Imaging and Clinical Features in a Child with Loeys-Dietz Syndrome

A Case Report

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Key words: gene mutation, Loeys-Dietz syndrome, transforming growth factor-beta receptor, Marfan syndrome

Summary

We describe a boy with Loeys-Dietz syndrome (LDS) a genetic and recently described condition that affects connective tissues belonging to a group of Marfan-related disorders. Since there are only a few cases reported misdiagnosis may not be uncommon. Radiological findings in our patient include pectus excavatum, aortic root dilatation, diffuse dilatation of the intracerebral vessels and a Chiari I malformation. We describe the imaging findings, clinical presentation and diagnosis criteria of this entity.

Introduction

Loeys-Dietz syndrome (LDS) is a newly identified connective tissue disorder with clinical features similar to those of Marfan syndrome (MFS) and the vascular type of Ehlers-Danlos disease. It is autosomal-dominant and characterized by mutations in genes encoding transforming growth factor beta receptor I (TGFBR1) or II (TGFBR2) [1,2].

LDS affects the skeletal, vascular, craniofacial, and cutaneous systems. Aortic aneurysms and abnormal organization of blood vessels are its hallmarks. Aneurysms are prone to rupture at smaller size putting children at great risk. Thus, aggressive treatment of aneurysms may be considered [3].

Many affected children have a characteristic phenotype leading to the initial recognition of the syndrome [4]. We describe an African-American boy who presented with typical LSD caused by a TGFBR2 mutation.

Case Report

A 13-year-old African-American male with a history of pectus excavatum and patent ductus arteriosus closure presented with shortness of breath and decreased exercise tolerance. Physical examination revealed a bifid uvula, deep pectus excavatum, thoracolumbar kyphoscoliosis, hip asymmetry, reduced limitation of elbow movement and borderline macrocephaly and dolichocephaly. Spirometry showed mild restrictive impairment. Echocardiogram revealed normal cardiac anatomy and connections, compression of the right ventricle anteriorly probably due to the pectus and aortic root dilation. MRI and MRA of the brain and neck demonstrated diffuse dilatation and tortuosity of all arteries (Figure 1), a Chiari I malformation, and dolicocephaly (Figure 2). Thoracic MRI revealed a prominent pectus excavatum with the heart displaced to the left (Figure 3). Neither parent had any signs of craniofacial dysmorphism and family history was non-contributory. Clinical manifestations and imaging findings suggested a collagen vascular disorder and molecular genetic testing identified a mutation in the TGFBR2 gene consistent with Loeys-Dietz syndrome.

Discussion

In 2005, a new syndrome caused by heterozygous mutations in the genes encoding transforming growth factor-β (TGF-β) receptor called Loeys-Dietz syndrome was described. One year later, Loeys et al. described 30 addi-

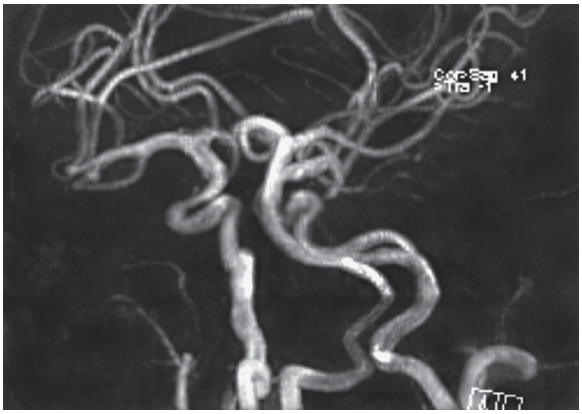

Figure 1 MR angiogram of the head, shows arterial ectasia and tortuosity of the intracranial vessels.

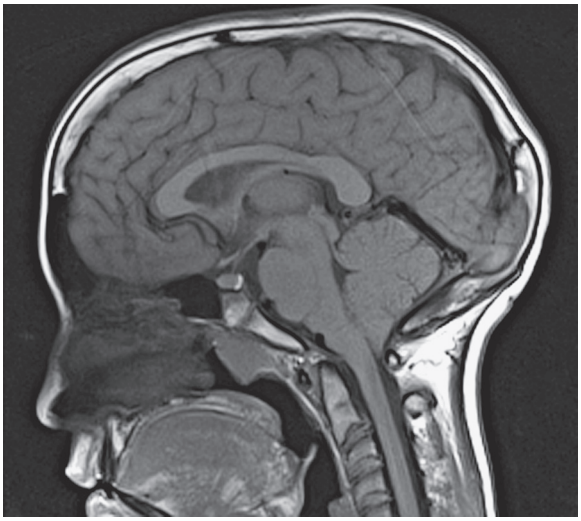

Figure 2 Sagittal non contrast T1 weighted image, demonstrates signs consistent in Chiari one malformation and scaphocephalic configuration.

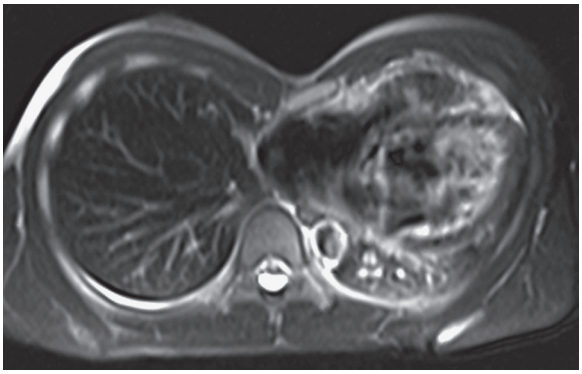

Figure 3 An axial T2 weighted fast spin echo image of the chest shows a prominent pectus excavatum with the heart shifted towards to the left and a right convex scoliosis.

tional individuals with the diagnosis of LDS and identified heterozygous mutations either in TGFBR1 or TGFBR2 [5].

LDS is clinically characterized by the triad of hypertelorism, cleft palate and/or bifid uvula, and aneurysms and arterial tortuosity. Recently, the syndrome has been subdivided into type I (LDSI) and type II (LDSII) based on presence or absence of craniofacial involvement [2]. Approximately 75% of patients present with LDSI characterized by craniosynostosis, cleft palate and/or hypertelorism [2-5,6]. Other craniofacial findings are micro/retrognathia, blue sclera, strabismus and high arched palate with dental crowding. LDSII patients have an isolated bifid uvula but no other facial features although some subtle facial features such as a broad forehead, frontal bossing, high anterior hair line, hypoplastic supraorbital margins or myopathic face may be present [1-2,4]. It is important to remember that both types of LDS form a clinical continuum.

Skeletal findings include joint hyperlaxity, arachnodactyly, pectus deformities (carinatum or excavatum) and scoliosis that often overlap with those seen in MFS [4-5,7]. Skin abnormalities include a velvety, translucent skin with visible veins and easy bruising and are typical of LDSII but overall affect 25% all LDS patients [4].

The most important clinical finding is generalized arterial tortuosity commonly involving the head and neck blood vessels. The major source of mortality is progressive dilatation of the aorta, leading to aortic dissection and rupture, at a smaller size than MFS, which often results in early intervention [3-7,8]. Histology shows a loss of elastin content and disarrayed elastic fibers in the aortic media. An absence of inflammation suggests a defect in elastogenesis rather than secondary elastic fiber destruction [2,8]. Evaluation at presentation is best done MRA to identify arterial aneurysms and tortuosity. Approximately one-half of individuals with LSD have an aneurysm distant from the aortic root. Congenital heart diseases such as a patent ductus arteriosus or bicuspid aortic valve are frequent [4,8]. Differential diagnosis includes MSF, vascular Ehlers-Danlos syndrome,

familial thoracic aortic aneurysm dissection syndrome, and Shprintzen-Goldberg craniosynostosis [2]. Rarely MSF develop aneurysm in other arteries, in contradistinction, most (92%) Loeys-Dietz syndrome patients also had aneurysms of other vessels that are aggressive and carry a high risk of rupture [8]. It is important to emphasize that, unlike MFS, in which the arteriopathy seems to be confined to the ascending aorta, in LDS, aneurismal dilatation of the abdominal aorta, pelvic vessels and intracranial vessels can occur [9]. There are new publications that support the higher prevalence of vertebral artery tortuosity in LDS compared with MFS [10]. Given its substantial overlap with MFS it is important to assess the craniofacial and neuroradiologic manifestations that are not typical of this syndrome [2].

The diagnosis is suspected by clinical characteristics but confirmed by molecular genetic testing of TGFBR I or TGFBR II, the only two genes known to be associated with LDS. Family history may be important, although only 25% report it [2,4].

In our patient a mutation in 1598G< A in one of two TGFBR2 genes was found and thought be consistent with LDS. Our patient had diffuse dilatation and ectasia of the intracerebral vessels and aortic root dilatation. He also had mild anterior compression of his right ventricle due to a pectus excavatum. There is no specific treatment for LDS and medical intervention should be focused on symptoms and genetic counseling [4].

In summary, LSD is a newly recognized connective tissue disorder with severe vascular consequences which may occur at a young age particularly arterial dissections. Early recognition of the phenotype and imaging manifestations is essential for optimal management of this rare entity and to allow distinction of it from other disorders such as Marfan syndrome.

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