Arterial tortuosity and aneurysm in a case of Loeys-Dietz syndrome type IB with a mutation p.R537P in the *TGFBR2* gene

Esra Kılıç[1], Yasemin Alanay[1], Eda Ütine[1], Burçe Özgen-Mocan[2], Peter N. Robinson[3], Koray Boduroğlu[1]

[1]Divison of Clinical Genetics, Department of Pediatrics, and [2]Department of Radiology, Hacettepe University Faculty of Medicine, Ankara, Turkey, and [3]Charité - Universitätsmedizin Berlin, Institute for Human Genetics and Medical Genetics, Berlin, Germany

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We report a 13-year-old girl with Loeys-Dietz syndrome (LDS) caused by a known transforming growth factor beta receptor II *(TGFBR2)* gene mutation, who developed aortic root dilatation and saccular aneurysm of the internal carotid artery. LDS is a rare, autosomal dominant aortic aneurysm syndrome with multisystem involvement. The disease is typically characterized by the triad of arterial tortuosity and aneurysms, hypertelorism, and bifid uvula/cleft palate. The characteristic LDS symptoms observed in the reported case included craniofacial dysmorphism (hypertelorism, cleft palate, blue sclerae, malar hypoplasia, retrognathia), skeletal deformities (scoliosis, talipes equinovarus, pectus deformity, arachnodactyly), congenital heart defects (patent ductus arteriosus, PDA), and arterial tortuosity and aneurysms. Molecular genetic testing revealed a heterozygous mutation (c.1610 G>C, p.R528C) in the serine-threonine kinase domain of the *TGFBR2* gene. Magnetic resonance (MR) angiography showed aortic dilatation, tortuosity of bilateral supraaortic arteries, and saccular aneurysm on the right cervical internal carotid artery. LDS resembles Marfan-related disorders (Marfan, Shprintzen-Goldberg and vascular Ehlers-Danlos syndrome), but arterial tortuosity and aneurysms are characteristic for LDS, so a timely diagnosis of LDS is important for early diagnosis and intervention of aneurysms to prevent vascular events. Here, we describe a LDS patient who presented with arterial tortuosity and saccular aneurysm.

Key words: Loeys-Dietz syndrome type IB, TGFBR2, Marfan-related disorder, arterial tortuosity, aneurysm.

Loeys-Dietz syndrome (LDS) (OMIM 609192) is a rare, autosomal dominant aortic aneurysm syndrome with multisystem involvement. In 2005, Loeys et al.[1,2] described this genetic condition caused by mutations in transforming growth factor β-receptor type 1 (*TGFBR1*) or 2 (*TGFBR2*) genes, which cause an increase in TGF-β signaling. LDS closely resembles Marfan-related disorders (Marfan syndrome, Marfanoid craniosynostosis syndrome (Shprintzen-Goldberg syndrome [SGS]), and vascular Ehlers-Danlos syndrome [vEDS]), but it has different clinical and pathologic manifestations, such as aggressive arterial aneurysms. To date, more than 80 LDS patients have been described in the literature. The disease is typically characterized by the triad of arterial tortuosity and aneurysms, hypertelorism and bifid uvula/cleft palate. Other manifestations include blue sclerae, malar hypoplasia, retrognathia, craniosynostosis, dolichostenomelia, pectus deformity, scoliosis, arachnodactyly-camptodactyly, talipes equinovarus, joint laxity, velvety skin, congenital heart defects, and mild developmental delay[1,2]. Two types of LDS have been described. Individuals with LDS type I have both craniofacial and vascular disorders, whereas LDS type II patients have at least two

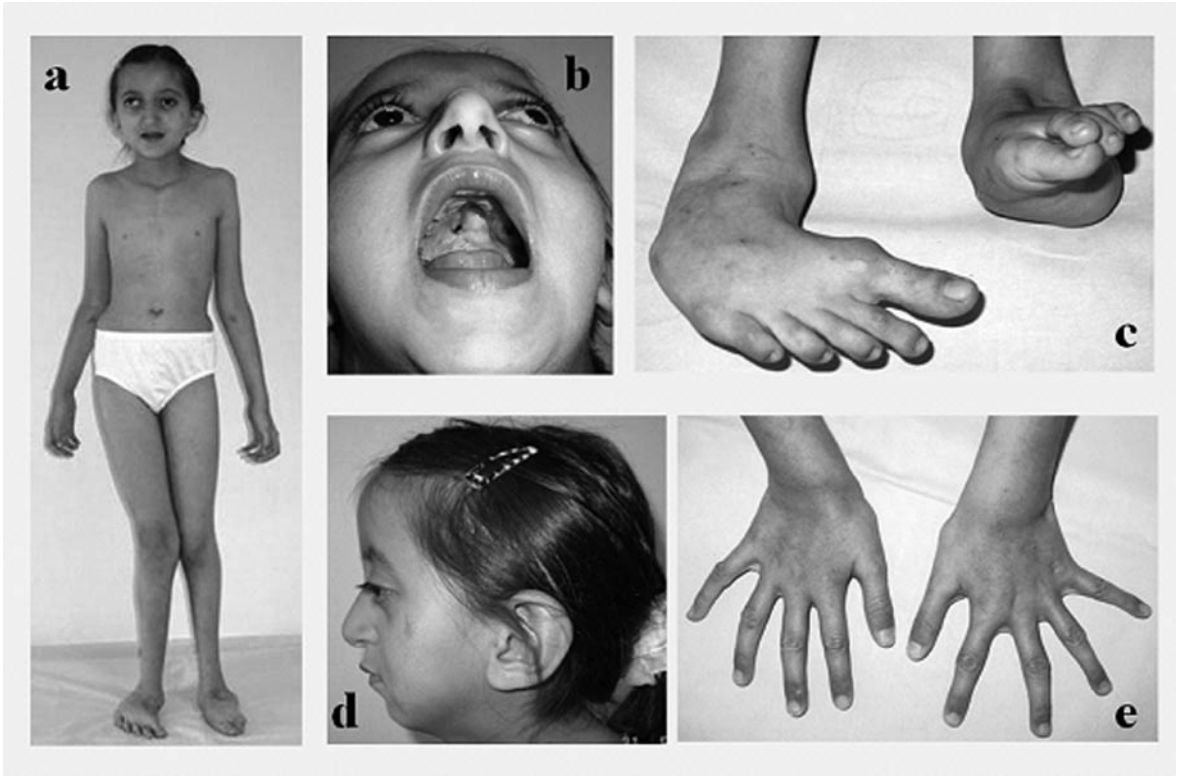

Fig. 1. Dysmorphic features of the patient at 8 years of age: **A)** Dolichostenomelia, pectus deformity, scoliosis, hypertelorism; **B)** Cleft palate; **C)** Talipes equinovarus; **D)** Malar hypoplasia, retrognathia, proptosis; and **E)** Arachnodactyly.

signs of vEDS (translucent/velvety skin, wide atrophic scars, bruisability, joint laxity, and visceral rupture) without typical craniofacial features, except isolated uvula bifida. Survival of LDS type II patients is longer than that of LDS type I patients because of cardiovascular complications. Both *TGFBR1* and *TGFBR2* gene mutations cause either LDS type I or type II. The two LDS types are subclassified into A or B depending on the mutated gene, *TGFBR1* or *TGFBR2*, respectively. LDS type IA and type IIA are allelic, as are LDS type IB and type IIB[1,2].

In this report, we describe a girl who showed supraaortic arterial tortuosity, saccular internal carotid artery aneurysm, and typical craniofacial, skeletal and vascular changes with typical LDS type IB caused by mutation (c.1610 G>C; p.R537P) in the *TGFBR2* gene.

Case Report

The patient, a 13-year-old girl, was the second child of healthy consanguineous Turkish parents. The parents were second cousins. Her brother was healthy. There was no family history of any genetic disease. She was born at 38 weeks of gestation by spontaneous vaginal delivery after an uncomplicated pregnancy. Her birth weight was 2800 g; birth length was not recorded. At birth, cleft palate, hypertelorism and talipes equinovarus were noted. She was first admitted to our hospital at 16 months of age for management of congenital heart defects (patent ductus arteriosus [PDA], atrial septal defect [ASD]). At that time, pectus deformity, retrognathia, cleft palate, and bilateral talipes equinovarus were noticed. Her karyotype analysis was normal, 46,XX. Since then, she underwent several operations for cleft palate, talipes equinovarus and correction of congenital heart defects. At eight years of age, she was referred for dysmorphology evaluation. On physical examination, marfanoid connective tissue anomalies, facial dysmorphism, pectus deformity, arachnodactyly, scoliosis, and joint hypermobility were noticed. The eye examination revealed strabismus and myopia, but there was no ectopia lentis. There was mild sensorineural hearing loss. In 2005,

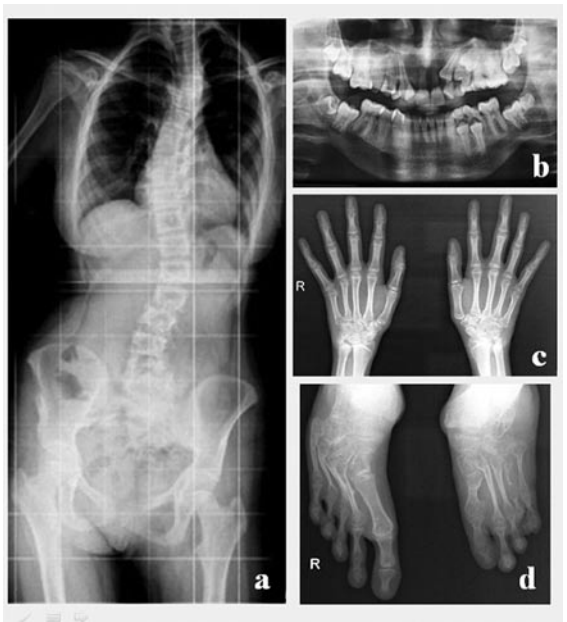

Fig. 2. Plain radiographs show scoliosis **(A)**, arachnodactyly **(C)** and equinovarus deformity **(D)**; Dental radiograph demonstrating malocclusion and crowded teeth **(B)** of the patient at 13 years of age.

at age 8, DNA sample was obtained with the provisional diagnosis of SGS. Because of the similarities between SGS and the newly defined LDS, a mutation screening in the *TGFBR1* and *TGFBR2* genes was carried out. This analysis identified heterozygous (c.1610 G>C) mutation in the serine-threonine kinase domain of the *TGFBR2* gene, which causes the substitution of the arginine residue at position 537 to a proline residue (p.R537P). The numbering of the mutation is based on the shorter isoform of the *TGFBR2* gene (NM_003242.5).

Since she did not show up for the follow-up visits, further cardiac evaluation of the aorta had not been possible until she was recently re-admitted with a history of severe headache for the last six months. At the age of 13 years, her height was 160 cm (50-75rd p), weight 42 kg (25-50rd p) and head circumference 54 cm (mean). She had hypertelorism, strabismus, myopia, malar hypoplasia, retrognathia, blue sclerae, operated cleft palate, bilateral mild hearing loss, dolichostenomelia, pectus deformity, bilateral talipes equinovarus, scoliosis, camptodactyly, joint laxity, and history of surgery for congenital heart defects (PDA, ASD) (Figs. 1, 2). The neurologic examination was normal, except limitation of introspection on the right eye. Her intelligence quotient was measured as 102. Routine laboratory work-up and cranial computerized tomography were normal. Magnetic resonance imaging (MRI) of the brain showed no structural malformation, and echocardiography showed moderate aortic root dilatation. Magnetic resonance angiography (MRA) of the head and neck, however, showed marked elongation and tortuosity of neck vessels, a 2 cm in diameter saccular aneurysm on the right internal carotid artery and aortic dilatation on ductus arteriosus localization (Fig. 3). Angiotensin-converting enzyme inhibitor (Losartan) treatment was started as 25 mg/day to prevent further progression of aortic root dilatation. The neurosurgery and interventional radiology departments refrained from further intervention due to the high operational risk. At present, she is under close follow-up without any clinical complaints.

Discussion

In 2005, Loeys et al.[1] described a new genetic syndrome in 16 individuals from 10 different families. This syndrome is characterized by heterozygous mutations in genes encoding type 1 or type 2 TGF-β receptors, with a newly described human phenotype that includes cardiovascular, craniofacial and neurocognitive abnormalities as well as anomalies of skeletal development. Mutations in either *TGFBR1* or *TGFBR2* cause predisposition to aggressive and widespread vascular disease. Mutations in TGF-β receptors increase downstream signaling of the cytokine in blood vessels, leading to overproduction of collagen, loss of elastin content, and disarray of elastic fibers. These ultrastructural changes result in a weakened vascular media that leads to dilatation and dissection of the vessel wall[1-3]. Several genetic disorders have been associated with mutations in *TGFBR1* or *TGFBR2* genes, such as LDS, Marfan syndrome and SGS. The clinical presentation of LDS closely resembles Marfan-related disorders (Marfan syndrome, SGS and vEDS). Of these genetic syndromes, LDS is associated with a greater risk of arterial rupture or dissection because of the aggressive arterial aneurysms[4-6]. Similar to LDS, vascular complications can be seen in vEDS. It is important to distinguish them. In the differential diagnosis, craniofacial dysmorphism, arterial tortuosity, craniosynostosis, blue sclerae,

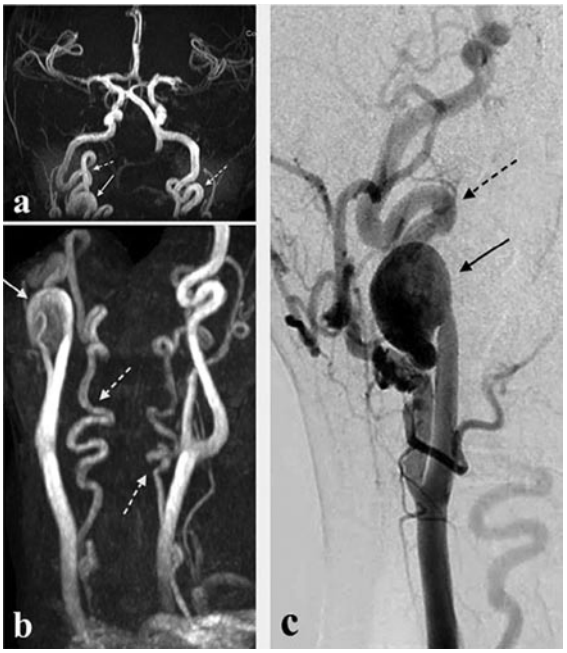

Fig. 3. A) 3D time of flight MRA of the brain and **B)** neck. A 2 cm, large saccular aneurysm of the distal right internal carotid artery (straight arrow) can be seen on both MRAs. Both distal cervical internal carotid arteries, dotted arrows in image **(A)**, and vertebral arteries, dotted arrows in image **(B)**, reveal extensive tortuosity with multiple vascular loops. **C)** Digital subtraction angiography with marked elongation and tortuosity of internal carotid arteries (dotted arrow), with large saccular aneurysm (straight arrow) on the right cervical internal carotid artery.

talipes equinovarus, congenital heart defects, and developmental delay are not associated with Marfan syndrome. In SGS, developmental delay, mental retardation and craniofacial dysmorphism with Marfanoid habitus are typical, but arterial tortuosity or aneurysms have not been reported. Thus, the presence of cleft palate and orbital hypertelorism are helpful to distinguish LDS from Marfan syndrome and vEDS. Arterial tortuosity and aneurysm are not associated with SGS but are characteristic for LDS[1,2]. Importantly, vascular surgery has a better prognosis in children with LDS compared with vEDS[7].

The patient we describe was diagnosed as LDS type IB because of findings such as facial dysmorphism, skeletal abnormalities, aggressive vascular complications, and heterozygous mutation of *TGFBR2* (c.1610 G>C; p.R537P). The p.R537P substitution in the serine threonine kinase domain of *TGFBR2* was previously reported in LDS patients[8]. Aortic root aneurysms are present in 98% of LDS patients. The angiotensin-converting enzyme inhibitors (Enalapril, Losartan) can be used to prevent progression of aortic valve dilatation[9]. In LDS, abdominal aortic aneurysms have been identified in 10% of patients, while head and neck aneurysms occur in 10% of patients[10]. Additionally women affected by LDS are at risk of obstetrical complications[11].

Unruptured intracranial aneurysms most often remain asymptomatic, but may cause headache, focal signs and symptoms or seizures[12,13]. Possible pathogenic mechanisms of headache include mass effect (caused by gradual or sudden growth of an aneurysm), intramural dissections or transmitted pulsations[14]. The presented case complained of intermittent severe right-sided headache for the last six months. This headache could be attributed to the right- sided unruptured saccular internal carotid artery aneurysm. The six-month duration and then spontaneous remission of headache without treatment could be explained by the transient saccular aneurysm mass.

After the diagnosis of LDS has been confirmed, genetic counseling and screening of the family members are recommended. LDS is inherited in an autosomal dominant manner, and approximately 25% of patients diagnosed with LDS have an affected parent; 75% of patients have LDS as the result of a *de novo* mutation. The chance of having an affected baby for a patient with LDS is 50% for each pregnancy. If the disease-causing mutation is known, prenatal diagnosis becomes possible[15].

In conclusion, we have described herein a patient with LSD type IB, showing characteristic craniofacial features, skeletal features, arterial tortuosity, and intracranial aneurysm. Widespread vascular manifestations can be found in LDS involving aortic malformations, such as distortions, aneurysms and dissections. MRI is a useful tool to assess vascular abnormalities. For the patients with the malformations described above, cardiovascular screening and genetic testing for *TGFBR1* and *TGFBR2* mutations are recommended. It is important to keep LDS in mind for early diagnosis and timely intervention of aneurysms to prevent catastrophic vascular events.

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