

Loeys-Dietz Syndrome

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Abstract

Loeys-Dietz syndrome (LDS) is a rare connective tissue disorder typically caused by mutations in 1 of 6 different genes. There are several different subtypes, most of which have unique clinical features. The different clinical features can be an early clue of disease and lead to imaging and genetic testing. Early diagnosis of LDS is key to improving patient survival. Once diagnosed, patients are imaged with CT or MRA to assess for aneurysms, dissection, or vascular tortuosity. Regular imaging surveillance is necessary to monitor disease progression. Therapy depends on the disease features. Outcomes are variable and depend on the type and severity of the syndrome features.

Keywords: syndrome, congenital, multisystem

Case Summary

An adolescent with a known history of Loeys-Dietz syndrome (LDS) underwent surveillance MRI.

Imaging Findings

MRA (Figure 1) showed tortuous vessels of the head, neck, chest, and abdomen.

Diagnosis

Loeys-Dietz syndrome.

Differential diagnoses include Marfan syndrome, Shprintzen-Goldberg syndrome (SGS), vascular Ehlers-Danlos syndrome (vEDS), familial aortic aneurysm and dissection syndrome (FAADS), and arterial tortuosity syndrome (ATS).

Discussion

LDS is a rare connective tissue disorder that was differentiated from the closely related Marfan syndrome in 2005 by Drs Bart Loeys and Harry Dietz.¹ It is caused by various mutations in the transforming growth factor β (TGF- β) receptor and ligand or SMAD gene isoforms, which create a variety of vasculopathies and characteristic craniofacial and musculoskeletal deformities. The classic findings of the disorder include arterial tortuosity and aneurysms, hypertelorism, and bifid uvula or cleft palate.¹ LDS may be inherited in an autosomal-dominant fashion, but 75% of patients diagnosed have a de novo mutation.²

There are 4 subtypes of LDS. The subtypes may have variable presentations. However, all subtypes have a high risk of aneurysms of the aorta and aortic arch (present in 99% of cases). These aneurysms are known to

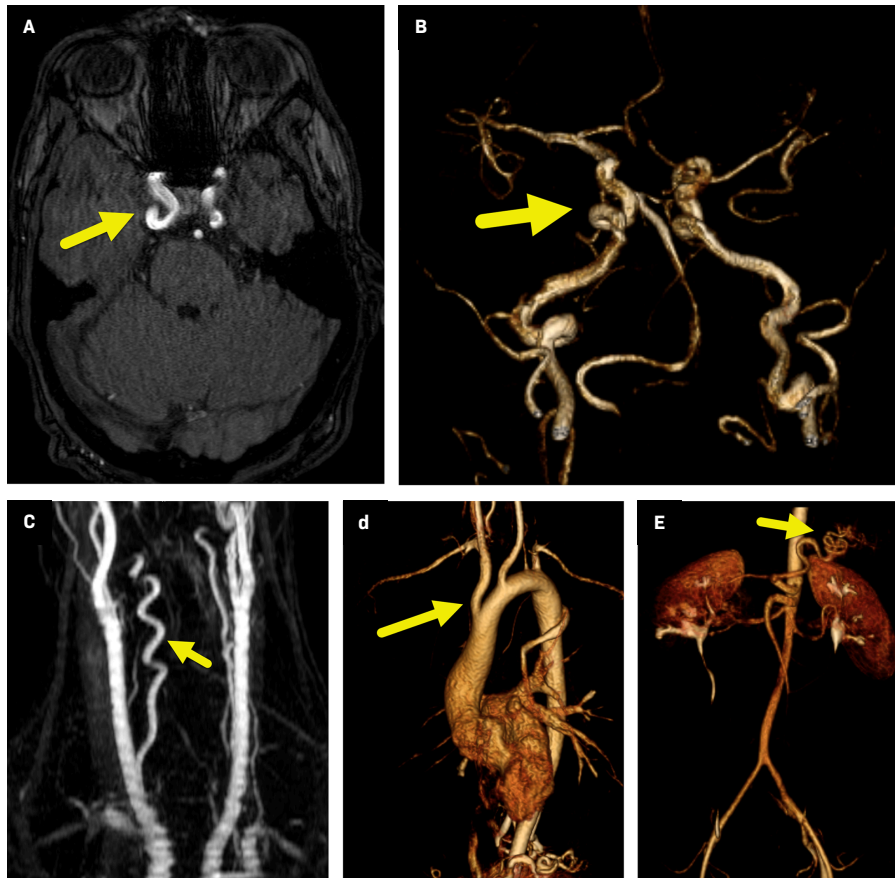
expand rapidly and rupture at relatively small diameters compared with Marfan syndrome.² Aneurysmal rupture leads to high mortality in pediatric and adolescent populations.² LDS shares features related to weakened connective tissue, vascular and skeletal abnormalities with Marfan syndrome, SGS, and severe forms of vEDS. Genetic testing and imaging are the primary methods of differentiating LDS from similar pathologies.

Type 1 LDS is caused by mutations in the *TGFBR1* gene. It is associated with craniofacial abnormalities, including hypertelorism, cleft palate, bifid uvula, craniosynostosis, Chiari I malformation, and hydrocephalus. Type 2 LDS (vascular Ehlers-Danlos-like LDS) is caused by mutations in the *TGFBR2* gene. It has cutaneous manifestations, including easy bruising, translucent skin, and blue sclerae. Type 3 LDS (aneurysm-osteoarthritis syndrome) is caused by mutations in the *SMAD3* gene. This subtype of LDS is associated with joint hyperlaxity, early-onset osteoarthritis, and arterial aneurysms. Type 4 LDS is caused by mutations in the *TGFBR2* gene. Affected patients have Marfanoid-like musculoskeletal features. Type 5 LDS is caused by mutations in *TGFBR3*. This subtype of LDS has no characteristic presentation.

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Figure 1. (A) Source images from MRA showing a tortuous configuration (arrow) of the internal carotid arteries as they pass through the cavernous sinus. (B) Three-dimensional (3D) reformatted MRA of the head showing the tortuous internal carotid arteries (arrow) as they pass through the cavernous sinus. Note, however, that the entire course of the carotid arteries is tortuous. (C) Maximum-intensity reconstructed image showing the right vertebral artery (arrow) with a tortuous course. (D) 3D reformatted MRA of the aorta showing the aorta to have a tortuous course with mild dilation of the aortic root. The left brachiocephalic artery (arrow) is tortuous near its origin. (E) 3D reformatted images of the abdominal aorta and its branches showing the splenic artery (arrow) with a tortuous course. Other vessels are ectatic.



Instead, it closely resembles type 2 LDS. Finally, type 6 LDS is caused by mutations of the *SMAD2* gene. In some instances, patients with this subtype have dextrocardia. While there are characteristic features of each subtype, patients with LDS have variable phenotypes due to incomplete penetrance. Other potential features common in LDS include developmental delay, skin striae, cardiac malformations (atrial septal defect, bicuspid aortic valve, mitral valve prolapse, patent ductus arteriosus), spontaneous pneumothorax, allergic atopy, exotropia, clubfoot, peripheral neuropathy, and dural ectasia.³

Radiologic imaging can help classify characteristic features of LDS and screen for disease progression. The American Heart Association's current guidelines recommend thorough monitoring and follow-up after diagnosis of aortic disease with baseline and lifelong surveillance imaging.⁴ After diagnosis, baseline angiography with whole-body CTA or MRA should be obtained to determine disease severity and examine for aortic, cervical, and cerebral aneurysms, dissection, or tortuosity. If baseline imaging is normal, surveillance imaging may be performed every 2-3 years, or more frequently based on family history

of disease severity.⁴ If abnormalities are present, repeat CTA or MRA should be performed every 6 months.⁴

Echocardiography is used for detection of bicuspid aortic valve and mitral valve prolapse and for screening for the development of valvular insufficiency.⁴ Baseline cervical spine x-rays are also commonly obtained to assess for cervical instability. Additional imaging may be obtained for specific syndromic features, such as foot x-rays for clubfoot, thoracic and lumbar spine x-rays for scoliosis, cranial imaging for craniosynostosis, fluoroscopic swallow studies for cleft palate, and dental x-rays for oro-dental anomalies.

LDS can be differentiated from other hereditary connective tissue disorders with genetic testing. Therefore, it is important to recognize the characteristic features of other related disorders. Marfan syndrome has many similar musculoskeletal features to LDS, including aortic aneurysms and dilation, but does not feature arterial tortuosity.⁵ Additionally, there is little overlap in craniofacial features of Marfan syndrome and LDS. Patients with Marfan syndrome have a long, narrow face, enophthalmos, and a highly arched, narrow palate, while patients with LDS have hypertelorism, bifid uvula, cleft palate, and craniosynostosis.^{2,5} Patients with SGS have a Marfanoid habitus and aortic dilation (significantly milder than patients with LDS). The differentiating features of SGS are developmental delay and intellectual disability (93% of patients), craniosynostosis, and minimal subcutaneous fat.⁶ vEDS has significant overlap with the clinical features of LDS, including similarly high risk for aortic and arterial aneurysms and rupture (with or without aneurysms) in pediatric patients. vEDS can be differentiated from LDS by its lack of arterial tortuosity, the presence of spontaneous solid organ rupture, and craniofacial features, including prominent eyes, thin pitched nose, hollow cheeks, and lobeless ears.⁷

Table 1. Summary of the Clinical Features of Loeys-Dietz Syndrome and Its Differential Diagnoses

Feature	Loeys-Dietz Syndrome	Marfan Syndrome	Shprintzen-Goldberg Syndrome	Vascular Ehlers-Danlos Syndrome	Familial Aortic Aneurysm and Dissection Syndrome	Arterial Tortuosity Syndrome
Genetic mutations	TGFB1, TGFB2, SMAD3, TGFB2, TGFB3, SMAD2	FBN1	SKI	COL3A1	Multiple genes, including ACTA2, TGFB1, TGFB2	SLC2A10
Inheritance	Autosomal dominant (75% de novo)	Autosomal dominant	Autosomal dominant	Autosomal dominant	Autosomal dominant	Autosomal recessive
Arterial tortuosity	Present in Loeys-Dietz syndrome	Absent	Absent	Absent	Absent	Present
Aortic aneurysms	High risk, present in 99% of cases	Present	Present	Present	Present	Present
Aortic rupture risk	High risk even at small diameters	High risk, but at larger diameters	Lower risk compared with Loeys-Dietz Syndrome	High risk, with or without aneurysms	High risk	High risk
Craniofacial features	Hypertelorism, bifid uvula, cleft palate, craniosynostosis	Long, narrow face, enophthalmos, high-arched palate	Craniosynostosis, minimal subcutaneous fat	Prominent eyes, thin nose, hollow cheeks, lobeless ears	Typical facial features, not distinctive	Blepharophimosis, downslanting palpebral fissures, midface retrusion
Skin	Translucent skin, easy bruising, blue sclerae (type 2)	Striae, less translucent skin	Variable, usually less involvement	Translucent skin, easy bruising	No specific skin features	Soft, velvety skin, easy bruising
Musculoskeletal features	Joint hyperlaxity, early onset osteoarthritis (type 3)	Joint hyperlaxity, arachnodactyly, scoliosis	Marfanoid habitus, joint hypermobility	Joint hypermobility, talipes equinovarus	No specific musculoskeletal features	Joint hypermobility, arachnodactyly, scoliosis
Other features	Clubfoot, peripheral neuropathy, dural ectasia, mitral valve prolapse	Ectopia lentis, mitral valve prolapse	Developmental delay, intellectual disability (93%)	Spontaneous organ rupture, sigmoid colon perforations	Lack of arterial tortuosity	None unique beyond those overlapping with Loeys-Dietz syndrome

Spontaneous colonic perforations and carotid-cavernous sinus fistula formation are considered diagnostic criteria for vEDS. ATS also has significant overlap with the clinical features of LDS, including diffuse arterial tortuosity of the aorta and its branches, arterial aneurysms, and similar musculoskeletal abnormalities. Again, patients with ATS can be differentiated from those with LDS by their unique craniofacial features. These features include blepharophimosis (narrow horizontal opening of eyelids), down-slanting palpebral fissures, and midface retrusion.⁸ FAADS is another hereditary connective tissue disorder with significant overlap with the vascular and musculoskeletal features of LDS. However, FAADS lacks arterial tortuosity.⁹ Characteristics of the different syndromes are summarized in Table 1.

There are a multitude of complications in LDS that can cause early mortality. These risks include aortic aneurysms

and dissections, early onset of and rapid progression of aortic disease, and a heightened risk of aneurysm rupture. The life expectancy is quite variable based on disease severity.

Conclusion

LDS is a rare connective tissue disorder typically caused by mutations in 1 of 6 different genes. There are several different subtypes, most of which have unique clinical features. The different clinical features can be an early clue of disease and lead to imaging and genetic testing. Early diagnosis of LDS is key to improving patient survival. Once diagnosed, patients are imaged with CT or MRA to assess for aneurysms, dissection, or vascular tortuosity. Regular imaging surveillance is necessary to monitor disease progression. Therapy depends on the disease features.

Outcomes are variable and depend on the type and severity of the syndrome features.

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