v. 3, n. 70, 2023

International Journal of Health Science

MARFAN SYNDROME IN A FAMILY IN THE INTERIOR OF MINAS GERAIS CASE REPORT AND REVIEW

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INTRODUCTION

Marfan Syndrome was narrated for the first time in 1896, by the French Antonie Bernard and Jean Marfan, as an autosomal dominant genetic alteration resulting from mutations in the FBN1 gene, located in 15q21. extracellular matrix of connective tissue (VERSTRAETEN et al., 2016).

It is a multisystem disease, whose main phenotypic manifestations involve the skeletal, cardiovascular and ocular systems (RESENDE et al., 1984). The main skeletal manifestations are: chest and spine deformities, dolichostenomelia, arachnodactyly and tall stature. The main ocular manifestations are: lens subluxation, myopia and retinal detachment. Among the cardiac manifestations, there are mainly: mitral valve prolapse, aortic dilatation and dissecting aortic aneurysm. In addition, manifestations in the Central Nervous System may also occur, such as dural ectasia, lumbar and sacral meningocele, dilated cisterna magna, learning disorders and hyperactivity (SALLUM; CHEN; PEREZ, 2002).

It is estimated that its occurrence ranges from 1:5,000 to 10,000 live births (BARRIL; ANDRADE; BARBOSA, 2020) although this estimate depends on the complete recognition of all affected and genetically predisposed individuals. Multiple factors may contribute to an underestimation of the prevalence of the disease. This is because the phenotype becomes more evident with increasing age and many of the external manifestations are common in the general population (MARX et al., 2017). It must be taken into consideration, that this disorder sporadically discerns a dominant trait in about 25% of cases, resulting from new mutations, and that the predominance lies in the mutation of the FBN1 gene, which encodes the matrix protein fibrillin-1 (AALBERTS et al. al., 2014).

The diagnosis of FMS can be performed clinically through the Ghent nosology criteria or by molecular biology examination to identify mutations in the fibrillin-1 gene. The Ghent nosology is marked by the presence of manifestations considered "major" or "minor" in several different devices. In cases where there is no family history, for the diagnosis to be defined, it is necessary to fulfill major criteria in at least two different systems. For a family member with at least one first-degree relative with SMF or mutation in the FBN1 gene, the presence of a major criterion in a system is satisfactory for defining the diagnosis (BARRIL; ANDRADE; BARBOSA, 2020).

The preferred treatment is multimodal. A priori, elementary prevention must be considered, which is based on genetic counseling, considering the rate of recurrences, reproduction options and the existence of new cases in other family members, bearing in mind the variability of the phenotype within and between families. the families. Then, to prevent complications, monitoring by specialized professionals is recommended. In cases of cardiovascular complications, treatment is always surgical (JONDEAU; MICHEL; BOILEAU, 2011).

Due to the rarity of the disease and the limited literature description, an interdisciplinary approach is essential, since the disease presents great inter and intrafamilial phenotypic variability, which makes the diagnosis difficult and associated with uncertainty (SALLUM; CHEN; PEREZ, 2002).

METHODS

This is a qualitative and exploratory case report study with the presentation of data obtained through retrospective analysis of medical records in a Basic Family Health Unit in a municipality in the interior of Minas Gerais, followed by a literature review of the theme.

CASE REPORT

J.M.N.D. (Patient 1), female, 56 years old, divorced, steady partner, born and resident of Araguari-MG. Patient smoker, smoking history of 9 pack-years and social drinker, with a pathological personal history of Keratoconus, Glaucoma and Cataract, in addition to Marfan Syndrome and its cardiovascular repercussions. She reports three pregnancies and one miscarriage, two of which are living children with FMS and one who died at the age of 24 due to complications related to the syndrome. In 2004, she underwent cardiac surgery, performed through longitudinal median thoracotomy, pericardiotomy, with the installation of a cardioplegic solution and extracorporeal circulation, consisting of correction of an ascending aortic aneurysm with a valved tube., number 27 *Saint Jude* and reimplantation of coronary ostia. Exams carried out on 08/24/2020 showed moderate increase in the right ventricle; discrete biatrial enlargement; left ventricle with moderate concentric hypertrophy, preserved systolic function and grade III diastolic dysfunction; mild mitral regurgitation; mechanical prosthesis in aortic position with mild stenosis and mild paravalvular reflux; mild tricuspid insufficiency. The patient complained of vertigo, headache, palpitations and dyspnea, being submitted to a new electrocardiogram, on 07/02/2022, showing supraventricular tachycardia and, for evolutionary control, two new exams were performed in the following days, revealing atrial fibrillation with high ventricular response and diffuse changes in ventricular repolarization. In the last echocardiogram performed in March 2023, the patient presented mild dilatation of the left atrium, aortic root (36mm), valved tube in the ascending aorta (30mm); moderate left ventricular concentric hypertrophy, with the basal portion presenting more important hypertrophy (17.5 mm), but without leading to subvalvular hemodynamic repercussions; global and segmental systolic performance of both ventricles preserved; mechanical prosthesis in aortic position (Valved Tube) showing dysfunction, opening of only one of the discs, leading to significant stenosis, by Transthoracic ECHO: Peak velocity: 4.2 m/s, Average gradient: 42 mmHg, DVI: 0, 20, Valve Area by continuity equation 0,8 cm^2, by transesophageal ECHO: Peak velocity: 4.57 m/s, Average gradient: 51 mmHg, planimetry of 0.81cm^2, and mild central regurgitation (2 jets). Images compatible with thrombus were not visualized, however it is emphasized that the technical quality of the exam was suboptimal; mild mitral regurgitation, with slight thickening of the leaflets; mild tricuspid regurgitation, allowing assessment of PASP at 26 mmHg. He is currently on Marevan 5mg therapy (1 pill a day). In addition to warfarin, she uses Carvedilol 6.25mg daily (1 tablet in the morning and 1 tablet at night) and eye drops: Bimatoprost 0.03% (1 drop at night) and Brinzolamide 1% (1 drop, twice a day). On physical examination, the patient was in good general condition, eupneic, afebrile, nourished and hydrated, normal color, acyanotic, anicteric, atypical gait, slim body type, good peripheral perfusion, without edema or jugular swelling; BP 120/80mmHg, regular HR 69bpm, weight 59Kg and height 1.64m, BMI 21.9. On examination, the oral cavity was preserved, absence of deformations, lesions, cervical tumors, with no movement limitations. On cardiovascular examination,

presence of scar in the sternal region of 21 cm, rhythmic heart sounds in 2 times, with systolic murmur in accessory aortic focus (hyperphonesis of the second sound in accessory aortic focus), protodiastolic click. Asymmetrical chest, thoracoabdominal breathing pattern, preserved expandability, without percussion alterations, physiological vesicular murmur, without adventitious sounds. Abdominal cavity without alterations, flaccid abdomen, without bulging or retractions, bowel sounds present, painless on palpation. As for the osteoarticular apparatus, elongated upper limbs, presence of accentuated lordosis in the lumbar region, evident in the Adams test; Walker-Murdoch sign, thumb sign (Steinberg) and flatfoot with hallux valgus; arachnodactyly. The patient is awaiting cardiovascular surgery to replace the mechanical aortic prosthesis, which is currently non-functional, and remains under specialized follow-up until the conclusion of this report, in August 2023.

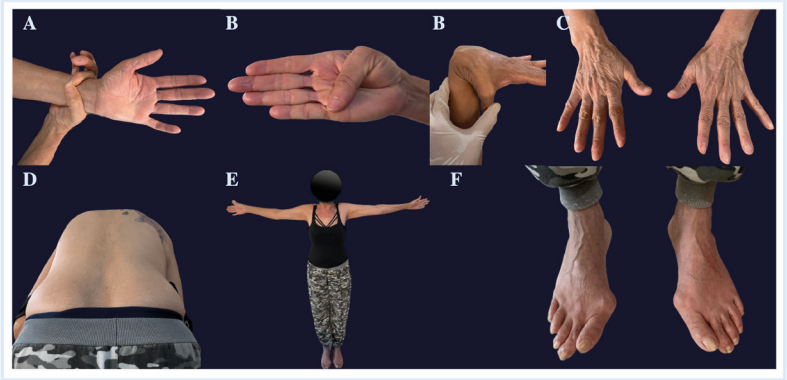
K.N.S., female, 24 years old, with FMS, as well as her brother, J.E.F. (Patient 2), male, 33 years old. Patient with previous surgical report of implantation of metallic valve prosthesis in 2010, due to aortic artery dilation and aneurysm. He was hospitalized on 08/24/2020 with a diagnosis of posterior temporal stroke and left thalamus, for PAT / INR control due to the use of warfarin. He attended the Basic Family Health Unit to present the results of tests carried out on 06/02/2021, which revealed testimonial prothrombin time: 13.3 seconds; patient prothrombin time: 22.3 seconds, prothrombin activity: 38% and INR: 1.95; followed by a historical control prothrombin time: 11.1 seconds; patient prothrombin time: 15.4; prothrombin activity: 39% and INR: 1.53, on 12/08/2020; on 09/08/2020 and 06/19/2020, the report showed a testimonial prothrombin time: 13.3 seconds; patient prothrombin time: 19.7 and 13.5 seconds; prothrombin activity: 49% and 98%; RNI: 1.56 and 1.02, respectively. Patient difficult to approach and adherence to treatment. He remains under specialized follow-up, under drug therapy of sodium warfarin 5mg (2 pills a day), until the completion of this report in August 2023.

E.G.F. (Patient 3), male, 10 years old, born and raised in Araguari-MG, with Marfan Syndrome. The patient attends the Reference Center for Inclusion in Araguari, a school where students with disabilities and/or learning disorders are treated. In December 2022, a Psychopedagogy service observation report was received, which described that the patient is at a pre-syllabic level, does not demonstrate knowledge about reading and writing some letters, words, syllables and phrases, coinciding with the family's report on their late development, hyperactivity and inattention, very evident in school activities. As for personal history, patient born at term, at 29 weeks and 2 days, cesarean delivery, uneventful, neonatal screening tests without changes. In a consultation in 2014 (1 year and 7 months old), caregivers reported a complaint of feet with a slight tortuous accentuation, causing the child to face difficulty in the process of walking, delaying this developmental milestone. In addition to the aforementioned complaint, the family reported recurrent episodes of conjunctival hyperemia, high height for age, constant falls and gait changes. The patient remains under observation and specialized follow-up until the conclusion of this report in August 2023, under therapy with propranolol, ½ tablet in the morning and ½ tablet in the evening.

Systemic Scores for Marfan Syndrome				
Characteristics	**Score**	**Patient 1**	**Patient 2**	**Patient 3**
Thumb fist E sign	3	+	+	+
Fist OR thumb sign	1	-	-	-
Pectus carinatum	2	-	-	-
Pectus excavatum or chest asymmetry	1	+	+	+
Foot deformity	2	+	+	+
Flat feet	1	+	-	-
Dural ectasia	2	E.I.	E.I.	E.I.
Acetabular protrusion	2	E.I.	E.I.	E.I.
Reduced upper/lower segment ratios and increased arm span/height and no severe scoliosis	1	+	+	+
Thoracolumbar scoliosis or kyphosis		+	+	+
Reduced elbow extension		-	-	-
Dolichocephaly	(3/5) = 1	-	-	-
Enophthalmos		-	-	-
Palpebral fissures with inferolateral tilt		-	-	-
Malar hypoplasia		-	-	-
Retrognathism		-	-	-
stretch marks on the skin	1	+	+	-
Myopia > 3 diopters	1	-	+	+
Mitral valve prolapse (all types)	0,25	+	+	-
Spontaneous pneumothorax	2	-	-	-
Family history		+	+	+
Ectopia lentis		-	-	-
Aortic root z-score ≥ 2		E.I.	E.I.	E.I.
**** +: present, -: absent, E.I.: Exam Unavailable***				

Table 1 – Clinical characteristics and systemic scores of patients for Marfan syndrome

Source: Authors.



Picture 1 – Clinical features of Marfan Syndrome (Patient 1)

Source: Authors

Subtitle:* **A: Sign of *Walker-Murdoch*. **B:** thumb sign (*Steinberg*). **C:** Arachnodactyly. **D:** Marked lordosis in the lumbar region in the Adams test. **E:** Reduced upper/lower segment ratios and increased arm span/height. **F:** Flat foot with *hallux valgus*.

DISCUSSION

Showing an autosomal dominant inheritance pattern, Marfan Syndrome has a penetrance of approximately 100%, and on average, 90% of the attested mutations are of a single type and affect an individual or family; 20% of those affected did not inherit the mutations, being interpreted as new mutants (LIMA et al., 2018). This rare syndrome usually has a multisystem course, including the musculoskeletal, ocular, cardiovascular, pulmonary, nervous, and integumentary systems. It is estimated that its occurrence ranges from 1:5,000 to 10,000 natives (BARRIL; ANDRADE; BARBOSA, 2020).

Among the main clinical characteristics, there are: height increase, rib cage deformation; arachnodactyly, alteration identified by the long and thin fingers; in addition to dolicostenomelia, which is characterized by the disproportion between the ratio of wingspan and height; lens subluxation, retinal detachment, myopia, glaucoma, and early cataracts; aortic root dilation, mitral valve prolapse, ventricular dysfunction and arrhythmias (LIMA et al., 2018)

Unfortunately, genetic testing as a diagnostic method remains limited. To date, more than 500 mutations that give rise to the disease have been documented (COLLOD-BÉROUD et al., 1998). And even in families where all affected individuals share the same mutation, the phenotypic variation is very large, making it difficult to establish a comparison between genotype and phenotype (DISABELLA et al., 2006). Similar to the above, in order to make an effective diagnosis, it is necessary to use specific clinical tools, such as the Ghent criteria, to distinguish diagnoses; where the agreement of clinical findings involving "major" and "minor" manifestations in different organ systems is made (BARRIL; ANDRADE; BARBOSA, 2020). The functional capacity of its carriers is reduced, due to its peculiarities and multisystemic manifestations (LIMA et al., 2018), these become more expressive with age, as it is usually the consequence of an altered tissue resistance ((JONDEAU; MICHEL; BOILEAU, 2011).

The treatment of Marfan Syndrome is symptomatic, since there is no cure for the disease. The aim is to prevent and/or repair anomalies before more serious complications arise. Concomitant to the treatment process, it is necessary for patients to have good lifestyle habits, such as a balanced diet, physical exercise, regular sleep, cessation of smoking and alcoholism, among others. That said, when patients are placed under integrated and specialized care in all relevant areas, the syndrome can be effectively managed (BARRIL; ANDRADE; BARBOSA, 2020).

CONCLUSION

Marfan Syndrome is a rare pathology, of autosomal dominant origin, due to variable gene expression. Due to the rarity and the lack of literature, management is difficult and uncertain, in addition, the need for an interdisciplinary approach for early diagnosis is essential, in order to improve the prognosis. The wide clinical spectrum in which the disease can manifest itself often makes detection difficult, thus, the analogy to specific exams becomes fatuous for the responsible professional team, because with a greater network of information, the closer is the identification of the case. It is necessary, in addition to the above mentioned, a prosperous clinical experience and a wide laboratory investigation, see tests and genetic analyzes when available. Efforts must be made to treat patients homogeneously and comprehensively, and new studies are needed to improve prognosis and outcomes. This path, therefore, proved to be the closest to the quick finding, evolution in therapies and decline in morbidity and mortality.

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