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INFORME DE CASO: SÍNDROME DE MARFAN

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Case Report: Marfan Syndrome

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ABSTRACT

Marfan syndrome (MFS) is a heritable disorder of connective tissue resulting from pathogenic variants of the fibrillin-1 gene (FBN1). MFS is rare and the most severe form of MFS, involving rapidly progressive cardiovascular dysfunction leading to death during early childhood. The constant enrichment of the MFS mutation spectrum is helpful to improve our understanding of genotype–phenotype correlations in the disease. Our patient carries a de novo variant of FBN1, homozygous c.1415 G > A (C472Y), heterozygous 1875 T > C (N625), heterozygous IVS 17-46 A > G, IVS 35-19 A > G, IVS 40-13_14insT, IVS 45+28_29insT, IVS 51-85 T > C, IVS 53-21 A > T, heterozygous 6855 T > C (D2285), homozygous IVS 56+17 C > G, homozygous IVS 60-113 C > A, heterozygous IVS 62 + 8 A > C. There is a case report in which a patient is diagnosed with missense variant S713G, this sequence analysis also identified a heterozygous 6289 G > T nucleotide change in the FBN1 gene of this individual. At this time, there is not sufficient information to classify this allele as a disease-associated mutation or a benign variant not associated with disease

Keywords: marfan syndrome; FBN1 gene, pathogenic variants, genotype-phenotype correlations, missense variant

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Informe de Caso: Síndrome de Marfan

RESUMEN

El síndrome de Marfan (MFS) es un trastorno hereditario del tejido conectivo que resulta de variantes patogénicas del gen de la fibrilina-1 (FBN1). El MFS es raro y la forma más grave de MFS implica una disfunción cardiovascular rápidamente progresiva que lleva a la muerte durante la infancia temprana. El constante enriquecimiento del espectro de mutaciones del MFS es útil para mejorar nuestra comprensión de las correlaciones genotipo-fenotipo en la enfermedad. Nuestro paciente presenta una variante de novo del FBN1, homocigoto c.1415 G > A (C472Y), heterocigoto 1875 T > C (N625), heterocigoto IVS 17-46 A > G, IVS 35-19 A > G, IVS 40-13_14insT, IVS 45+28_29insT, IVS 51-85 T > C, IVS 53-21 A > T, heterocigoto 6855 T > C (D2285), homocigoto IVS 56+17 C > G, homocigoto IVS 60-113 C > A, heterocigoto IVS 62 + 8 A > C. Hay un informe de caso en el que a un paciente se le diagnosticó una variante de sentido erróneo S713G; este análisis de secuencia también identificó un cambio nucleotídico heterocigoto 6289 G > T en el gen FBN1 de este individuo. Actualmente, no hay suficiente información para clasificar este alelo como una mutación asociada a la enfermedad o como una variante benigna no asociada con la enfermedad.

Palabras clave: síndrome de marfan, gen FBN1, variantes patogénicas, correlaciones genotipo-fenotipo, variante de sentido erróneo

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INTRODUCTION

Marfan syndrome (MFS) is an autosomal dominant genetic disorder, characterized by the synthesis of abnormal fibrillin-1 protein (FBN1) [1]. French pediatrician Antonin Marfan in 1896 first reported this syndrome as arachnodactyly, as clinical features included abnormally long, slender or spidery fingers and toes [2]. Patients with MFS have complications in multiple organs [3], but those affecting thecardiovascular system are most detrimental. In adults, clinical manifestations include dilation of aortic root, proximal ascending aorta and pulmonary artery, calcification of mitral and aortic valves, dilated cardiomyopathy and arrhythmia [4] with dissection from thoracic aortic aneurysm (TAA) being the most life-threatening complication.

Although less frequently diagnosed, clinical manifestations in infants include severe mitral valve prolapse (MVP), valvular regurgitation and aortic root dilation with congestive heart failure [5,6]. Early detection of aortic dissection risk could radically change the prognosis of MFS patients [2]. Aortic diameter and dilatation rate, measured with transthoracic echocardiography, are actually considered to be the only clinical predictors of aortic dissection risk but their value is limited, as aortic dissection may also occur unexpectedly in nondilated aortas [3] and after prophylactic aortic root surgery [4].

Moreover, it has not been possible so far to obtain a clear risk profile for vascular complications in MFS by means of genotype characteristics [5,6]. In MFS, genetic defects in structural proteins of the arterial wall, as in the FBN1, lead to changes in the elastic properties of the large arteries. A significant alteration in viscoelastic properties of aorta was shown in murine models of MFS, in which the absence of FBN1 leads to enhanced elastolysis in arterial wall [7]. In humans with MFS, a greater rigidity of the large elastic arteries, and particularly of the aorta.

MFS is classified as a disorder affecting the connective tissues. In 1991, the FBN1, which encodes a 350 kDa glycoprotein that was found abundantly in the extracellular matrix (ECM) [8], The FBN1 gene (N200 kb) comprising 65 exons resides on the long arm of chromosome 15 (15q15-q21.1) [4] and encodes a 2871 amino acid protein. Fibrillin-1 has a modular structure comprising 47 repeats of six-cysteine EGF-like motifs, 7 eight-cysteine motifs bearing homology with latent TGF-β-binding proteins and a proline-rich region. Evidence of its role in MFS surfaced when gene targeting studies in mice demonstrated that FBN1 mutations in mgΔ mouse model [14] and fibrillin-1 under-expression in a mgR

mouse model [15] led to MFS phenotypes. Various combinations of normal and mutant fibrillin-1 show different phenotypic severity, suggesting the existence of a threshold for disease manifestation [15], which could explain varying disease penetrance. For instance, mgΔ mice bearing deletions of the region between exons 19 and 24 display a more severe phenotype and die much earlier when compared to mgR mice bearing insertions in the intronic region between exons 18 and 19.

Case presentation

A 24-year-old male patient who at 15 years consults the doctor in the company of his mother who says that despite family size they have noticed accelerated growth in the last 10 months, he also reports that the patient fits 45. Being assessed by the general practitioner who auscultates heart murmur so he decides to refer to cardiology. They perform an echocardiogram that reports left ventricular dilation, mitral valve insufficiency, tricuspid and pulmonary valve insufficiency. It brings ophthalmology concept without subluxation or dislocation of the lens.

In view of the accelerated height gain, longuilinea constitution, chest deformity, suspected diagnosis of SMF is raised, so it is referred to genetics.

Genetic evaluation was done with mutations that cause a stop codon in position 2097 generating truncated protein that to date had not been described. Cardiology evaluation with catheterization ruled out congenital heart disease and in occasional holter ventricular extrasystoles.

The physical findings revealed:

Good general conditions, tall stature, longuilineum, normocephalus, eyes without apparent alterations, normo atrial pavilions implanted without alteration, high palate mouth, long neck without injuries, asymmetric chest, pectus carinatum predominantly on the right side, dorsolumbar scoliosis of left convexity, cardiopulmonary: audible vesicular murcullo in both lung fields, rhythmic heart sounds with systolic murmurs. Abdomen: side, depressible, without megalias, normoconfigured male genitalia, limbs: cubitus valgus, limitation for extension, arachnodactyly, positive steinberg and Walker sign, neurological: preserved, skin: stretch marks in lateral pelvic region and lateral knees

Figure 1. The patient shows (A) aracnodactilia, (B, C) ligamentary laxitude and (D) dolicostenomelia

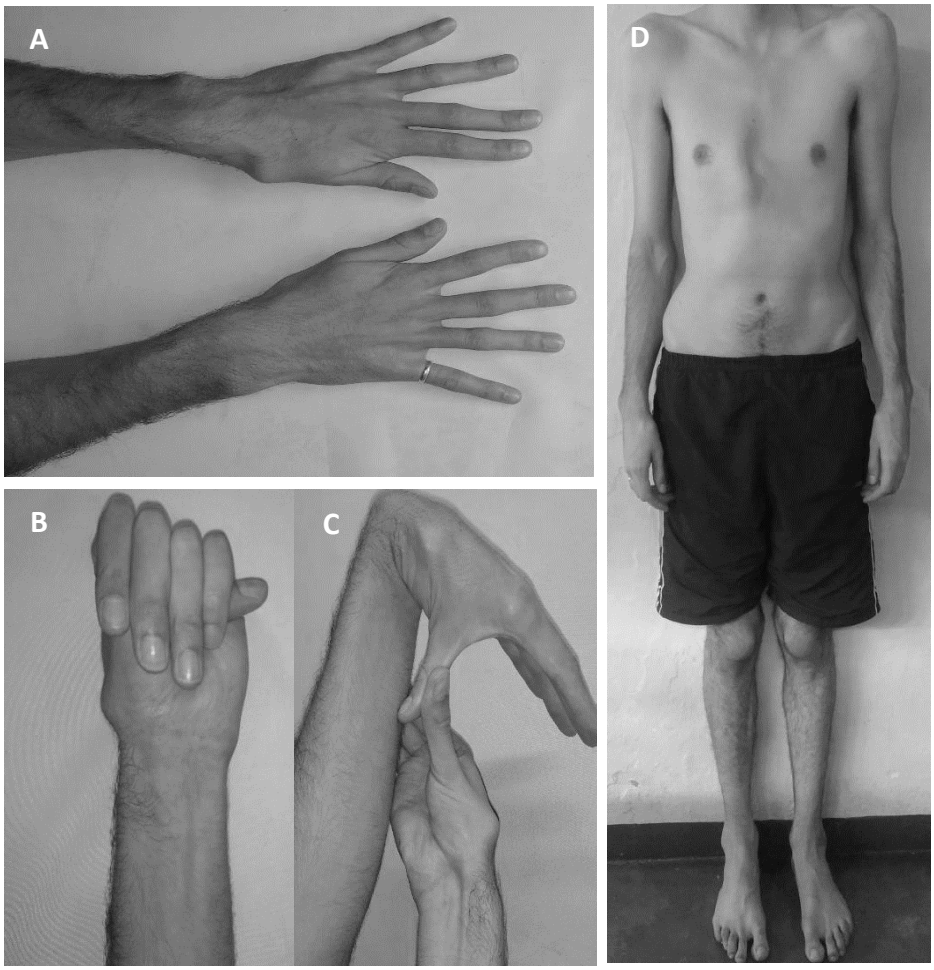
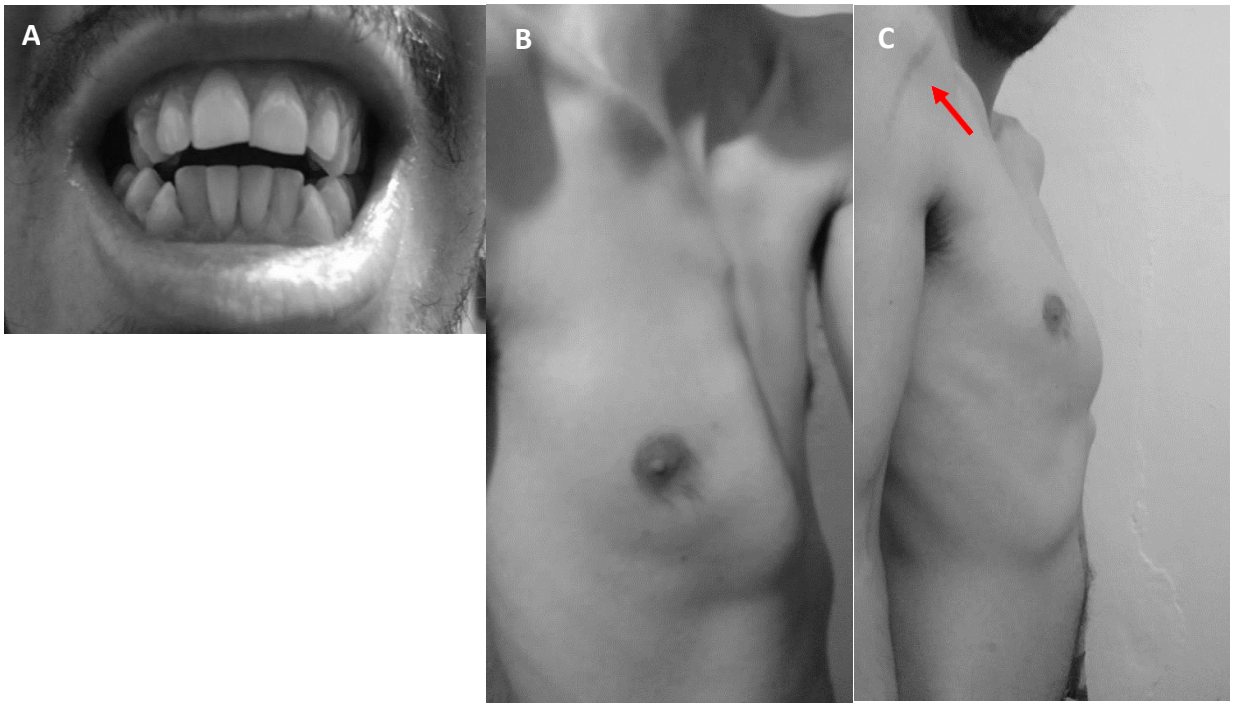


Figure 2. Mouth and torax photographs of the patient showing (A) applied teeth, (B) torax carinatum (C) torax carinatum and estria.



Differential diagnosis

Hypergrowth or gigantism resembles SMF by accelerating growth speed, however, in gigantism excess growth hormone is found, while SMF is due to mutations in the FBN1 gene.

Treatment

For the treatment of occasional ventricular extrasystoles, treatment with propanolol of 50mg was started every 12 hours. He currently takes 100 mg metropolol every 12 hours.

Result and follow-up

The patient reduced the enlargement rate of the aortic diameter by reducing the risk of aortic dissection.

DISCUSSION

SMF is a rare genetic disease that presents with a prevalence in the population of 1:5000 to 1:20,000 people according to different studies. It is characterized by alterations in the cardiovascular system, skeletal muscle, ocular and sometimes pulmonary.

The diagnosis is established with clinical criteria, family history and molecular. In the case of the patient, it presents three major and three minor criteria for the skeletal system, none for the eyepiece, two minor criteria for the cardiovascular system and one criterion for the skin. The patient has criteria to establish the presence of connective tissue pathology, however, to complement the study molecular tests were performed.

Of the 2,088 MFS patients on the UMD-FBN1 mutations database (last update, 28/08/14), with 1847 different mutations and 1096 proteic variants totaling 3077 mutations. Our patient carries a de novo variant of FBN1, homozygous c.1415 G > A (C472Y), heterozygous 1875 T > C (N625), heterozygous IVS 17-46 A > G, IVS 35-19 A > G, IVS 40-13_14insT, IVS 45+28_29insT, IVS 51-85 T > C, IVS 53-21 A > T, heterozygous 6855 T > C (D2285), homozygous IVS 56+17 C > G, homozygous IVS 60-113 C > A, heterozygous IVS 62 + 8 A > C. These polymorphisms have been previously reported in the NCBI Single Nucleotiode

Polymorphism database (www.ncbi.nlm.nih.gov). This sequence analysis also identified heterozygous 2137 A > G nucleotide change in one copy of the FBN1 gene of this individual. This nucleotide change predicts an amino acid substitution of Serine to Glycine at amino acid residue 713 (S713G). However, this amino acid substitution has not been identified as a disease- associated mutation in other patients.

At this time, there is not sufficient information to classify this allele as a disease-associated mutation or a benign variant not associated with disease.

In addition to the missense variant S713G, this sequence analysis also identified a heterozygous 6289 G > T nucleotide change in the FBN1 gene of this individual. This nucleotide change predicts an amino acid change of Glutamic acid to a premature translation stop at codon 2097 (E2097E). Although this nonsense mutation was not previously reported as a disease-associated FBN1 mutation. Thus, the identification of FBN1 mutation is consistent with the clinical features of this individual.

There is a case report in which a patient is diagnosed with SMF, its nonsense mutation generated a codon of premature stop at position 2228, in terms of its clinical manifestations, the one that was most particular was myopia which is in favor of one of the most common clinical features of SMF (4), against our patient when having a nonsense mutation with a stop codon in position 2097, its clinical manifestations are notoriously.

There is evidence in numerous studies that 80% of patients with SMF develop ectopia lentis, which is almost always bilateral (8); In a physiological way, fibrillin goes through a glycosylation process which generates an assembled structure called myofibril, which together with elastin is part of the ciliary zonules that are going to connect the lenses of the eye to the ciliary muscles. However, in our case, the patient does not have visual disturbances of any kind.

In a first case report, a 29-year-old woman with a diagnosis of SMF from the age of 9, presented persistent dyspnea on exertion, this patient had never smoked and had a pathological history of pneumothorax on three occasions. A chest X-ray was performed showing a severe spinal deformity and diffuse emphysematous change of the lungs, although no direct relationship was found with the SMF if there is a high suspicion that this has caused the emphysematous change because one of the systems Affected by this disease is the lung (9). However, in our case, the patient does not have any respiratory condition of this magnitude; except in his childhood he presented an asthma period, but he currently has no clinical symptoms.

In a second case report, there is a 24-year-old Ugandan woman, who was referred to a neurology opinion after complaining of a one-year history of retro-orbital stabbing pain on the right side. Brain imaging revealed an aneurysm of the left ophthalmic artery coinciding with 3 millimeters. Marfanoid habit was

observed; After further investigations, he was diagnosed with mild aortic root dilation, subtle dislocation of the lens and SMF. Its symptoms were secondary to a temporomandibular joint dysfunction, a poorly recognized complication of SMF. However, its ophthalmic artery aneurysm is likely to be a coincidental finding and not directly related to SMF (10). In this case, a very characteristic SMF clinic is described, however, none of the manifestations previously presented in our patient.

A particular fact is that the majority of mutations registered to date are of the Missense type, which represents 72% of the total and of these, the majority alter the cbEGF domain which in terms of percentages is 53% of the total (9). However, in our case the mutation is heterozygous nonsense type, which confirms the great variability of mutations in the SMF.

Most of the mutations in fibrillin-1 occur in the EGF domain, a fact that generates part of the SMF phenotype (3). But in the case of our patient the mutation is given in the TGFB domain, which is an important cytokine in cell proliferation and differentiation, apoptosis and extracellular matrix formation; and the increase in TGF- β signaling plays an important role in the pathogenesis of SMF and gives the characteristics of its variability and clinical presentation (8).

CONCLUSIONS

The diagnosis of the severe disease MFS can be aided by identifying known MFS- causing variants through continuous enrichment of the MFS mutation spectrum. In the present study, we identified a novel dominant FBN1 mutation, 6289 G > T. This nucleotide change predicts an amino acid change of Glutamic acid to a premature translation stop at codon 2097 (E2097E). This finding will be helpful for the clinical diagnosis, prenatal diagnosis, and genetic counseling in patients with the same mutation. Our brief review, based on the latest database information, summarized the distinctive features of MFS-associated mutations relative to mutations for classic and incomplete MFS, which will be valuable for evaluating the pathogenicity of novel FBN1 variants for MFS.

Consent

Written informed consent was obtained from the patient for publication of this Case report including the results of genetic testing and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

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