

CASE REPORT

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Neonatal Marfan syndrome: a case report of a novel fibrillin 1 mutation, with genotype-phenotype correlation and brief review of the literature

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Abstract

Background Neonatal Marfan syndrome (nMFS) is a rare condition characterized by severe phenotype and poor prognosis. nMFS is caused by mutations in a specific region of the fibrillin 1 gene (FBN1). Prompt recognition of typical signs of neonatal presentation, such as characteristic facial anomalies with senile appearance, arthrogryposis, and campto-arachnodactyly, is fundamental for performing an early cardiological examination. This usually reveals rapidly progressive cardiovascular disease due to severe atrioventricular valve dysfunction.

Case presentation Herein, we report the case of an early-onset cardiac failure in a neonate with Marfan syndrome, with a brief review of the literature of cases with cardiac involvement in neonatal age. Clinical exome sequencing identified the novel heterozygous *de novo* missense variant c.3152T > G in FBN1 gene (NM_000138.4), causing the aminoacidic change p.Phe1051Cys. Phenotype-genotype correlation led to a multidisciplinary diagnostic and management workflow.

Conclusion The prompt recognition of a typical phenotype such as that of Marfan syndrome should lead to a detailed evaluation and close follow-up of cardiac morphology and function. Indeed, multi-disciplinary evaluation based on genotype-phenotype correlations of nMFS cases is essential to finding out the best medical and surgical approach, predicting the relevant impact on patient prognosis, and adequately counseling their families.

Keywords Neonatal Marfan syndrome, Cardiac failure, Phenotype-genotype correlation, Clinical genetics, Case report

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Background

Neonatal Marfan syndrome (nMFS) is a rare condition characterized by severe phenotype and poor prognosis, caused by mutations in the specific “neonatal region” of the fibrillin 1 gene (FBN1) [1]. Prompt recognition of typical signs of neonatal presentation, such as characteristic facial anomalies with senile appearance, arthrogyrosis, and campto-arachnodactyly, is fundamental for performing an early cardiological examination. This usually reveals rapidly progressive cardiovascular disease due to severe atrioventricular valve dysfunction.

Herein, we report the case of an early-onset cardiac failure in a neonate with Marfan syndrome, with a brief review of the literature of cases with cardiac involvement in neonatal age. Clinical exome sequencing revealed a *de novo* missense variant of the FBN1 gene. Phenotype-genotype correlation led to a multidisciplinary diagnostic and management workflow.

Case presentation

A female neonate spontaneously conceived was born in a 2nd-level hospital at 39 weeks of gestational age (GA), to a 32-year-old primigravida through spontaneous delivery. Oligohydramnios and multiple complex choroid cysts were noticed in the last two weeks of pregnancy. No invasive prenatal testing was performed. Family history revealed a first-degree cousin (from the paternal side) affected by *de novo* Baraitser-Winter syndrome, and a paternal aunt whose pregnancy was interrupted because of a not-specified chromosomal disorder.

Apgar score was 8 and 9 at the 1st and 5th minutes, respectively. Birth weight was 2750 gr (16th centile, z-score: -1.01 SDS according to INES charts [2]), length 49 cm (47th centile, z-score: -0.07 SDS), and head circumference 35 cm (86th centile, z-score: 1.06 SDS). At

birth, several dysmorphic features were noticed, including brachycephaly, triangular and asymmetric face with a typical “senile” appearance (Fig. 1.A) and hypertelorism, down-slanted palpebral fissures, blepharophimosis, blue sclerae, anteverted nares, narrow mouth, micrognathia, and low-set ear. A distal arthrogyrosis of the upper (Fig. 1.B) and lower limbs and severe arachnodactyly of hands (Fig. 1.C) and feet were evident. In particular, the Steinberg sign (well-known as the “thumb” sign) was positive in both hands (Fig. 1.C).

Cerebral ultrasound (CUS) performed within the first days of life confirmed multiple microcysts of the choroid plexus and increased echogenicity in the periventricular white matter. Brain magnetic resonance imaging (MRI) revealed a dysplastic appearance of cerebellar vermis and hemispheres, with a markedly thickened cerebellar cortex and loss of normal arborization of white matter. Hypoxic-ischemic lesions were noticed in the right frontal area. Chest computed tomography (CT), performed because of respiratory distress, showed a right posterolateral diaphragmatic relaxation with ipsilateral atelectasis of lung tissue. Skeletal X-ray showed no significant malformations. Echocardiography within the first 5 days of life yielded patent foramen ovale and patent ductus arteriosus (both with left-to-right shunt), mild tricuspid insufficiency, and moderate mitral insufficiency. A mild dilatation of the aortic bulb was also observed.

The neonate was admitted on the 15th day of life to our 3rd-level children’s hospital to perform a specialistic evaluation. Physical examination revealed fair general conditions with polypnea and mild dyspnea; a 3/6 systolic murmur was audible. Cardiomegaly and dilation of the left ventricle were detected by echocardiography, with a mild-to-moderate biventricular dysfunction. A severely dysplastic mitral valve showed severe multi-jet



Fig. 1 Dysmorphic features of our patient: **A)** senile facial appearance; **B)** distal arthrogyrosis of upper limbs; **C)** severe arachnodactyly of hands and positive Steinberg sign (or thumb sign) of left hand

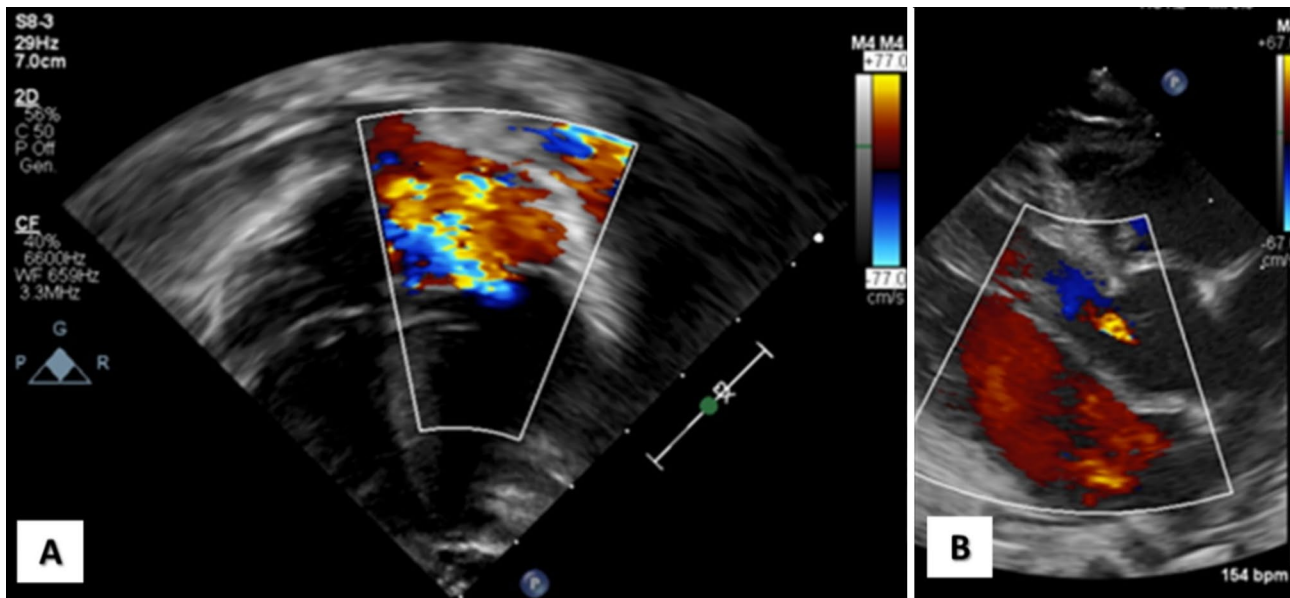


Fig. 2 Cardiac involvement in our patient: **A)** severe mitral insufficiency from a 4-chamber view; **B)** aortic valve insufficiency from long axis view

insufficiency (Fig. 2.A), and aortic valve showed mild insufficiency (Fig. 2.B) and moderate dilation of Valsalva sinuses. The right ventricle was mildly dilated, with mild-to-moderate insufficiency of the tricuspid valve, and a dysplastic pulmonary valve with moderate insufficiency was also observed. The ophthalmological examination did not reveal pathological signs. Multivalvular involvement required initial conservative medical treatment using intravenous furosemide (up to 3 mg/kg) associated with oral spironolactone and captopril. Medical treatment led to a gradual decreasing trend of brain natriuretic peptide (BNP) and troponin values. The baby was discharged in her 5th month of life.

Blood karyotype and Chromosomal Microarray Analysis using platform Illumina® CytoSNP 850k showed no pathogenic results. After these negative results, at 2 months of life, clinical exome analysis of trios was performed on DNA extracted from circulating leukocytes using kit Twist Custom Panel (Twist Bioscience) on the Illumina sequencing platform (NovaSeq6000, San Diego, CA). Next Generation Sequencing (NGS) analysis identified the novel heterozygous *de novo* missense variant c.3152T>G in FBN1 gene (NM_000138.4), causing the aminoacidic change p.Phe1051Cys. The variant was never described in the literature; it was not on the Genome Aggregation Database (gnomAD) and was classified as probably pathogenic (class 4) according to guidelines of the American College of Medical Genetics and Genomics (ACMG) [3].

Subsequently, severe feeding intolerance and gastroesophageal reflux led to progressive malnutrition and a significant impact on children's physical growth; at the 6th month of life, the infant was admitted again to our

hospital and required nutrition support through the placement of a percutaneous endoscopic gastrostomy (PEG) tube. Despite maximal medical treatment and PEG placement, the infant progressively developed symptoms of congestive heart failure resulting from severe multivalvular insufficiency. At about 7 months of life, she underwent cardiosurgical intervention with mitral valvuloplasty and the use of annuloplasty, tricuspid, and pulmonary valvuloplasty.

Unfortunately, at 9 months and 19 days, the infant died of complications related to cardiac failure and severe malnutrition status (weight at death time 5070 gr, z-score: -3.04 according to WHO charts [4]).

Methods

In order to review the literature about cardiac involvement in neonatal Marfan syndrome and compare other cases to ours, an extensive literature search in the MEDLINE database (via PubMed) has been performed up to December 31st, 2022. The following keywords, “neonatal,” “Marfan,” and “syndrome,” were searched as entree terms as well. All 239 retrieved articles of the last 20 years were screened, and then full texts of records deemed eligible for inclusion were assessed. References in the relevant papers were also reviewed. Papers written in languages other than English were excluded. Papers reporting a full description of the cases were included.

We systemically collected and summarized information on patients' characteristics, cardiac involvement and procedures, and molecular findings.

Table 1 Brief review of nMFS cases in the last 20 years. NA: not available

Author, year	Sex	GA (weeks)	Delivery mode	Birthweight (centile) / Length (centile) / Head circumference (centile)	Mitral valve insufficiency / prolapse	Tricuspid valve insufficiency / prolapse	Aortic root dilation / Aortic valve regurgitation	Cardiac procedures	Molecular findings	Inheritance pattern	Age at last follow-up visit, outcome
Jacobs et al., 2002	F	At term	Vaginal delivery	2615 g (10th) / 52 cm (90th) / 32.5 cm (5th-10th)	Yes	Yes	Yes	Not performed	FBN1, T3276C, exon 24	NA	3.5 months, died
Shinawi et al., 2005	M	At term	Cesarean section	2880 g (25th) / 56 cm (> 95th) / NA	Yes	Yes	No	Balloon dilatation of pulmonary valve (4 days)	FBN1, IVS31-2 A>G, intron 31	NA	4.5 months, died
Ramaswamy et al., 2006	NA	At term	NA	3600 (75th) / 52 cm (75th)	Yes	Yes	Yes	Mitral valve repair (10 months)	NA	NA	15 months, alive
Sutherland et al., 2007	M	At term	NA	3300 (25th) / 51.5 cm (75th) / 34.5 cm (25th)	Yes	Yes	Yes	Medical treatment	FBN1, novel missense mutation, c.3256T>C, exon 26	De novo	4 days, died
Tekin et al., 2007	M	40	NA	3650 g (50th) / NA / NA	Yes	Yes	Yes	Medical treatment	NA	NA	3 months, died
Kochilas et al., 2008	F	37	Cesarean section	2900 g / NA / NA	Yes	Yes	Yes	Palliative care	FBN1, heterozygous 3256T>C, exon 26	De novo	69 days, died
Brito-Filho et al., 2013	M	At term	Cesarean section	3630 g / 51 cm / NA	Yes	Yes	Yes	Bentall-De Bono procedure (2 years), two mitral valve replacements (4 and 7 years)	NA	NA	7 years, alive
Šipek Jr et al., 2014	F	40	Vaginal delivery	3670 (75th) / 53 cm (97th) / 34.5 (50th)	Yes	Yes	No	Medical treatment	FBN1, novel intronic c.4211-32_-13 del mutation, exon 35	Maternally inherited	7 months, died
Elshershari & Harris, 2014	M	At term	NA	3200 g (25th) / 51 cm (50th) / NA	Yes	No	Yes	Medical treatment	FBN1, a heterozygous c.3959G: A, exon 31	Paternally inherited (mosaicism)	3 months, alive
Amado et al., 2014	F	38	Cesarean section	3130 g (25th) / 46.5 cm (5-10th) / 35.5 cm (50-75th)	Yes	Yes	Yes	Mitral valvuloplasty (6 months)	FBN1, c.3458 G>A, exon 26	De novo	2 years and 10 months, alive
Ozyurt et al., 2015	F	39	Vaginal delivery	NA / NA / NA	Yes	Yes	Yes	Medical treatment	Not performed	NA	68 days, died
Bhunia et al., 2016	NA	At term	Vaginal delivery	NA / NA / NA	Yes	Yes	Yes	Medical treatment	Not performed	NA	3 months, died
Kitahara et al., 2016	M	38	Cesarean section	2295 g / 43.7 cm / NA	Yes	No	Yes	Mitral commissuroplasty (18 months), palliative procedure (3 years and 8 months)	NA	NA	11 years, alive
Le Gloan et al., 2016	F	39	Cesarean section	2950 g (-0.5 SD) / 50 cm (0 SD) / 33.5 cm (-1 SD)	Yes	Yes	Yes	Mitral and tricuspid valve annuloplasty (2 months)	FBN1, intronic mutation c.6163+3_6163+6del, exon 49	Maternally inherited	4 months, died
Maeda, 2016	M	40	NA	3768 g (90-97th) / 52.9 cm (> 97th) / NA	Yes	No	Yes	Medical treatment	FBN1, missense mutation (c. 3217 G>A), exon 26	NA	7 months, died

Table 1 (continued)

Author, year	Sex	GA (weeks)	Delivery mode	Birthweight (centile) / Length (centile) / Head circumference (centile)	Mitral valve insufficiency / prolapse	Tricuspid valve insufficiency / prolapse	Aortic root dilation / Aortic valve regurgitation	Cardiac procedures	Molecular findings	Inheritance pattern	Age at last follow-up visit, outcome
Maeda, 2016	F	37	Cesarean section	2850 g (25-50th) / NA / NA	Yes	Yes	No	Mitral and tricuspid valve annuloplasty (5 months); mitral valve replacement (12 months)	FBN1, exon-skipping mutation (c.1VS29+1G>A), exon 29	NA	22 months, died
Maeda, 2016	F	37	Cesarean section	2592 g (10-25th) / 50 cm (50-75th) / NA	Yes	Yes	No	Mitral and tricuspid valve annuloplasty (1 month)	FBN1, exon-skipping mutation (c.1VS30+1G>A), exon 30	NA	2 months, died
Peng et al., 2016	F	At term	Vaginal delivery	2600 g / NA / NA	Yes	Yes	Yes	NA	FBN1 missense mutation c.3331 T>C (p.Cys1111Arg), exon 26	De novo	8 months, alive
Heo et al., 2017	M	36	Vaginal delivery	3000 g (75-90th) / 54.5 cm (> 99th) / 35.5 cm (99th)	Yes	No	Yes	Surgical repair of rupture of mitral chordae (6 months)	FBN1, missense mutation (c.3217 G>A), exon 26	NA	NA
Solé-Ribalta et al., 2019	NA	36	NA	NA / NA / NA	Yes	Yes	Yes	Palliative care	FBN1, heterozygous mutation (NM_000138.4): c.[3208+5G>A]	De novo	1 month, died
Tognato et al., 2019	M	At term	Cesarean section	3690 g (70th) / 56 cm (100th) / 36 cm (86th)	Yes	Yes	Yes	Mitral and tricuspid valve annuloplasty (11 months)	FBN1, heterozygous mutation c.3143 T>C (p.Ile1048Thr) w	NA	3 months, alive
Wojcik et al., 2019	NA	40	Vaginal delivery	NA	Yes	No	Yes	Aortic root replacement (3 months); mitral and tricuspid annuloplasty (12 months)	FBN1, heterozygous 385 bp deletion [GRCh38; exon 33]	De novo	3 years, died
Veiga-Fernández et al., 2020	NA	37	Cesarean section	2530 g / NA / NA	Yes	No	No	Palliative care	NA	NA	3 months, died
Postma et al., 2021	F	32	Cesarean section	1710 g / NA / NA	Yes	Yes	Yes	Mitral annuloplasty and tricuspid commissuroplasty (7 months)	FBN1, heterozygous splice site variant, 1VS21+2T>C, exon 15	Paternally inherited	14 months, died
Yoon and Kong, 2021	M	40	Cesarean section	3560 g (75th) / 56.5 cm (90th) / 36 cm (90th)	Yes	No	No/Yes	Palliative care	FBN1, c.3964+1G>T, exon 32	NA	32 days, died
Motonaga et al., 2022	F	40	Vaginal delivery	3008 g / NA / NA	Yes	No	Yes	Mitral valve replacement (6 months)	FBN1, heterozygous missense variant (c.3379G>T), exon 27	De novo	16 years, alive
Kawamura et al., 2022	M	38	Vaginal delivery	NA	Yes	Yes	No	Mitral and tricuspid valve annuloplasty (6 months); mitral valve and tricuspid valve replacement (7 months)	FBN1, heterozygous missense variant of c.3706T>C (p.Cys1236Arg), exon 29	NA	13 months, alive

Results

A brief review of the literature on nMFS cases with cardiac involvement in the last 20 years is displayed in Table 1 [1, 5–28]. Beyond our case, we included other 27 cases, of whom three were born preterm. All 28 cases except one (reported by Postma et al.) had a birthweight greater than 2500 g. The mitral valve was involved in all cases, whereas the tricuspid valve was in 20/28 patients (71.4%). Aortic structures were involved in 23/28 cases (82.1%). Fifteen patients (53.6%) underwent cardiac procedures. FBN1 was the involved gene in all patients where a genetic diagnosis was available (21/28: 75%). Thirteen patients (46.4%) died at the time of writing.

Discussion and conclusion

We compared the severe cardiac involvement of a neonate with Marfan syndrome to the cases available in the literature. Cardiac involvement is the main determinant in the prognosis of neonates with Marfan syndrome, and it is usually life-threatening. Severe valvular disease affecting mostly mitral and tricuspid valves quickly progresses to congestive heart failure and premature death within the first 2 years of life [1, 21, 22, 29, 30]. Indeed, cardiac involvement in neonates is usually characterized by severe multivalvular insufficiency instead of aortic structures involvement, which is a typical feature in adults and older children [31, 32].

Congenital pulmonary emphysema is also often detected in nMFS [33]. Rarely, patients with nMFS may develop progressive but not fatal heart failure; some young adults have been described [34].

Molecular analysis shows that most nMFS mutations are sporadic and occur in the so-called “neonatal region” of *FBN1* gene mapping between exons 24 and 32 [35, 36].

In our case, we identified a novel missense variant, p.Phe1051Cys, located in exon 26 of the *FBN1* gene inside the “neonatal critical region” that was not previously reported in the literature.

Interesting genotype-phenotype associations for both cardiovascular and extra-cardiovascular manifestations were identified in the pediatric population [37]. Previous studies and case reports demonstrated that mutations located in *FBN1* “neonatal region” are usually associated with a rapidly worsening cardiac disease, poor response to medications [36], and severe congestive heart failure, which represent the main cause of early death. In particular, patients carrying variants in a specific region (amino acids 1028–1088, corresponding to exon 25 and a few residues from exon 26) show a worse prognosis with heart failure-related death within the first year of life, irrespective of gender [38].

Early genotype analysis and prompt phenotype recognition can potentially drive accurate genetic counseling. Indeed, the prompt recognition of a typical phenotype

such as that of Marfan syndrome should lead to a detailed evaluation and close follow-up of cardiac morphology and function. Timely diagnosis is increasingly important in looking for genotype-phenotype characterization and improving early therapeutic strategies.

Despite their low quantity in skeletal matrices, MFS causes severe skeletal defects, highlighting the importance of fibrillin-1 and microfibrils in bone formation and function [39]. The extent of musculoskeletal disease is quite significant in older patients with Marfan syndrome: scoliosis, pectus deformity, and deformity of the foot. Many will need a specific follow-up, requiring corrective surgery during their life span [40].

Similarly, fibrillin-1-containing microfibrils are ubiquitous in the normal eye. Ectopia lentis in MFS patients is likely caused by an *FBN1* mutation that prevents fibrillin-1 production. If they survive, MFS patients experience different ocular features depending on the mutation and severity of the illness. Patients with MFS typically acquire lenticular and/or axial myopia before the age of ten and should see an ophthalmologist to examine their near-sightedness [39].

Multi-disciplinary evaluation based on genotype-phenotype correlations of nMFS cases is essential to determine the best medical and surgical approach, predict the relevant impact on patient prognosis, and adequately counsel their families. MFS is an example of a syndrome where an early personalized approach to address a dynamic, genetically determined condition can make a difference in outcome [41].

In light of this, a careful evaluation of all clinical signs by neonatologists is mandatory: in particular, the Steinberg sign (also known as the thumb sign) presence should be considered a potential handle sign for diagnostic suspicion, and every neonatologist should rule out Marfan syndrome in cases like this. This can be useful to perform a correct differential diagnosis, like, for example, with distal arthrogyriosis syndromes or other congenital defects with cardiac involvement, with the aim of timely reaching the correct diagnosis [42, 43].

The current databases should be updated with the genomic and phenotypic findings of the present patient in order to provide a better characterization of such a rare disease. Additional patients and the identification of new mutations will increase the knowledge of the molecular bases and the pathogenic mechanisms underlying Marfan syndrome with neonatal onset.

Finally, clinicians must be aware of the possibility that neonates may have a severely poor outcome, even in the absence of symptoms in the first weeks of life.

Abbreviations

ACMG	American College of Medical Genetics
CT	Computed tomography
CUS	Cerebral ultrasound

FBN1	Fibrillin 1
GA	Gestational age
gnomAD	Genome Aggregation Database
MRI	Magnetic resonance imaging
NGS	Next Generation Sequencing
nMFS	Neonatal Marfan syndrome
PEG	Percutaneous endoscopic gastrostomy
SDS	Standard deviation
WHO	World Health Organization

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None.

Author contributions

FP took care of the patient, reviewed the literature, and drafted the first version of the manuscript. DUDR took care of the patient, reviewed the literature, collected the clinical data, and revised the manuscript. MCD and MM contributed to the acquisition of genetic data and revised the manuscript. AB and AD took care of the patient and revised the manuscript. LV performed a surgical assessment and follow-up. AT performed cardiological assessment and follow-up. ADP conceptualized the report, revised the manuscript, and gave final approval of the version to be submitted. All authors approved the final manuscript as submitted.

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Data availability

All data generated or analysed during this study are included in this published article.

Declarations

Ethical approval and consent to participate

Clinical data were obtained in accordance with the ethical standards of our hospital and Helsinki Declaration. Personal data were restricted to essential information, and were treated in order to guarantee the respect of privacy of the involved patients, as specifically stated by Italian Law D.Lgs n.196 of 2003 about personal data protection. Therefore, the study did not require preliminary evaluation by the local Ethical Committee. Written informed consent was obtained from the parents for publication of this case report and accompanying images.

Consent for publication

Written informed consent was obtained from the parents for publication of this case report and accompanying images.

Competing interests

The authors declare that they have no competing interests.

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