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Connective Tissue Disorders: One of The Main Differential Diagnosis of Congenital Hypotonia

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ABSTRACT

Loeys-Dietz syndrome (LDS) is an autosomal dominant connective tissue disorder that has been associated with mutations involving the TGFBR1/2, SMAD2/3, and TGFB2/3 genes. It is characterized by aneurysms, arterial tortuosity, hypertelorism and bifid uvula. We present the case of a full-term infant born with significant hypotonia and congenital anomalies who was eventually diagnosed with LDS. Physical findings were significant for decreased muscle tone, redundant skin on nape of the neck, small chin, widely spaced nipples, and bilateral club feet. Due to the multiple anomalies noted above, genetics consultation was obtained. A chromosomal analysis with reflex to SNP microarray analysis was performed, showing a normal female 46,XX. Given the complex nature of the patient's presentation and normal initial genetics studies, Whole Exome Sequencing (WES) was ordered, revealing a heterozygous –likely De Novo, pathogenic variant in the TGFBFR1 gene (p.Glu239del), consistent with autosomal dominant LDS. Upon literature review, different cases of LDS associated with congenital hypotonia have been described. Nevertheless, medical attention was often sought for other clinical indications such as musculoskeletal and cardiac abnormalities, with some cases mislabeled as Larsen or Beals syndrome. We propose that connective tissue disorders should be included in the main differential diagnosis of congenital hypotonia.

Keywords: *Loeys-Dietz Syndrome (LDS), Congenital Hypotonia, Connective Tissue Disorders*

Introduction

Loeys–Dietz syndrome (LDS), an autosomal-dominant connective tissue disorder characterized by vascular findings (arterial aneurysms/dissection), skeletal manifestations, craniofacial features (hypertelorism, bifid/broad uvula and cleft palate) and cutaneous findings (velvety and translucent skin, easy bruising and dystrophic scars) (MacCarrick *et al*., 2014). It shares many clinical characteristics with Marfan syndrome, with an even higher risk for early aortic dilation and dissection (Meester *et al*., 2017). Mutations in the TGFBR1 and TGFBR2 genes were the first reported genetic causes of LDS, followed by mutations in the SMAD3 and TGFB2 genes (Lindsay *et al*., 2012; Loeys *et al*.,

2005; Regalado *et al*., 2011). These defects translate in alterations of the transforming growth factor-β (TGF-β) signaling, with individuals showing similar cardiovascular, craniofacial, cutaneous, and skeletal features. Although decreased muscle tone has been reported in the neonatal period, medical attention is often turned to musculoskeletal complains, including joint contractures and joint hypermobility (Yetman *et al*., 2007). We present the case of a full-term infant diagnosed with LDS who was born with congenital hypotonia associated with other anomalies.

Case Presentation

The infant was born to a 26-year-old mother, G1P0 at 39 weeks of gestation via spontaneous vaginal delivery. Birth weight was 3.845 kg. Pregnancy was achieved naturally. Prenatal history was unremarkable for exposures to medications, alcohol, recreational drugs, tobacco, radiation or maternal illness. A fetal USG showed bilateral choroid plexus cysts, bilateral club feet and bilateral renal cysts. NIPT was positive for Trisomy 13. Amniocentesis was declined. The baby was admitted to the NICU due to respiratory distress and to rule out Trisomy 13. The respiratory distress was likely due to TTN and resolved after 2 days on CPAP. There were no clinical features suggestive of Trisomy 13 but physical exam was significant for redundant skin on nape of the neck, small chin, widely spaced nipples, bilateral club foot, hypotonia, and pectus excavatum. A postnatal renal USG was normal. Head USG revealed small subependymal cysts. Echocardiogram was significant for PFO with left to right flow.

A Genetic consultation was obtained due to the above findings. Initial genetic workup included a chromosomal analysis with reflex to SNP microarray, both of which were normal 46, XX. During a follow up genetics evaluation at two months of age her physical examination was significant for right frontal hair whorl, deep set eyes and epicanthal folds, smooth philtrum, pectus excavatum, long fingers and bilateral clubbed feet in casts, and generalized hypotonia with significant head lag. Given the complex nature of the patient's clinical presentation and the normal karyotype and microarray results, Whole Exome Sequencing (WES) was performed. A heterozygous–likely de novo, pathogenic variant in the TGFBR1 gene was detected, which is consistent with autosomal dominant Loeys Dietz Syndrome.

Discussion

In 2005, Loeys *et al*. described a newly recognized genetic syndrome characterized by altered cardiovascular, craniofacial, neurocognitive and skeletal development, now known as Loeys-Dietz Syndrome (Regalado *et al*., 2011). It is inherited in an autosomal dominant pattern. It is characterized by features such as hypertelorism, bifid uvula, cleft palate, cardiovascular manifestations e.g. vascular aneurysms and dissection, and musculoskeletal features e.g. hypotonia, pectus excavatum or carinatum, scoliosis, joint laxity and arachnodactly (Drera *et al*., 2009).

The signs and symptoms of LDS can become apparent anytime from childhood to adulthood, with a variable expressivity and severity. Our patient mainly presented with musculoskeletal features during the newborn period -including hypotonia, pectus excavatum and bilateral club foot, and was diagnosed with Loeys-Dietz Syndrome at five months of age by Whole Exome Sequencing.

Upon literature review, reports of cases with similar musculoskeletal abnormalities during the neonatal period had been made, including diffuse hypotonia, bilateral club foot, and dislocation of hips and knee in addition to cardiovascular findings. These patients were initially misdiagnosed with either Larsen syndrome or Beals syndrome based on their clinical presentation (Caza *et al*., 2016; Riise *et al*., 2018). LDS was later diagnosed based on genetic testing. Moreover, more than half of the reported patients required surgical intervention for progressive aortic enlargement and one died due to cardiovascular complications and inadequate cardiac follow-up.

In conclusion, a delay in the diagnosis of a connective tissue disorder like Loeys-Dietz Syndrome during the neonatal period can be life threatening due to the increased risk of aortic aneurysm and aortic dissection. We propose that it is of paramount importance to consider connective tissue disorders as one of the main differential diagnosis of congenital hypotonia in order to decrease morbidity and mortality and improve cardiovascular and developmental outcomes.

Abbreviations: Loeys-Dietz Syndrome (LDS), Transforming Growth Factor-beta Receptor (TGFBR), Single Nucleotide Polymorphism (SNP), Whole Exome Sequencing (WES), Ultrasound (USG), Noninvasive Prenatal Testing (NIPT), Transient Tachypnea of Newborn (TTN), Continuous Positive Airway Pressure (CPAP)

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