Neonatal Marfan Syndrome

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The Marfan syndrome (MFS) is an autosomal dominant disorder of connective tissue resulting from pathogenic variants of the fibrillin-1 gene (FBN1) with skeletal, cardiac, and ocular involvement. Neonatal Marfan syndrome (nMFS) is rare and it is the most severe form of this disease. NMFS has a poor prognosis, with a mean survival age of only 16.3 months. The main reason for death is congestive heart failure (CHF).

Early diagnosis of nMFS allows a timely approach and an appropriate, multidisciplinary follow-up, making, thus, possible to identify early complications with subsequent improvement of an otherwise poor prognosis, since nMFS carries a high likelihood to cause mortality in infancy or early childhood.

Materials and Methods

We report on a full-term male neonate, born from unplanned Cesarean section due to failure of progression during labor. His birth weight was 3,690 g (70th centile), length 56 cm (100th centile), and head circumference 36 cm (86th centile). His Apgar’s score was 7 and 9 at 1st and 5th minutes, respectively. There was no family history of inherited disorders and/or congenital heart disease. On 34th and 39th weeks of pregnancy, ultrasonography reported a femoral length higher than 95th centile as well as oligohydramnios. At birth, the neonate featured several dysmorphisms, namely enophthalmos, dawn-slanting palpebral fissure, crumpled ears, retromicrognathia, with characteristic “senile” facial appearance, redundant skin folds, wrist and thumb sign, dolichostenomelia, limited extension of the elbow and knee joint, long slenders fingers, and toes with arachnodactyly, pectus carinatum, dorsolumbar scoliosis, and plain pes planus. Cardiac examination revealed a grade 2/6 systolic murmur. Echocardiography showed ectasia aortic root at sinuses of the Valsalva (Z-score > 2), proleptic mitral valve with severe regurgitation (2 + /3 + ), and proleptic tricuspid valve with low to moderate regurgitation. Patent ductus arteriosus (spontaneously closing at 11 days of life) and foramen ovale pervium with minor left–right shunt were also detected; echocardiogram (ECG) tracing was normal. Ophthalmological examination revealed lens subluxation. The chest and abdomen X-ray, the ultrasound study of his abdomen, and brain were normal. The evoked auditory potential test gave normal results. Chromosomal investigation showed a 46XY pattern. According to the revised Ghent criteria for the diagnosis of MFS, the above-listed series of dysmorphisms (score > 7) combined with the detection of severe cardiovascular disease, suggesting a diagnosis of nMFS.

disease prompted ultimately to the diagnosis of nMFS. Genetic investigations through molecular and sequencing techniques showed a mutation in heterozygosis on the fibrillin 1 (FBN1) gene: c.3143T > C (p.Ile1048Thr) with amino acid substitution of an isoleucine by a tyrosine at position 1,048.

**Outcome and Follow-up**

The neonate showed early respiratory distress requiring supplemental oxygen in the first few days of life. He was given antacid medications until the 3rd month of life due to severe gastroesophageal reflux. At 3 months of age, he underwent surgery for left inguinal herniation. At 1 month of age, ECG revealed a moderate worsening of the aortic root’s dilatation and mitral valve’s prolapse, hence diuretic therapy with furosemide was initiated and maintained over time. At 8 months of age, due to the progressive worsening of fatigue and dyspnea with failure to thrive, he added treatment with enalapril. Nevertheless, there was a progressive aggravation of the mitral and tricuspid valve’s prolapse and regurgitation with great dilation of the right atrium (area 20 cm²), left atrium (area 8 cm²), and aortic root (30 mm) that conditioned cardiothoracic surgery (mitral and tricuspid valvuloplasty) at 11 months of age. He was discharged 9 days after surgery on furosemide, captopril, carvedilol, and omeprazole. He is currently followed-up by a multidisciplinary team including pediatricians, cardiologists, ophthalmologists, physiotherapists, and rehabilitation nurses, along with geneticists. Currently, he is 13 months old, clinically stable, with a good catch-up growth after heart surgery (weight 7,820 kg, 3rd centile; length 80 cm, 80th centile; and head circumference 47 cm, 50th centile). He has an adequate neuropsychomotor development for his age.

**Discussion**

The MFS is a heritable disorder of connective tissue resulting from pathogenic variants of the FBN1, a large gene composed of 65 exons on chromosome 15q21.1. The gene encoder FBN1, a 320 kDa glycoprotein, is a main component of microfibrils in the extracellular matrix. The three foremost systems affected by this condition are the cardiovascular, ocular, and skeletal; being cardinal manifestation, (a) the aortic aneurysm with dissection, (b) ectopia lentis, and (c) long-bone overgrowth. This syndrome is notable for its variable expression, namely, in the severity of clinical manifestations, age at onset, and targeted tissues, among and within affected families. It can range from the most severe phenotype manifested in the neonatal period (nMFS) to a very mild clinical form. Owing to the penetrance of some features that is age-dependent, the Ghent criteria must be used with caution in children.¹ An international expert panel has established a revised Ghent nosology, which emphasizes the cardiovascular manifestations and identifies the aortic root aneurysm and the ectopia lentis as the cardinal clinical features. In the absence of any family history, the presence of these two manifestations is sufficient for the unequivocal diagnosis of MFS. In absence of either of these two, the presence of a bona fide FBN1 mutation or a combination of systemic manifestations is required. As for the latter, a new scoring system has been designed. In this revised nosology, FBN1 testing, although not mandatory, has greater weight in the diagnostic assessment.²

The nMFS is a rare condition relative to classic and incomplete MFS, and has the most severe phenotype and the worst prognosis. Its incidence is far lower than that estimated for MFS, that is, 1/5,000 to 1/10,000.³ There are both genotype and phenotype differences between nMFS and classic and incomplete MFS. Based on information from the Universal Mutation Database-FBN1 mutations database, some 92% of nMFS mutations were de novo, which is significantly higher than the number of de novo classic and incomplete MFS mutations (35.3%). Family history is negative in 70 to 100% of nMFS; however, whereas it is negative in only 20 to 30% of classic MFS patients.⁵ As for the genome, the distribution of the two types of mutations differs among FBN1 exons; in particular, most nMFS mutations (86.4%) cluster within exons 24 to 33, while the distribution of mutations for classic and incomplete MFS is more even with only 17.4% in the exon 24 to 33 region. Some 91.5% of nMFS mutations are located in cbEGF domains of which 43 (91.5%) affect the disulfide bond or Ca²⁺ binding site. An nMFS genotype–phenotype analysis showed that most of the mutations (88.4%) present exclusively in patients with nMFS. These observations strongly suggest that limited phenotype heterogeneity of nMFS-associated mutations is evident, although it should not be ignored that some mutations can also result in a later onset or classic presentation of MFS.³ The nMFS may be manifested in the prenatal period and is characterized, at birth, by some other features beyond the ones it shares with the classic form. These include flexion contractures, characteristic facial dysmorphology (crumpled ears, loose redundant skin, and a characteristic “senile” facial appearance), pulmonary emphysema, and severe cardiovascular disease. Mutations in the so-called “neonatal region” of FBN1, exons 24 to 33 are associated with a high risk of rapidly worsening cardiac disease. In contrast to the classic syndrome, in which main cause of death is aortic dissection or rupture, nMFS patients die mostly from CHF associated with mitral and tricuspid regurgitations and dilated aortic root. Skeletal manifestation, such as arachnodactyly, dolichosthenomelia, and pectus deformities are typically present.²,⁵ Medical therapies are not very successful in nMFS as CHF is often not responsive to medications, and valvular regurgitations are progressing severely and rapidly. Surgery may be needed to repair or replace the mitral or tricuspid valves and to replace the aortic root if this last is involved. However, surgery is difficult in infants due to the high risk for mortality and morbidity including complete heart block, thrombosis, and stroke. Heart transplantation may be the last option for patients with nMFS.⁸ Early diagnosis of this rare condition is critical for adequate management and treatment, with a clear impact on the prognosis. A constant update on the knowledge and information about the nMFS mutation spectrum is helpful to improve our understanding of genotype–phenotype correlations occurring with this disease.
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Conflict of Interest
None declared.

References
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