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Rare Coexistence of Neurofibromatosis Type 1 and Marfan Syndrome in a 13-Year-Old Boy: A Case Report

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Patient: Male, 13-year-old
Final Diagnosis: Marfan syndrome
Symptoms: Heart
Clinical Procedure: —
Specialty: Cardiology

Objective: Rare coexistence of disease or pathology

Background: Neurofibromatosis type 1 (NF1) and Marfan syndrome (MFS) are genetically determined systemic disorders. Their simultaneous occurrence is exceptionally rare, with only a few cases reported in the literature.

Case Report: A 13-year-old boy was admitted to a cardiology clinic due to mitral and tricuspid valve prolapse. He was tall, with severe scoliosis and distinctive dysmorphic features typical of MFS. More than 20 café-au-lait spots, characteristic of NF1, were present on his skin. The family history included NF1 in his twin brother, mother, maternal uncle, and maternal grandmother. The maternal uncle also exhibited phenotypic features of MFS and died at a young age from a suspected ruptured intracranial aneurysm. Genetic testing in our patient revealed an *NF1* mutation, as well as a 16p13.11 microduplication that could explain his developmental delay and speech difficulties. The diagnosis of MFS was based on characteristic dysmorphic features and the presence of aortic root dilation, despite negative findings concerning the fibrillin-1 (*FBN1*) mutation typically associated with MFS.

Conclusions: A thorough assessment of physical features is essential to detect atypical phenotypes and recognize potential coexistence of multiple genetic syndromes. This case highlights the clinical importance of systematic cardiac evaluation, given that cardiac abnormalities typical of MFS may be critical for its recognition. Reporting such an unusual coexistence of NF1 and MFS underscores the need for multidisciplinary care to improve long-term outcomes in patients with overlapping genetic disorders.

Keywords: Marfan syndrome • neurofibromatosis 1 • pediatrics

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Introduction

Neurofibromatosis type 1 (NF1), also known as von Recklinghausen disease, is a relatively common autosomal dominant disorder with an estimated incidence of approximately 1 in 2500 individuals worldwide [1]. It is caused by mutations in the *NF1* gene on chromosome 17, which encodes neurofibromin, a regulator of the RAS signaling pathway. NF1 is clinically diagnosed based on characteristic dermatological and ophthalmological findings, such as café-au-lait spots, axillary or inguinal freckling, Lisch nodules, and neurofibromas [2-4].

Marfan syndrome (MFS) is another autosomal dominant connective tissue disorder, with an estimated prevalence of 1 in 5000 to 10 000 individuals. Most cases are caused by mutations in fibrillin-1 (*FBN1*) on chromosome 15q21.1. MFS presents with a broad clinical spectrum, typically affecting the musculoskeletal, ocular, cardiovascular, and pulmonary systems. Diagnosis is based on the revised Ghent criteria, which integrate clinical features (eg, wrist and thumb sign, pectus carinatum, pectus excavatum, myopia, mitral valve prolapse, dural ectasia, and pneumothorax), family history, molecular confirmation of pathogenic *FBN1* variants, and key diagnostic manifestations, including aortic root dilatation and ectopia lentis (EL) [5]. This framework enables accurate classification of patients across the full phenotypic spectrum. The mortality rate among patients with MFS is approximately 30 times higher than that of the general population; aortic dissection and aneurysms represent leading causes of death [6].

Although both conditions are primarily diagnosed clinically, genetic testing provides important diagnostic confirmation. The use of array comparative genomic hybridization and whole-genome sequencing facilitates identification of genetic abnormalities, including deletions, duplications, and amplifications.

Both disorders are well characterized individually; their coexistence in a single patient is exceptionally rare, with only a handful of cases reported in the literature. This overlap creates challenges in diagnosis, as well as patient management. Clinical care must address the tumor predisposition and neurological risks associated with NF1, as well as the cardiovascular surveillance and surgical considerations required for MFS. The present case highlights the importance of comprehensive phenotypic evaluation and genetic analysis in children with unusual clinical presentations.

Case Report

A 13-year-old boy was admitted to a cardiology clinic due to mitral and tricuspid valve prolapse. He had been born from a dizygotic twin pregnancy. The first manifestations of NF1, café-au-lait spots, were recognized during the neonatal period. Since infancy, in addition to NF1, he had exhibited dysmorphic features such as dolichocephaly, muscle hypotonia, and developmental delays. As a newborn, he also had a cow's milk protein allergy and later developed selective eating behavior.

Because of the patient's dysmorphic features and developmental delay, genetic evaluation began during the first year of life with karyotype testing, which revealed no chromosomal abnormalities. He remained under clinical observation, and at 4 years of age, NF1 was genetically confirmed by identification of a pathogenic *NF1* gene mutation. At 5 years of age, MFS was first suspected clinically. Array comparative genomic hybridization was performed but did not identify an *FBN1* mutation, which is typically associated with MFS. However, it revealed a microduplication on the short arm of chromosome 16 (16p13.11p13.12). Subsequent fluorescence in situ hybridization testing of the patient's parents demonstrated that this genetic aberration was maternally inherited.

Despite the absence of molecular confirmation of MFS, the patient fulfilled the revised Ghent criteria for 2 independent diagnostic pathways: (1) the coexistence of aortic root dilatation and EL and (2) a systemic score exceeding 7 points in the presence of aortic involvement. His marfanoid habitus (**Figure 1**) included positive wrist and thumb signs with pronounced arachnodactyly. He exhibited pectus carinatum with chest asymmetry, severe scoliosis, pes planus, and genu valgum. Throughout childhood, his height remained above the 97th percentile for age, with disproportionately long extremities, reflected by an upper segment-to-lower segment ratio of 0.68. Additional findings included myopia of up to -8 diopters. Craniofacial features encompassed dolichocephaly, prominent ears, malar hypoplasia, and retrognathia (**Figure 2**). Collectively, these manifestations corresponded to a systemic score exceeding 7 points in the Ghent nosology. At 5 years of age, the patient was diagnosed with EL, which was successfully treated surgically.

He was first referred to a pediatric cardiology clinic at 3 years of age due to an audible systolic murmur over the precordial area, with maximal intensity at the apex. An electrocardiogram revealed repolarization abnormalities, specifically ST-T segment depression in the limb leads. Chest radiography showed no cardiac enlargement. Transthoracic echocardiography (TTE) demonstrated moderate (grade II/III) mitral and tricuspid regurgitation due to myxomatous prolapsing leaflets. At 12 years of age, aortic root dilatation measuring 38 mm (Z-score = +3) was identified on TTE. This finding established a definitive clinical diagnosis of MFS. Pharmacological treatment with losartan, an angiotensin receptor blocker, and spironolactone was subsequently initiated. Because episodes of tachycardia were confirmed by 24-hour Holter monitoring, the β-blocker bisoprolol was added.

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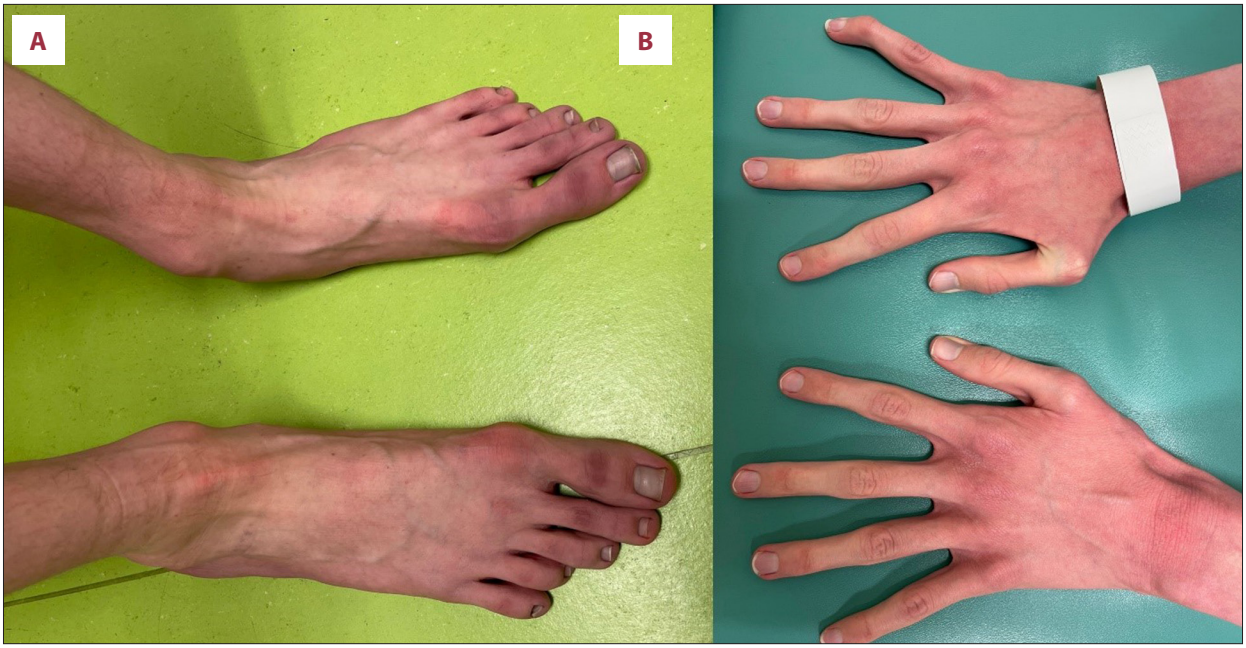

Figure 1. (**A**) Foot deformities. (**B**) Hand deformities, including arachnodactyly and phalangeal hypoplasia, characteristic of Marfan syndrome.

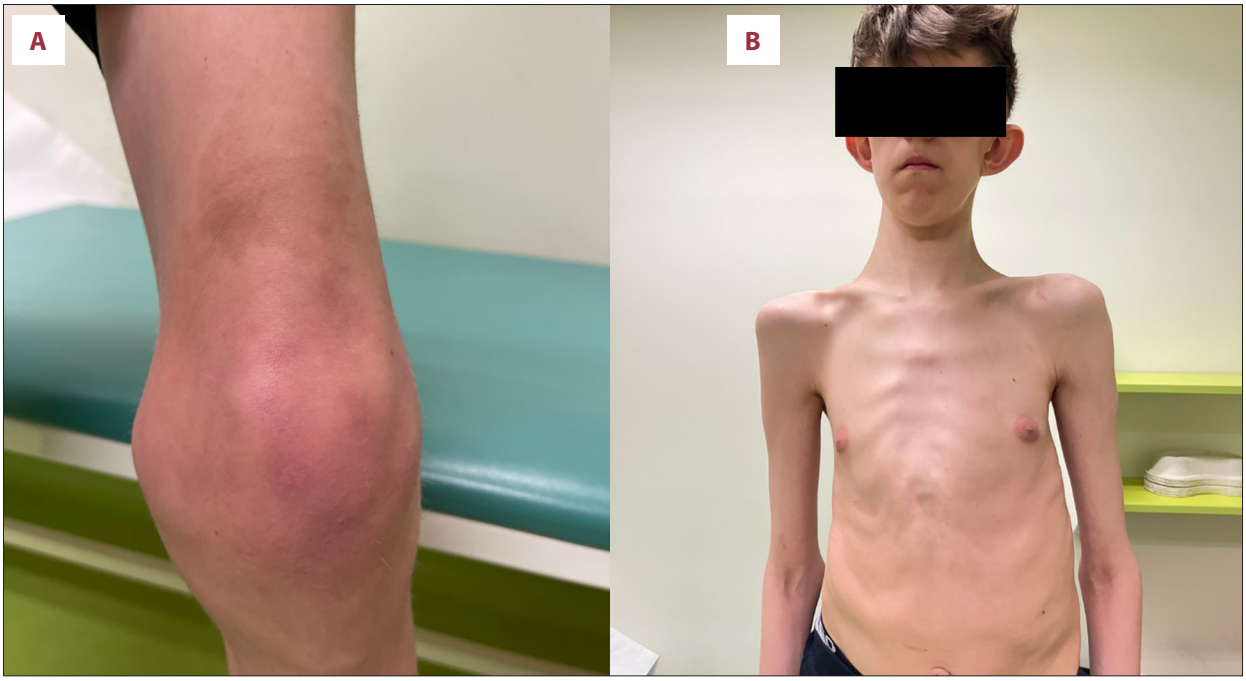

Figure 2. (**A**) Left knee deformity. (**B**) Thoracic and abdominal asymmetry with pectus carinatum, prominent ears, and underweight status characteristic of Marfan syndrome.

Until 6 years of age, the patient spoke in poorly articulated sentences and had a limited vocabulary that was largely intelligible only to family members. Despite this early language delay, he did not exhibit clinically significant cognitive deficits and later demonstrated only minor learning difficulties. At 11 years of age, radiographic assessment demonstrated markedly advanced skeletal maturation, equivalent to that of a 15-year-old boy. An optic pathway glioma was clinically suspected; however, magnetic resonance imaging excluded this diagnosis. Segmental dilatation of the optic nerves was identified. The patient also experienced recurrent fractures after low-energy trauma. He sustained a left carpal bone fracture

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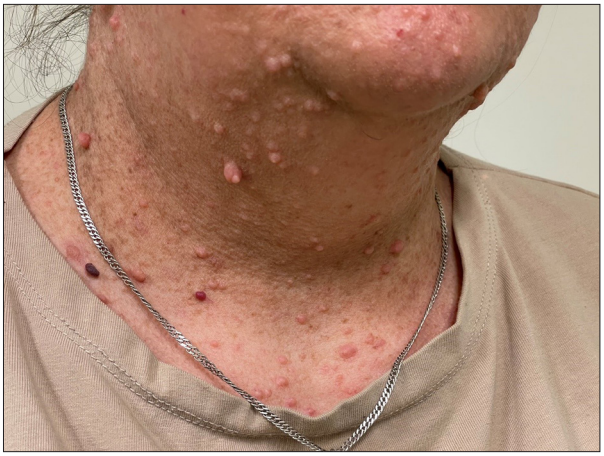

Figure 3. Numerous neurofibromas on the head and neck of the patient's mother.

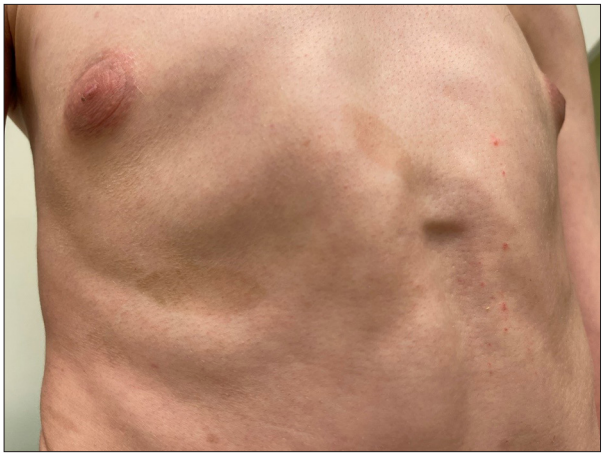

Figure 4. Multiple café-au-lait spots on the patient's thorax.

that required surgical fixation. His mobility was limited by severe scoliosis and thoracic kyphosis. He underwent 2 major spinal surgeries, the second of which was complicated by cerebrospinal fluid leakage.

Family history revealed that the patient's mother had genetic-testing-confirmed NF1. Numerous cutaneous neurofibromas were visible on physical examination (**Figure 3**). Her mother and brother were also affected by the condition. According to the patient's mother, her brother also exhibited phenotypic features suggestive of MFS and died at a young age from a ruptured intracranial aneurysm. However, this information could not be verified because no medical records were available, and the diagnosis remains unconfirmed. The patient's dizygotic twin brother also had NF1; he exhibited inguinal freckling and plexiform neurofibromas, as well as feeding difficulties and clinically significant impairments in speech, learning, and concentration. No history of NF1 or MFS was reported on the patient's paternal side.

Currently, at 13 years of age, the patient is 180 cm tall and weighs 43 kg (body mass index 13.3 kg/m^2, below -2 standard deviations for age), with a substantially reduced layer of subcutaneous tissue. TTE demonstrates aortic root dilatation measuring 44 mm (Z-score = +5). He remains in stable cardiac condition. He attends annual follow-up in a pediatric cardiology clinic, including routine TTE and 24-hour Holter monitoring to guide pharmacological management. Regarding NF1, physical examination revealed more than 20 café-au-lait spots ranging from 1 to 8 cm in diameter (**Figure 4**).

Discussion

This case illustrates the rare coexistence of genetically confirmed NF1 and a fully expressed clinical phenotype of MFS despite negative molecular findings concerning *FBN1*. It highlights the diagnostic challenges posed by overlapping connective tissue disorders and the limitations of current genetic testing methods.

The coexistence of MFS and NF1 has rarely been documented [7-10]. In 1974, Witwicki et al [10] described the first reported case, involving a 22-year-old woman with heart disease, paraparesis due to neurofibroma, and coexisting MFS and NF1. Leramo et al [9] and Hartlapp et al [8] also reported cases of concurrent NF1 and MFS resulting from de novo mutations. In contrast, our patient had a positive family history suggestive of both NF1 and MFS.

Suspicion of NF1 in our patient was based on the presence of café-au-lait spots visible during the newborn period. These findings fulfilled 2 of the updated 2021 diagnostic criteria for NF1 [2]: the presence of more than 6 café-au-lait spots and a positive family history. These features supported the diagnosis, which was subsequently confirmed by genetic testing. The patient did not exhibit cognitive impairment, perceptual abnormalities, or concentration deficits; he demonstrated appropriate learning abilities but experienced some difficulties with mathematics, a feature commonly noted in patients with NF1. He also did not exhibit excessive psychomotor activity or attention-deficit/hyperactivity disorder, which occurs in approximately 55% of children with NF1 [11], including his twin brother.

The diagnosis of MFS in our patient was suspected during infancy and established at 12 years of age. Although molecular testing did not identify a pathogenic *FBN1* variant, he fulfilled the revised Ghent criteria for MFS [5] through 2 independent diagnostic pathways. First, the coexistence of aortic root dilatation and EL is sufficient to establish the diagnosis regardless of genetic findings. Second, even in the absence of EL, the combination of aortic involvement and a positive systemic score

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would be sufficient for diagnosis. Although the family history could not be fully verified in the present case, a confirmed family history of MFS would further lower the diagnostic threshold; the presence of aortic root dilatation, a positive systemic score, or EL alone would satisfy the criteria. The ability to diagnose MFS solely based on clinical features emphasizes that genetic testing is not sufficiently sensitive to exclude the disease when diagnostic clinical criteria are fulfilled.

Several conditions that can mimic MFS were considered in the differential diagnosis, including homocystinuria, Loeys-Dietz syndrome, congenital contractural arachnodactyly, and certain forms of Ehlers-Danlos syndrome. However, the absence of metabolic abnormalities, presence of EL, characteristic pattern of skeletal involvement, and progressive aortic root dilatation made these alternative diagnoses unlikely and strongly supported MFS as the primary diagnosis.

According to international consensus recommendations for aortic root dilatation in MFS, indications for prophylactic aortic root replacement include an aortic root diameter greater than 50 mm on TTE or cardiac magnetic resonance, aortic root growth exceeding 8 to 10 mm per year, or progressive aortic valve insufficiency [12]. In our patient, aortic root dilatation measured 44 mm on both TTE and cardiac magnetic resonance, and pharmacological treatment was initiated. Angiotensin receptor blocker therapy was introduced first, followed by the addition of a β-blocker, in accordance with current guidelines and supported by documented aortic progression and symptomatic tachycardia. Both agents reduce hemodynamic stress on the aortic wall in patients with MFS. Exercise restriction serves as an additional supportive measure in this population. Given the coexistence of NF1, the possibility of increased vascular fragility was also considered. However, current evidence does not contraindicate standard antihypertensive therapy, but it emphasizes the need for careful cardiovascular and neurovascular surveillance.

Currently, there is no aortic valve regurgitation; however, given the existing aortic root dilatation, the patient remains at risk for developing regurgitation and potentially heart failure in the future. Coexisting myxomatous prolapse of both the mitral and tricuspid valves with associated regurgitation, also characteristic of MFS, further contributes to his risk of future cardiac dysfunction.

Because the causative genes for NF1 and MFS are located on different chromosomes, these conditions should be regarded as 2 independent genetic disorders rather than manifestations of a single expanded phenotype. The 16p13.11p13.12 microduplication represents a separate genomic abnormality that can modify certain aspects of the patient's presentation; however, its contribution remains uncertain. Although some reports suggest that copy number variants in this region are associated with developmental delay and speech difficulties—features described in more than 80% of affected individuals [13]—the available evidence is limited, and any contribution in the present case should be considered speculative. The patient's early feeding difficulties, cow's milk protein allergy, and later severe food selectivity are consistent with features reported in individuals exhibiting this microduplication. However, such symptoms also occur in many other genetic syndromes and thus warrant cautious interpretation. Although 16p13.11 microduplication is not classically associated with connective tissue disorders, occasional reports have described joint laxity, skeletal anomalies, and cardiovascular abnormalities, implying that this copy number variant could act as a phenotypic modifier in patients with overlapping syndromic features. In our patient, the microduplication may therefore represent a confounding or contributory factor, particularly with respect to neurodevelopmental manifestations; the cardinal connective tissue features remain most consistent with MFS. Overall, the patient's phenotype evolved gradually over time, with new manifestations emerging at different developmental stages and progressively enhancing diagnostic certainty.

At present, the patient's primary goal is to improve physical fitness through supervised rehabilitation, given that weakness of the vertebral column substantially limits comfortable sitting and walking. He wishes to attend a conventional school rather than receive homeschooling due to his health issues. Even after successful surgical interventions, specialized physical therapy will be essential to help him achieve this goal.

Due to MFS, the patient requires lifelong cardiology follow-up. Moreover, he should be monitored closely for the development of neoplasms associated with NF1. Given the genetic diagnoses and the family history of a fatal intracranial aneurysm, enhanced neurovascular surveillance, including baseline magnetic resonance imaging or magnetic resonance angiography, appears warranted. This clinical situation requires frequent specialist follow-up and ongoing preventive management. Early identification of changes in aortic dimensions, blood pressure, vision, neurological status, or growth patterns allows timely intervention and may substantially reduce morbidity. Previous studies have shown that the mean age at death among individuals with NF1 is 8 to 15 years lower relative to the general population [1]. We suspect that life expectancy could be further reduced in patients with coexisting NF1 and MFS, although data are currently insufficient to evaluate such a reduction. This dual diagnosis also has important implications for long-term quality of life and future reproductive planning, underscoring the need to provide anticipatory counseling and coordinated multidisciplinary follow-up as the patient transitions into adulthood.

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Conclusions

Pediatricians should carefully assess dysmorphic features and consider the possibility of coexisting genetic syndromes. Cardiac evaluation and the identification of MFS-specific cardiac abnormalities are particularly valuable in establishing the diagnosis. This report highlights the importance of clinical vigilance and coordinated multidisciplinary follow-up in patients with complex or overlapping phenotypes.

Department and Institution Where Work Was Done

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Patient Consent

The patient's guardians gave written consent to publication of the patient's images and use of their medical data.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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