealed a severely dilated aortic root and ascending thoracic aorta measuring 6.8 cm (Fig. 1), an acute type A aortic dissection, and large hemopericardium. Echocardiogram further elucidated tamponade physiology, torrential aortic valve insufficiency, and right coronary artery dissection. The patient was flown to our institution where he underwent emergent non-valve sparing aortic root and hemiarch replacement.

Upon stability in clinical status, complete evaluation for underlying connective tissue disease was performed. A bifid uvula (Fig. 2) and hypertelorism were noted on physical exam and demonstrated on subsequent imaging. Screening CTA of the head and neck revealed marked arterial tortuosity involving the vertebrobasilar system and proximal anterior cerebral arteries (Fig. 3). In addition, arterial tortuosity of the mid and upper cervical internal carotid and lower cervical vertebral arteries was noted. CTA of the abdomen and pelvis revealed aneurysmal dilation of the proximal superior mesenteric artery to 1.4 cm. Genetic testing revealed a missense

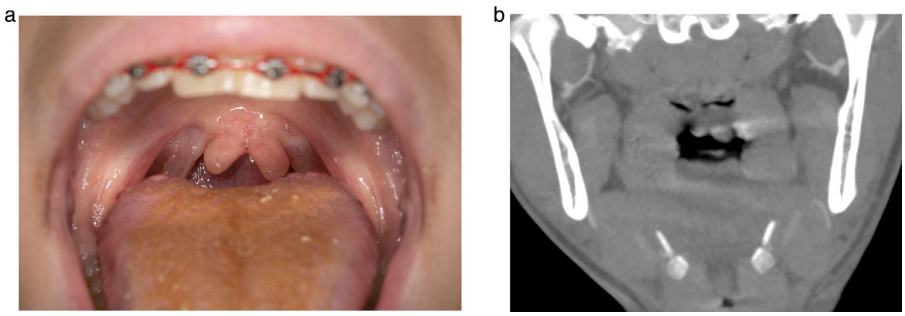

Fig. 2 – (A) Photograph of the mouth demonstrating the patient's bifid uvula. (B) Computed tomographic angiogram (CTA) maximum intensity projection (MIP) demonstrates bifid uvula.

variant in TGFBR1 (VUS TGFBR1 c.1445G>A (p.Arg482Lys) heterozygous).

Discussion

LDS is a relatively recently described connective tissue disorder associated with mutations affecting the TGFBR pathway, with multiple genetic mutations being implicated [1–3]. The described case serves to help understand both overlapping and distinguishing features of LDS from other CTDs. It illustrates an acute presentation of thoracic aortic dissection with several clinical and imaging findings characteristic of LDS with subsequent supportive genetic testing.

The classic clinical findings of LDS include arterial tortuosity and aneurysms in the context of hypertelorism and either bifid uvula or cleft palate. Hypertelorism was originally reported in in 93% of patients with LDS and cleft palate/bifid uvula in 100% of LDS patients [1]. These clinical features help distinguish LDS from other similar genetic aortopathies as they are nearly always present in patients with LDS and have not been associated with MF [3,11]. The presence of ectopia lentis suggests an alternative diagnosis, as it has not been associated with LDS, in contrast with MF and SGS [3,11]. Notably, hypertelorism is not associated with MF but is frequently associated with SGS [3]. Numerous other clinical findings can be seen in LDS, including talipes equinovarus, malar hypoplasia, arachnodactyly, blue sclerae, pectus deformity, scoliosis, and joint laxity. Clinical findings show significant overlap with other connective tissue disorders and must be considered in conjunction with radiologic findings and other aspects of patient presentation for accurate diagnosis.

Imaging features of the cardiovascular manifestations of LDS are utilized in diagnosis, surveillance, and surgical management. Aortic root involvement is ubiquitous [4], and the aggressive nature of aortic aneurysm and dissection helps distinguish LDS from other connective tissue disorders. Surgical management is often considered once thoracic aortic diameter reaches 4.0 cm [2,4,5]. Other central cardiovascular system manifestations include patent ductus arteriosus, atrial septal defects, and mitral valve prolapse. Aneurysmal disease of patent ductus arteriosus, coronary arteries, and pulmonary arteries has also been described [3].

Systemic arterial involvement helps distinguish LDS from other connective tissue disorders including Marfan syndrome and SGS [3]. Arterial tortuosity is frequently associated with LDS while not being associated with either MF or SGS [3]. The neck vessels are the most common site of arterial tortuosity in patients with LDS [2,3], the severity of which is often profound. One study found arterial tortuosity of the head or neck in all 25 reviewed patients [9]. Marked carotid bifurcation widening as measured using quantitative techniques has been proposed as a possible distinguishing feature specifically for the diagnosis of LDS [12]. This finding has recently been proposed to be named the “chalice sign.” Other reproducible diagnostic quantitative methods for the measurement of intracranial artery tortuosity have been described, showing high specificity for the diagnosis of both LDS as well as Marfan syndrome [13]. Furthermore, increased vertebral artery tortuosity in patients with connective tissue disease may have prognostic value in determining the likelihood of developing major adverse cardiovascular outcomes including severe aortic root dilation, younger age of aortic dissection, and death [14].

Additional important neurovascular manifestations of LDS include intracranial aneurysms, which have been reported in up to 28% [10] of patients. Cerebral bleeding has been reported as the third leading cause of death [4] in patients with LDS. As such, radiology plays an important role in identifying aneurysm for possible intervention. Endovascular as well as surgical treatment techniques have been safely and effectively utilized in the treatment of intracranial aneurysms in the setting of LDS [15–17]. Diagnostic as well as serial head and neck imaging are an essential part of clinical management.

Aneurysmal involvement of peripheral arteries has been described in internal mammary, common iliac, popliteal, and visceral arteries with successful surgical and endovascular interventions having been reported [3]. Computed tomographic angiography plays an important role in assessing for widespread arterial involvement.

Aside from central and peripheral vascular manifestations, other reported imaging findings associated with LDS include dural ectasia, Chiari I malformation, and hydrocephalus.

The prognosis for patients with LDS necessitates early diagnosis. The average age of death has been reported at as young as 26 years [4] with the leading cause of death being thoracic aortic dissection [4]. Despite the severely dilated thoracic aorta in the described case, aortic dissection and rupture can occur before significant dilation is present. Nonetheless, the patient described in our case report had a successful post-surgical outcome following thoracic aneurysmal repair and is currently followed clinically. In addition to the significant mortality secondary to thoracic aortic dissection, abdominal aortic dissection and cerebral bleeding have been reported as the second and third leading causes of death in patients with LDS [4].

The described patient displayed classic thoracic, neurovascular, and craniofacial phenotypic traits of LDS. This case report serves to help understand the clinical and imaging features of LDS. Accurate and timely diagnosis is critical to effective clinical management of patients with LDS given the propensity for significant aortic and multisystem arterial disease. Given similarities between LDS and other connective tissue disorders, radiology plays an important role in clinical workup and management of these patients.

Patient consent

Written informed consent has been obtained on behalf of the patient. Documentation has been recorded in the patient’s medical record.

REFERENCES

[1] Loeys BL, Chen J, Neptune ER, Judge DP, Podowski M, Holm T, et al. A syndrome of altered cardiovascular, craniofacial,

neurocognitive and skeletal development caused by mutations in TGFBR1 or TGFBR2. Nat Genet 2005;37(3):275–81. doi:10.1038/ng1511.
[2] MacCarrick G, Black JH 3rd, Bowdin S, El-Hamamsy I, Frischmeyer-Guerrerio PA, Guerrerio AL, Sponseller PD, Loeys B, Dietz HC 3rd. Loeys-Dietz syndrome: a primer for diagnosis and management. Genet Med 2014;16(8):576–87. doi:10.1038/gim.2014.11.
[3] Loughborough WW, Minhas KS, Rodrigues JCL, Lyen SM, Burt HE, Manghat NE, Brooks MJ, Stuart G, Hamilton MCK. Cardiovascular manifestations and complications of Loeys-Dietz syndrome: CT and MR imaging findings. Radiographics 2018;38(1):275–86. doi:10.1148/rg.2018170120.
[4] Loeys BL, Schwarze U, Holm T, Callewaert BL, Thomas GH, Pannu H, et al. Aneurysm syndromes caused by mutations in the TGF-beta receptor. N Engl J Med 2006;355(8):788–98. doi:10.1056/NEJMoa055695.
[5] Hughes GC. Aggressive aortic replacement for Loeys-Dietz syndrome. Tex Heart Inst J 2011;38(6):663–6.
[6] Welby JP, Kim ST, Carr CM, Lehman VT, Rydberg CH, Wald JT, et al. Carotid artery tortuosity is associated with connective tissue diseases. AJNR Am J Neuroradiol 2019;40(10):1738–43. doi:10.3174/ajnr.A6218.
[7] Van Hemelrijk C, Renard M, Loeys B. The Loeys-Dietz syndrome: an update for the clinician. Curr Opin Cardiol 2010;25(6):546–51. doi:10.1097/HCO.0b013e32833f0220.
[8] Johnson PT, Chen JK, Loeys BL, Dietz HC, Fishman EK. Loeys-Dietz syndrome: MDCT angiography findings. AJR Am J Roentgenol 2007;189(1):W29–35. doi:10.2214/AJR.06.1316.
[9] Rodrigues VJ, Elsayed S, Loeys BL, Dietz HC, Yousem DM. Neuroradiologic manifestations of Loeys-Dietz syndrome type 1. AJNR Am J Neuroradiol 2009;30(8):1614–19. doi:10.3174/ajnr.A1651.
[10] Kim ST, Brinjikji W, Kallmes DF. Prevalence of intracranial aneurysms in patients with connective tissue diseases: a retrospective study. AJNR Am J Neuroradiol 2016;37(8):1422–6. doi:10.3174/ajnr.A4718.
[11] Meester JAN, Verstraeten A, Schepers D, Alaerts M, Van Laer L, Loeys BL. Differences in manifestations of Marfan syndrome, Ehlers-Danlos syndrome, and Loeys-Dietz syndrome. Ann Cardiothorac Surg 2017;6(6):582–94. doi:10.21037/acs.2017.11.03.
[12] Benson JC, Brinjikji W. The Chalice sign: characteristic morphology of the cervical carotid bifurcation in patients with Loeys-Dietz syndrome. Clin Neuroradiol 2020;30(4):713–20. doi:10.1007/s00062-019-00838-5.
[13] Spinardi L, Vornetti G, De Martino S, Golfieri R, Faccioli L, Pastore Trossello M, et al. Intracranial arterial tortuosity in Marfan syndrome and Loeys-Dietz syndrome: tortuosity index evaluation is useful in the differential diagnosis. AJNR Am J Neuroradiol 2020;41(10):1916–22. doi:10.3174/ajnr.A6732.
[14] Morris SA, Orbach DB, Geva T, Singh MN, Gauvreau K, Lacro RV. Increased vertebral artery tortuosity index is associated with adverse outcomes in children and young adults with connective tissue disorders. Circulation 2011;124(4):388–96. doi:10.1161/CIRCULATIONAHA.110.990549.
[15] Kim ST, Brinjikji W, Lanzino G, Kallmes DF. Neurovascular manifestations of connective-tissue diseases: a review. Interv Neuroradiol 2016;22(6):624–37. doi:10.1177/1591019916659262.
[16] Levitt MR, Morton RP, Mai JC, Ghodke B, Hallam DK. Endovascular treatment of intracranial aneurysms in Loeys-Dietz syndrome. J Neurointerv Surg 2012;4(6):e37. doi:10.1136/neurintsurg-2011-010138.
[17] Carr SB, Imbarrato G, Breeze RE, Wilkinson CC. Clip ligation for ruptured intracranial aneurysm in a child with Loeys-Dietz syndrome: case report. J Neurosurg Pediatr 2018;21(4):375–9. doi:10.3171/2017.10.PEDS17193.