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Importance of the Clinical Recognition of Loeys-Dietz Syndrome in the Neonatal Period

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Abstract

We describe 5 patients who presented with musculoskeletal abnormalities in the neonatal period. All patients were initially suspected to have Larsen syndrome or Beals syndrome but were subsequently diagnosed with a *TGFBR2* mutation diagnostic of Loeys-Dietz syndrome. Patients had progressive aortic enlargement, which necessitated surgical intervention for 3 patients and resulted in the death of 1 patient. Delay in diagnosis of Loeys-Dietz syndrome may be associated with adverse prognosis.

Keywords

aortic aneurysm; aortic dissection; gene mutation

In 2005, Loeys et al[1] reported on a newly identified genetic syndrome, Loeys-Dietz syndrome. The syndrome shares many clinical characteristics with Marfan syndrome, including the propensity for early aortic dilation and dissection.[1] The cellular mechanisms that underlie the aortic pathology in Loeys-Dietz syndrome are similar to Marfan syndrome, including altered activity of the cytokine family transforming growth factor β (TGF-β).[2] Unlike patients with Marfan syndrome, those with Loeys-Dietz syndrome do not have an alteration in the *FBN-1* gene encoding the fibrillin protein but, rather, a mutation in the serine-threonine kinase domain of 1 of 2 TGF-β receptors, *TGFBR1* or *TGFBR2*.[2] To date, reports from 2 series (totaling 52 cases) of patients with Loeys-Dietz syndrome have been published, with the majority of patients having reached adulthood.[1,2] Given the very recent recognition of the syndrome, the natural history of the clinical features and the timing of presentation remain unknown.

Here we describe 5 patients with genetically confirmed Loeys-Dietz syndrome who presented for medical attention in the neonatal period with a clinical picture of joint contractures and joint hypermobility. Despite the fact that all the patients had progressive cardiac pathology during childhood, most had inadequate cardiac follow-up, because all had been misdiagnosed.

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CASE REPORTS

Patient 1 was a term infant who was referred to a tertiary pediatric care center on day 1 of life for additional evaluation of a genetic syndrome in the setting of a murmur, diffuse hypotonia, macrocrania, and upper- and lower-limb abnormalities (Table 1). Weight was in the 3rd percentile, height was in the 10th percentile, and head circumference was >97th percentile. The patient was evaluated by the department of genetics, and a differential diagnosis including Larsen syndrome, Beals syndrome, and other "arthrogryposis complexes" was considered in light of the multiple joint dislocations and contractures. Family history was unremarkable. Initial investigations included normal chromosomal study results, skeletal imaging (Table 1), computed tomography (CT) of the head that demonstrated no intracranial abnormalities or abnormalities of the skull, and an echocardiogram that revealed a structurally normal heart, dilated pulmonary artery, dilated aortic root (Table 2), and a small patent ductus arteriosus (PDA) without aneurysm. Annual cardiology follow-up was arranged. Surgical interventions during infancy included repair of talipes equinovarus and metatarsus adductus foot deformities, umbilical hernia repair, and repair of bilateral exotropia. At 1 year of age, the patient was noted to have had significant progression in aortic dilation. She was placed on β-blocker therapy with no subsequent change in the rate of aortic dilation. She was subsequently referred to our Marfan subspecialty clinic, at which time she was started on an angiotensin-converting enzyme (ACE) inhibitor and followed every 3 months with echocardiography. Aortic dilation stabilized with no additional increase in percent-predicted aortic diameter. After the recent report in *Nature Genetics*,[1] DNA sequencing was performed and confirmed the presence of a previously reported mutation in *TGFBR2* (Table 3). At 2 years old, solely as a result of the genetic diagnosis, MRI of the cervical spine was obtained, which demonstrated spinal canal stenosis caused by cervical vertebral subluxation (Table 1). The patient was followed by neurosurgery and noted to have progressive spinal cord stenosis necessitating surgical intervention at 30 months old.

Patient 2 was a term infant who was referred to a tertiary pediatric center on day 1 of life for additional evaluation of a genetic syndrome in the setting of a murmur, diffuse hypotonia, macrocrania, and musculoskeletal abnormalities including bilateral knee dislocations and hip dislocations (Table 1). Weight was in the 97th percentile, height was in the 97th percentile, and head circumference was at > 99th percentile. Because of the lower-extremity abnormalities and a finding of "abnormal facies" with hypertelorism, the patient was suspected to have Larsen syndrome. Family history was unremarkable. Investigations included normal chromosomal study results, skeletal imaging (Table 1), CT of the head that demonstrated no intracranial abnormalities, and an echocardiogram that demonstrated a large ductal aneurysm with thrombus, as well as pulmonary artery and aortic root enlargement (Table 2). Surgical interventions during the neonatal period included PDA ligation. Because of the ductal aneurysm and the other clinical features (Table 1), genetic studies for Loeys-Dietz syndrome were performed. DNA sequencing demonstrated a missense mutation in the kinase domain of *TGFBR2* (Table 3). At the age of 10 weeks, the patient was noted to have progressive aortic root enlargement (Table 2) and was started on an ACE inhibitor. At 6 months of age the aortic root diameter was stable. The patient is being followed by neurosurgery for cervical vertebral abnormalities (Table 1).

Patient 3 was a term infant who was referred to a tertiary pediatric center on day 1 of life for apnea, diffuse hypotonia, and musculoskeletal abnormalities (Table 1). All growth parameters were within normal limits. Head circumference was in the 97th percentile. Because of the lower-extremity abnormalities and facial appearance, the patient was suspected to have Larsen syndrome. Family history was unremarkable. Investigations included normal chromosomal study results and skeletal imaging (Table 1). Surgical

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interventions during childhood included serial orthopedic interventions for bilateral talipes equinovarus, inguinal hernia repair, and repair of bilateral exotropia. The patient presented acutely for medical attention at 6 years of age with arm numbness and was noted to have spinal cord compression secondary to C2–C3 subluxation. He went on to require spinal fusion. The patient re-presented at 9 years of age with jaw pain and was found to have an aortic dissection in the setting of a markedly dilated aortic root. The dissection extended into the vertebral and carotid arteries and, despite successful surgical intervention, the patient was left with a diffuse hypoxic-ischemic cerebral insult that resulted in death. Because of the aortic dissection at a young age and the presence of a bifid uvula noted on intubation, the patient underwent genetic testing at the time of surgical intervention. DNA sequencing demonstrated a missense mutation in the kinase domain of *TGFBR2* (Table 3).

Patient 4 was a term infant who was noted to have marked hypotonia and several musculoskeletal abnormalities (Table 1) that prompted an outpatient orthopedic evaluation. Growth parameters were within normal limits. The patient was diagnosed with arthrogryposis, and the question of Larsen syndrome was raised. Family history was unremarkable. Investigations included normal chromosomal study results and skeletal imaging (Table 1). Surgical interventions during childhood included correction of lower-extremity abnormalities, repair of bilateral strabismus, bilateral hernia repair, and repair of an acquired Morgagni hernia. Clinical course was marked by persistent panligamentous laxity that required lower-body bracing to allow ambulation. The patient was noted to have a murmur during the first month of life and was noted to have a small restrictive PDA, a dilated pulmonary artery, and a dilated aortic root. The patient was subsequently lost to cardiology follow-up until re-presenting at 2 years of age with respiratory symptoms. Echocardiography at that time demonstrated a markedly dilated aortic root, which measured 51 mm, with mild aortic insufficiency (Table 2). The patient underwent ductal ligation and a valve-sparing aortic root-replacement procedure and was placed on an ACE inhibitor with a subsequently stable cardiac course. At 6 years of age, the patient began complaining of lower-extremity weakness. Cervical spine abnormalities were noted at that time (Table 1). Because of the cervical spine abnormality, genetic studies with DNA sequencing were performed and confirmed a *TGFBR2* mutation (Table 3).

Patient 5 was a term infant who was referred to a pediatric center on day 1 of life for diffuse hypotonia, macrocrania, and multiple musculoskeletal abnormalities. Weight was at <3rd percentile, height was in the 5th percentile, and head circumference was at >98th percentile. The patient was suspected to have Beals syndrome. Family history was unremarkable. Investigations included normal chromosomal study results, fibrillin study results, skeletal imaging (Table 1), and CT of the head (which demonstrated no significant intracranial abnormalities or any abnormality of the skull with the exception of extremely shallow ocular orbits). At 2 months of age the patient presented with acute loss of consciousness. CT of the head and neck at that time demonstrated no abnormalities with the exception of an abnormal, hypoplastic C3 vertebra. The patient was followed closely in this regard and noted to have complete C2–C3 subluxation with spinal cord compression, which necessitated stabilization and subsequent fusion. At the time of orthopedic intervention, the patient developed supraventricular tachycardia, and a cardiology consult was performed. Subsequent echocardiography demonstrated a dilated aortic root. Because of rapidly progressive dilation, the patient underwent a valve-sparing aortic root-replacement procedure at 3 years of age with good results. Because of the cervical abnormalities and the aggressive aortic disease, the question of Loeys-Dietz syndrome was raised. DNA sequencing confirmed the diagnosis, with identification of a previously reported splice-site mutation in *TGFBR2* (Table 3).

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DISCUSSION

Loeys-Dietz syndrome is a newly recognized genetic condition.[1,2] As we have demonstrated, patients with this syndrome may present in the neonatal period with a number of clinical features including PDA with or without ductal aneurysm, macrocrania without craniosynostosis, and joint contractures and/or marked ligamentous laxity.

In their original patient description, Larsen et al noted a combination of multiple joint contractures and dislocations and abnormal facial appearance including hypertelorism.[3] However, several reports followed that noted the presence of cardiac abnormalities and cervical spine abnormalities in association with joint contractures and labeled this constitution of findings "Larsen syndrome."[4–6] The clinical overlap between these patients and those with genetically proven Loeys-Dietz syndrome suggests that Loeys-Dietz syndrome may be more common than initially realized. Misdiagnosis may not be uncommon. Recent discovery of the genetic abnormalities in both Larsen and Loeys-Dietz syndromes should help clarify this situation.[7] Confirmatory genetic testing is imperative if either diagnosis is considered, because clinical follow-up will differ.

Beals syndrome, otherwise known as congenital contractural arachnodactyly, occurs as a result of a mutation in the fibrillin 2 gene. It shares some common features with Loeys-Dietz syndrome but is supposed to be devoid of cardiac or ocular involvement.[8] Again, cases have been reported that involve aortic pathology, which raises questions regarding the accuracy of the diagnosis in these previous publications.[9]

Ductal aneurysms have been reported to occur in association with diffuse aortic enlargement and marfanoid features in both children[10] and adults,[11] which suggests that Loeys-Dietz syndrome should be part of the differential diagnosis for these patients as well.

In our cohort of patients, cervical spine abnormalities were universally present, and significant, which is a finding that was not previously reported. The lack of cervicospinal abnormalities in previously reported patients may represent clinical variability or absence of diagnosis in asymptomatic patients. We recommend imaging of the cervical spine in all patients who are suspected of having a *TGFBR1* or *TGFBR2* mutation.

Although the majority of previously reported patients with Loeys-Dietz syndrome have had diffuse aneurysmal formation, our patients, despite thorough magnetic resonance angiography evaluation, had aneurysmal involvement confined to the aortic root. There was a corkscrew appearance of the head and neck vessels in all patients, but there were no additional aneurysms of the arterial tree. The young age of our patient cohort may help explain this finding and suggests that patients need to be followed for developmental alterations in the vascular system over time.

CONCLUSIONS

Children who present with diffuse hypotonia, joint laxity, and/or joint contractures and in whom a diagnosis of arthrogryposis, Larsen syndrome, or Beal syndrome is being entertained should undergo thorough genetic evaluation to rule out a *TGFBR1* or *TGFBR2* mutation. Frequent cardiovascular imaging and imaging of the cervical spine are required for such patients.

Abbreviations

TGF-β transforming growth factor β

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CT	computed tomography
PDA	patent ductus arteriosus
ACE	angiotensin-converting enzyme

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TABLE 1

Clinical Manifestations

Manifestation	Patient No.				
	1	2	3	4	5
Cranium					
Hypertelorism	+	+	+	+	+
Blue sclerae	+	+			+
Macrocrania	+	+	+		+
Strabismus	+		+	+	+
High arched palate	+	+	+	+	+
Bifid or broad uvula	+	+	+	+	+
Neck					
Age at diagnosis of C3 hypoplasia with vertebral subluxation ± cord compression	2 y	1 mo	6 y	9 y	2 mo
Musculoskeletal: upper					
Radial-ulnar dislocation				+	
Metacarpophalangeal dislocations	+			+	+
Camptodactyly	+	+	+	+	+
Musculoskeletal: lower					
Talipes equinovarus	+	+	+	+	+
Metatarsus adductus	+			+	
Knee dislocations		+		+	
Hip dislocation		+		+	
Calcaneal-cuboid dislocation			+	+	
Herniae					
Acquired diaphragmatic				+	
Inguinal		+	+	+	+
Umbilical	+				

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TABLE 2

Cardiac Manifestations

Patient No.	Age at Diagnosis of Aortic Dilation	Current Age	% Aortic Root[a]	Arch Vessels	Other	Outcome
1	2 d	30 mo	147	Tortuous	PDA	Stable on medication
2	2 d	6 mo	140	Tortuous	PDA	PDA ligation; stable on medication
3	9 y	9 y	200	Tortuous	Aortic dissection	AVR with aortic replacement; death
4	1 mo	9 y	170	Tortuous	PDA	Valve-sparing surgery
5	6 mo	6 y	178	Tortuous	SVT	Valve-sparing surgery

SVT indicates supraventricular tachycardia; AVR, aortic valve replacement.

[a]Aortic root diameter as a percent of predicted on the basis of body surface area– established normal values. Value was obtained at last clinic follow-up before surgical intervention.

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TABLE 3

Genetic Test Results

Patient No.	Mutation	Nucleotide	Amino Acid
1	*TGFBR2* Exon 7	c. 1583G→A	Arg528His
2	*TGFBR2* Exon 7	c. 1570G→A	Asp524Asn
3	*TGFBR2* Exon 5	c. 1318G→A	Glu440Lys
4	*TGFBR2* Exon 4	c.865–873delACAGAGAAG	Thr289_Lys291del
5	*TGFBR2* IVS5–1G→A (splice-site mutation)		