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Blended Phenotype of Marfan Syndrome and Larsen Syndrome: A Case Report

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ABSTRACT

Background and Objective: Previously, the coincidence of two different disease phenotypes in a single patient was considered to be a new phenotype or a phenotypic extension of a single known disease. However, with the advent of whole exome sequencing, it has become clear that in many cases it is a new phenotype or phenotypic extension. This case report represents a blended phenotype of Marfan and Larsen syndrome. Up to the time of reporting this case, we could not find a similar case in the sources.

Case Report: A full-term male infant delivered vaginally by a primi-mother in a non-consanguineous marriage was transferred to the intensive care unit because of respiratory distress, meningomyelocele and dysmorphism. On clinical examination, the baby had a heart murmur. The baby required oxygen support but no pressure. We slowly weaned off oxygen and gradually started feeding. An ultrasound and echocardiography were performed to rule out malformations. Using molecular and next-generation exome sequencing techniques, the infant was found to have heterozygous variations of the FBN1 gene c.6094A>T p.Thr2032Ser (depth -36x), a novel variant, and the FLNB gene c.2956C>Tp.Arg986Trp (depth -48x), suggesting for neonatal Marfan syndrome (nMFS) and Larsen syndrome phenotype, which was compatible with the phenotypic findings of the neonate. Unfortunately, the infant died because of sepsis and aspiration.

Conclusion: In extremely rare cases, there may be more than one syndrome. Under these circumstances, the prognosis is grim, as usual. When the syndromic phenotype varies, advanced genetic testing is preferred.

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Introduction

Marfan syndrome, an autosomal dominant systemic connective tissue disorder, has been associated with mutations in the gene FBN1, which encodes fibrillin-1. Fibrillin is a structural component of the extracellular matrix [1]. Most defective gene mutations result in dysfunction of fibrillin-1. FBN1 is a large gene (65 exons) located on chromosome 15q-21.1. The most severe mutations occur in exons 25-32, so neonatal Marfan syndrome (nMFS) is diagnosed at birth. The prevalence of Marfan syndrome is approximately 2-3 per 10,000 people. The rare and severe manifestation of this disease is neonatal Marfan syndrome [2]. The most common cause of death in nMFS is mitral or tricuspid valve dysfunction leading to congestive heart failure.

Larsen syndrome is an osteochondrodysplasia defined by craniofacial deformities and joint dislocations. The prevalence of Larsen syndrome is 1 in 100,000. The classic form of Larsen syndrome follows an autosomal dominant mode of inheritance. Sometimes de novo mutations in the filamin B (FLNB) gene, which is located on the short arm of chromosome 3 (3p14), cause this syndrome. In rare cases, autosomal recessive patterns are also observed. The FLNB gene is responsible for the production of the connective tissue protein filamin B. This protein may affect joint formation, spinal segmentation, and endochondral ossification [3]. There are many reports that present it as a syndrome in its own right. However, according to the available literature, this is the first report of a blended case with both syndromes.

Case Report

A full-term male neonate was delivered by a mother from a nonconsanguineous marriage by normal vaginal delivery. The baby was delivered at Niloufer Hospital Hyderabad on January 2, 2023. During pregnancy, ultrasound revealed a meningomyelocele and polyhydramnios. A Targeted Imaging for Fetal Anomalies (TIFFA) scan revealed clubfeet. However, prenatal genetic testing was not performed. Birth weight, length, and head circumference were 3.2 kg (70th percentile), 55 cm (97th percentile), and 36 cm (86th percentile), respectively. There was no evidence of hereditary disease or congenital heart disease in the family.

At birth, the newborn suffered from respiratory distress and was immediately transferred to the neonatal intensive care unit. He had several features of facial dysmorphia, namely ocular hypertelorism, low-set ears (turned backward), frontal bossing, long and smooth philtrum with midface hypoplasia, high arched palate, and retro-micrognathia. Some musculoskeletal features include arachnodactyly, contracture of the metacarpophalangeal joint, redundant and loose skin folds, contralateral talipes equinovarus, and hyperextensible joints (**Figure 1**). The newborn has features of both Marfan syndrome and Larsen syndrome. Marfan syndrome is defined by a high arched palate, arachnodactyly, contractures, redundant and loose skin folds, and hyperextensible joints [4]. Larsen syndrome is supported by talipes equinovarus, hypertelorism, frontal bossing, and midface hypoplasia [5].

Echocardiography performed after a grade 3/6 systolic murmur was detected on cardiac examination. A large atrial septal aneurysm was visible on the echocardiogram (**Figure 2**), along with a large ductus arteriosus aneurysm (DAA) measuring approximately 2.2 cm with no evidence of thrombus formation or mitral regurgitation (**Figure 3**). Ultrasonography of the brain revealed hydrocephalus. Chest and abdominal radiography and ultrasonography of the abdomen were unremarkable. The baby was found to have overlapping phenotypic similarities between nMFS and hereditary connective tissue disease.

Given the dysmorphic features identified, genetic analysis was performed using molecular and next-generation exome sequencing techniques, which revealed that the infant had concurrent heterozygous variants of the FBN1 gene c.6094A>T

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p.Thr2032Ser (depth -36x) on exon 50 a novel variant, the inheritance pattern was autosomal dominant, and heterozygous variants of the FLNB gene c.2956C>Tp.Arg986Trp (depth -48x) on exon 20, the inheritance pattern was autosomal dominant, resulting in a blended phenotype of nMFS and Larsen syndrome. The baby was treated symptomatically with respiratory and medical support. The baby became hemodynamically stable and achieved full feeding. However, on the 38th day of life, the baby gradually died from worsening heart failure caused by aspiration and sepsis.

Figure 1. Blended phenotypic baby on the third day of life showing long-leggedness, arachnodactyly, equinovarus, and mild frontal bossing

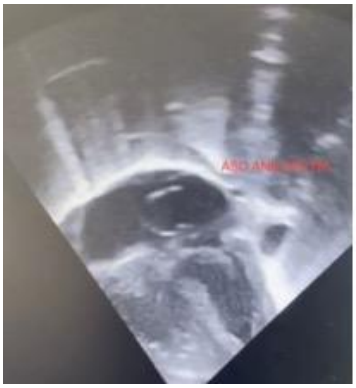

Figure 2. Atrial septal aneurysm

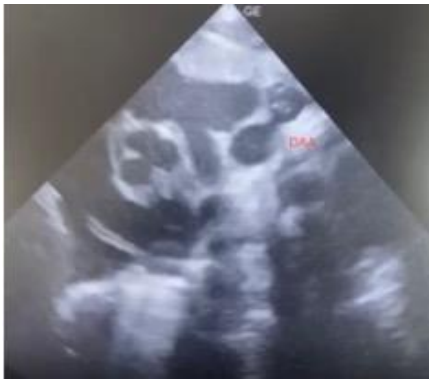

Figure 3. Ductus arteriosus aneurysm

Discussion

In this case report, we present a case of the blinded phenotype of neonatal Marfan and Larsen syndrome. The child had a distinct phenotype with a combination of Marfan and Larsen syndrome. A genetic study was performed using molecular and next-generation exome sequencing techniques, which confirmed both syndromes. These combined phenotypes are not uncommon; the article highlighted a child diagnosed at birth with Prader-Willi and diagnosed at five years of age with an infantile form of neuronal ceroid lipofuscinosis, confirmed by trio-whole exome sequencing (WES) [1]. Aggarwal et al. reported a case of Marfan syndrome and Beals syndrome in a 29-week-old neonate, although the genotype of the parents was not investigated in their case report, as in ours [6]. Gupta et al. described a newborn with Zellweger syndrome and Ullrich congenital muscular dystrophy type 1 [7]. It is estimated that multiple syndromes occur in a single

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patient in about 2-7.5% of diagnosed cases and more frequently in consanguineous families [1]. Most microfibrils of the extracellular matrix, known as fibrillin, serve t as a scaffold on which tropoelastin is deposited to form elastic fibers [8]. The aorta and ligaments, the major tissues affected by Marfan syndrome, contain particularly large numbers of microfibrils. Although most people have at least one affected parent, a de novo mutation in the FBN1 gene is present in 25% of patients [9]. Clinically, nMFS differs from traditional Marfan syndrome in that it has more severe cardiopulmonary manifestations [10]. Patients with NMFS generally have a worse prognosis, with death usually occurring before the age of two due to congestive heart failure [11, 12]. Increased bioavailability of transforming growth factor (TGF) due to the reduction or alteration of fibrillin is thought to be one of the pathogenic mechanisms of nMFS. The negative effect of excessive TGF signaling on vascular smooth muscle growth may lead to enlargement of the aortic root. An effective therapeutic target to favorably influence the pathophysiology of tissue damage in nMFS is angiotensin II type 1 receptor blockers that reduce TGF activity. Early recognition of nMFS and a multidisciplinary approach to determine the requirements for interventional cardiac surgery according to the patient's best interests have improved patient survival [13, 14].

Joint dislocations and facial deformities are two features of a rare congenital disorder known as Larsen syndrome. A cytoplasmic protein called filamin B regulates cytoskeletal processes. Mutations in this protein cause increased death of chondrocytes in the epiphyseal growth plates of bone, resulting in the lesions and associated symptoms seen in people with Larsen syndrome. The combination of orthopedic surgery, facial reconstructive surgery, and physical therapy has produced good results. The condition is life-threatening in patients with cervical kyphosis, so spinal stability is evaluated as early as possible.

In our case, Marfan syndrome had a de novo missense mutation, which has not been reported previously. This variant is not classified as pathogenic or benign. For a pathogenic conformation, segregation analysis and residual variation intolerance score should be used. For Larsen syndrome, we found a pathogenic variant. In recent years, whole genome sequencing (WGS) and triexome sequencing have changed the diagnosis of these complex phenotypes.

Limitations of the study

Genetic testing of the parents is required for confirmation. Rapid genetic advances are taking place in several areas. Knowing that relapses may occur, Sanger sequencing and other genetic testing have been suggested for parents. If the same mutation is found again, the parents will request early termination. Nevertheless, they delayed to do it because of financial constraints.

Conclusion

The report illustrates how different coexisting variants might present with blended or compound clinical pictures, posing a challenge for clinicians to diagnose. The literature supports the clinical utility of exome sequencing. WES enables unbiased and comprehensive mutation screening. Our report supports the adoption of exome sequencing testing as a first-stage diagnostic test for higher yield and more accurate evaluation, especially in equivocal cases. High-throughput genetic sequencing analysis is particularly useful because of genetic heterogeneity and substantial overlap in clinical manifestations.

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Ethical approval

Parents gave us written informed consent for publication. There were no ethical issues to be addressed in this case report. There was no funding source for our study.

Authors' contributions

PMVB prepared the original draft; RK reviewed and edited the manuscript. Conceptualization was done by TR, and final approval and monitoring

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were done by AM. All authors read and approved the final manuscript.

Conflict of interest

We declare no conflict of interest.

References

1. Rosina EA, Pezzani L, Pezzoli L, et al. Atypical, composite, or blended phenotypes: how different molecular mechanisms could associate in double-diagnosed patients. Genes (Basel) 2022; 13(7): 1275.
2. Posey JEB, Harel T, Liu P, et al.: Resolution of disease phenotypes resulting from multilocus genomic variation. N Engl J Med 2017; 376(1): 21-31.
3. Milewicz DM, Braverman AC, De Backer J, et al. Marfan syndrome. Nat Rev Dis Primers 2021; 7(1): 64.
4. Ghandi Y, Zanjani KS, Mazhari-Mousavi SE, Parvaneh N. Neonatal marfan syndrome: report of two cases. Iran J Pediatr 2013; 23(1): 113-7.
5. Park BM, Han CD, Lee YT. Larsen's syndrome: A Case Report. J Korean Orthop Assoc 1985; 20(6): 1202-6.
6. Aggarwal S, Bhowmik AD, Tandon A, et al. Exome sequencing reveals blended phenotype of double heterozygous FBN1 and FBN2 variants in a fetus. Eur J Med Genet 2018; 61(7): 399-402.
7. Gupta P, Anne RP, Deshabhotla SK, et al. An infant with blended phenotype of Zellweger spectrum disorder and congenital muscular dystrophy. Ann Indian Acad Neurol 2021; 24(5): 759-60.
8. Reinhardt DP, Keene DR, Corson GM, et al. Fibrillin-1: organization in microfibrils and structural properties. J Mol Biol 1996; 258(1): 104-16.
9. Faivre L, Collod-Beroud G, Loeys BL, et al. Effect of mutation type and location on clinical outcome in 1,013 probands with Marfan syndrome or related phenotypes and FBN1 mutations: an international study. Am J Hum Genet 2007; 81(1): 454-66.
10. Hennekam RC. Severe infantile Marfan syndrome versus neonatal Marfan syndrome. Am J Med Genet A 2005; 139(1): 1.
11. Kodolitsch YV, Raghunath M, Nienaber CA. The Marfan syndrome: prevalence and natural history of cardiovascular manifestations. Z Kardiol 1998; 87(3): 150-60.
12. Stheneur C, Faivre L, Collod-Béroud G, et al. Prognosis factors in probands with an FBN1 mutation diagnosed before the age of 1 year. Pediatr Res 2011; 69(3): 265-70.
13. Carande EJ, Bilton SJ, Adwani S. A Case of Neonatal Marfan Syndrome: A Management Conundrum and the Role of a Multidisciplinary Team. Case Rep Pediatr 2017; 2017: 8952428.
14. Strigl S, Quagebeur JM, Gersony WM. Quadrivalvar replacement in infantile Marfan syndrome. Pediatr Cardiol 2007; 28(5): 403-5.

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