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Neonatal Marfan syndrome with Novel Fibrillin-1 Gene Mutation: A Case Report

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Abstract

Marfan syndrome is a rare multi-systemic genetic disorder primarily affecting connective tissue. It manifests prominently in musculoskeletal, orbital and cardiovascular systems. Neonatal Marfan syndrome (nMFS) is distinguished by the occurrence of premature death resulting from rapidly progressive congestive heart failure. This case report presents the clinical presentation of a newborn girl exhibiting dysmorphic features, bilateral myopia and severe cardiac involvement. Genetic analysis revealed a previously unidentified mutation at nucleotide 3964 (c.3346G > A) within intron 26 of the fibrillin-1 gene. This mutation is located in the neonatal region encompassing fibrillin-1 exon 24 to 32. The patient was initially treated with atenolol, followed by a combination of atenolol and irbesartan, which potentially contributed to a reduction in the rate of aortic root dilation. While medical management can delay the progression of cardiac dysfunction, surgical intervention should be reserved as a last option.

Keywords: Neonatal Marfan syndrome • Fibrilin -1 gene mutation • Novel mutation

Abbreviations: MFS: Marfan Syndrome; nMFS: neonatal Marfan Syndrome; AoV: Aortic Valve; FBN1: Fibrillin-1 gene; WES: Whole Exome Sequencing; NGS: Next Generation Sequencing

Introduction

Marfan Syndrome (MFS) is a rare genetic disorder affecting connective tissue, characterized by skeletal, cardiac and ocular involvement. It is estimated to occur in approximately 1 in 5000 to 1 in 10,000 live births, without significant gender or racial predilection [1]. Neonatal Marfan syndrome (nMFS) represents a unique variant of MFS, displaying distinct genotypic and phenotypic features compared to typical MFS. This condition is exceptionally rare and carries a poor prognosis, with an average lifespan of only 16.3 months. Several mutations in the Fibrillin-1 gene (FBN1) on chromosome 15 have been implicated in the development of MFS, with a consistent clustering of *de novo* mutations in exons 23-32 of the gene [2]. Although the genotype-phenotype correlation remains challenging due to limited literature, it is noteworthy that mutations in exons 23-32 of the FBN1 gene may also be associated with classical Marfan syndrome, while mutations in exons 25-26 are specifically linked to worse survival in children diagnosed with FBN1 mutations before the age of 1 year [3]. In this case study, we present the birth, diagnosis and management of a child with nMFS, who exhibits no clinical symptoms but demonstrates significant aortic root dilation, aortic valve regurgitation and mitral valve insufficiency.

Case Presentation

This is a case report of a 5-day-old female neonate who was delivered full term by normal vaginal delivery without any complications. The newborn is the first child of healthy, nonconsanguineous and young parents. The parents expressed concern over the baby's physical features, leading to their referral to our hospital. The pregnancy was planned and anomaly scans at 33 weeks indicated normal findings according to the parents' reports. There is no known family history of hereditary diseases, genetic disorders of connective tissue, or congenital heart diseases.

At birth, the neonate's measurements were as follows: length of 53 cm (90th centile), head circumference of 35 cm (50th centile) and weight of 3.330 kg (25th-50th centile). Physical examination revealed several distinct features, including finger and toe arachnodactyly, loose skin, joint extensibility, hindfoot deformity, positive wrist and thumb sign and a characteristic 'senile' facial appearance with forehead wrinkling (Figure 1). The neonate was conscious and vital signs were normal without any heart murmur. The palate appeared normal. The eye examination revealed bilateral myopia without lenticular dislocation. Additionally, a kidney ultrasound showed unremarkable findings. The echocardiography findings revealed significant dilation in the aorta and sinuses of Valsalva (Figure 2). The measurements obtained revealed Aortic Valve (AoV) diameter 0.8 cm (z-score: 5.95) and sinuses of Valsava diameter: 1.7 cm (z-score 5.97).

Whole Exome Sequencing (WES) was performed using the Ion AmpliSeq™ Exome RDY Panel from Thermo Fisher Scientific, Life Technologies Corp., CA. The sequencing was carried out on the Next Generation Sequencing (NGS) S5/S5xl platform, also from Thermo Fisher Scientific, Life Technologies Corp., CA. Variant interpretation was done using eVai, enGenome from Pavia, Italy. The results revealed a heterozygous variant in exon 26 of the FNB1 gene (NM_000138.4), specifically the c.3346G>A (p.Glu1116Lys) variant. Sanger sequencing was used to confirm the presence of this variant.

Genetic investigation of the parents showed that neither of them carried the variant, ruling out non-paternity and non-maternity. This indicates that the c.3346G>A variant arose *de novo* in the patient, providing further support for the diagnosis of neonatal Marfan syndrome (nMFS).

On the fifth day of life, the patient was initiated on atenolol at a dose of 0.6mg/kg/d and was subsequently discharged home. At the age of 2.5 months, a follow-up echocardiography revealed an increasing aortic root size along with grade 1 aortic valve regurgitation. As a result, the patient's treatment was supplemented with irbesartan at a dose of 4mg/kg/d, administered twice daily.

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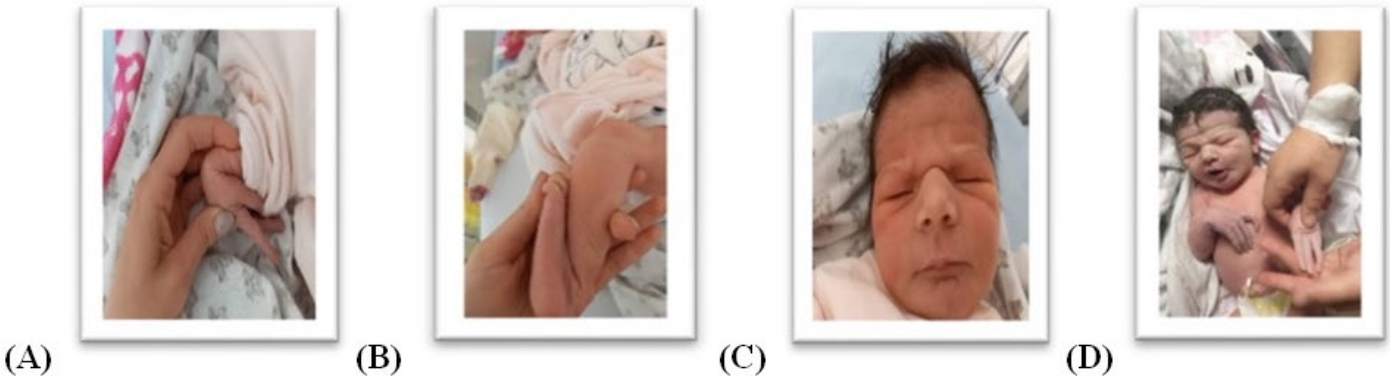

Figure 1. Neonate Marfan Syndrome and its dysmorphic features. **(A, B)** Joint extensibility, **(C)** 'Senile' facial appearance with forehead wrinkling and **(D)** Arachnodactyly.

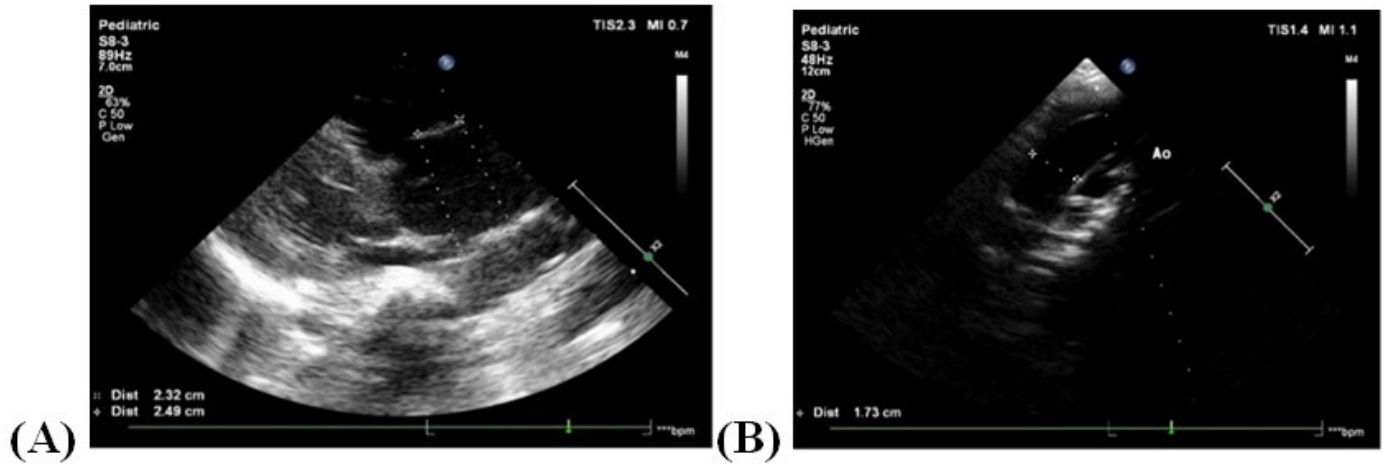

Figure 2. (A, B) A dilated aortic root measuring.

The irbesartan dose was gradually escalated by 2mg/kg/d on a weekly basis until reaching a maximum dose of 8-10mg/kg/d.

At 7 months of age, an echocardiogram showed significant deterioration of aortic root dilation, indicated by a z-score of 7. Additionally, the examination revealed grade 1 mitral valve insufficiency in conjunction with the previously identified grade 1 aortic valve regurgitation. Currently, the patient is undergoing treatment with propranolol and irbesartan at their maximum doses. The option of cardiac surgery will be considered when the absolute dimension of the aorta exceeds 4.5cm or when significant impairment of aortic valve function occurs. Repair of the mitral valve can be achieved using a ring, with or without an Alferi stitch.

Discussion

The first description of Marfan syndrome, an autosomal dominant disorder, was recorded in 1896 by the French pediatrician Antoine Marfan. It is a connective tissue disorder characterized by remarkable heterogeneity and clinical variability. The prevalence of the disease is approximately 1 in 5000-10000 individuals and it is caused by mutations in the FBN1 gene located on chromosome 15q21.1. The FBN1 gene encodes the FBN1 protein, a 320 kDa glycoprotein that plays a crucial role in the formation of microfibrils in the extracellular matrix [4].

More than 2000 mutations have been identified in the FBN1 gene and each mutation is associated with a distinct phenotype depending on its location. Attempts have been made to establish a correlation between genotype and phenotype, but the relationship between them is still not fully understood. The phenotypic spectrum of FBN1 mutations ranges from classical Marfan syndrome to neonatal Marfan syndrome (involving exons 23-32) and other connective tissue disorders [5].

The majority of Marfan syndrome cases (70-80%) are due to *de novo* mutations, as there is often no family history of the disease. The revised Ghent criteria are the most widely used diagnostic classification for Marfan syndrome. According to these criteria, a patient should exhibit a combination of aortic dilation and ectopia lentis, or aortic dilation and an FBN1 gene mutation, or aortic dilation and dysmorphic features, or ectopia lentis and an FBN1 gene mutation, along with a positive family history [6].

Systemic features of Marfan syndrome include arachnodactyly, loose skin, joint hyperextensibility, hindfoot deformity, positive wrist and thumb sign and a characteristic facial appearance characterized by dolichocephaly, enophthalmos, malar hypoplasia and retrognathia. However, the Ghent criteria do not specifically address the classification of patients with neonatal Marfan syndrome, as the characteristic features may manifest later in life.

In this study, we report a case of neonatal Marfan syndrome with a novel mutation (c.3346G > A) in the intron 26 region of the FBN1 gene. This mutation is a *de novo* mutation, as there is no family history of the disease. According to the existing literature, mutations in this region are associated with a poor prognosis, shorter life expectancy and increased risk of premature death before the first birthday. Our patient exhibits the characteristic features of neonatal Marfan syndrome and significant dilation of the aortic root and sinuses of Valsalva, accompanied by aortic valve regurgitation and mitral valve insufficiency.

The patient is currently undergoing treatment with propranolol and irbesartan at the maximum doses. Recent studies have shown that treatment with angiotensin II receptor blockers and/or beta-blockers may decrease the rate of aortic root dilation, potentially delaying the need for heart surgery [6-8].

Conclusion

In conclusion, the exact cause of the noteworthy change in aortic root Z-score is still unclear, whether it resulted from angiotensin II receptor blockers alone or from a combination of losartan and propranolol. However, it is recommended to initiate treatment with both medications as early as possible to achieve the best response.

Competing Interest

The authors have no competing interests to declare that are relevant to the content of this article.

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