

Marfan's Syndrome: General Informations and Odontologic Manifestations

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Abstract

Marfan syndrome (MS) is a multisystemic, inherited disorder of the connective tissue. It is caused by mutations in the gene FBN1, encoding fibrillin, a major component of microfibrils. Thus, this disturbance causes effects in many systems composed of connective tissue such as skeletal and cardiovascular mainly. The skeletal phenotype of patients with Marfan syndrome is characterized by tall stature, joint hypermobility, ligamentous laxity, protrusion acetabular arms and long legs, disproportionate fingers (arachnodactyly) dolichocephaly, high palate, scoliosis, protrusion (pectus carinatum) or depression (pectus excavatum) of the sternum; decreasing the relationship between the upper and lower third of the skeleton and espondilolistesis. The main cardiovascular manifestations are mitral valve prolapse and aortic dilation, and these increases the risk of dissection and rupture of the aorta and aortic regurgitation. Orofacial characteristics are frequently described and used in the diagnosis of the syndrome. The orofacial defects more prevalent are constriction of the maxilla and high palate, with concomitant dental crowding, posterior cross bite and open bite. The cranium and the face is present Benthic, usually the dolichocephalic and type II malocclusion is often found. The maxillary constriction can influence the increase in nasal resistance, which can cause severe obstructive sleep apnea, which has a high prevalence in These Patients who are respirators mouth often. The looseness of the capsular ligaments and muscles can hyperextensibility contribute to dysfunction and habitual movements or subluxation of the temporomandibular joint. Dental treatment of these patients is mainly focused on the resolution of orthopedic disorders, which include features like dolichocephaly, upper deep palate and occurrence of obstructive apnea. It is important to know the systemic features that accompany the syndrome to enable safe and proper treatment.

Key Words: Marfan syndrome, Connective tissue diseases, Oral manifestations

Introduction

Marfan syndrome (MS) is a multisystemic hereditary connective tissue disorder, occurring worldwide and equally affecting both sexes, manifesting itself mainly by changes in bone arrangement, eyes and cardiovascular system [1-3]. This syndrome is caused by mutations in the FBN1 gene, located on the long arm of chromosome 15q21 encoding fibrillin-1 protein, a major component of microfibrils⁴. The mutation in the gene encoding fibrillin-1 causes decrease in the amount and quality of this glicoproteína [1]. This defect is expressed by a dominant negative effect, namely in heterozygous mutant fibrillin destroys the normal arrangement of microfibrils, possibly by acting with the products of allele normal [4].

Microfibrils have an important role in the formation of elastic fibers, having a support function in some tissues. Moreover, it has been postulated that the normal fibrillin inhibit growth of the long bones and elastic fibers through its tension, so the change caused by MS produces exaggerated bone growth [4].

Incidence is commonly described between 2-3/10,000 individuals [3,5,6]. About 75% of classic Marfan cases are familial and transmitted by autosomal dominant inheritance, which approximately 25% of affected individuals present new mutations, favored by the effect of paternal advanced age [5,6].

In the past, it was assumed that the clinical manifestations were caused only by the dominant negative effect of changes in FBN1. However, the use of a rat model suggested that a limit in reducing FBN1 is necessary and that the dominant negative effect of their mutations alone does not explain the pathogenesis of Marfan syndrome. Recent investigations on

rats have shown that the fibrillin-1 deficiency causes increased activity of transforming growth factor beta (TGF-beta), and that this increase is directly related to some of the most severe manifestations of Marfan syndrome, especially those related with the weakness of aortic wall and appearance of dissecting aneurysm [7].

Clinical Features

The skeletal phenotype of Marfan syndrome patients is characterized by high stature, joint hypermobility, ligamentous laxity, acetabular protrusion, long arms, legs and disproportionately fingers (aracnodactilia), dolichocephaly, deep palate, scoliosis, protrusion (pectus carinatus) or depression (pectus excavatum) of the sternum; decreasing the ratio between the upper and lower tracking following the skeleton; spondylolisthesis, molar hypoplasia, retrognathia and flat feet [1-8]. Marfan syndrome is commonly found in athletes such as basketball and volleyball players, which tend to be tall and arms and legs relatively long [9].

Cardiovascular manifestations are more severe and are responsible for mortality in 70%-95% of cases. The main cardiovascular manifestations are mitral valve prolapse and aortic dilation, and these increases the risk of dissection and rupture of the aorta (the main cause of death), particularly in their ascending branch, which may be associated with aortic regurgitation.

Ocular changes are commonly present (prevalence about 70%) and progressive. The most found characteristic is the subluxation or dislocation of the lens (around 60% of patients with the syndrome). Ocular manifestations may include early

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and severe myopia, flat cornea, iris and ciliary muscle hypoplasia, causing decreased miopse [2,3].

The average life expectancy has increased significantly since 1972, approaching the general population. This is due, at least in part, to the benefits achieved by the cardiovascular surgery and drug therapy with beta-blockers [10].

Diagnosis is primarily based on physical findings. There are three forms of syndrome presentation:

Neonatal Marfan

There are few reported cases, many without historical family [11]. In echocardiography has been detected cardiomegaly with severe tricuspid insufficiency. Evidences at birth are skeletal, skin (long limbs with slender fingers, aged appearance, loose skin, hypotonia, chest changes, micrognathia) and cardiovascular (mitral regurgitation and severe tricuspid, cardiomegaly, aortic dilatation and pulmonary arrhythmia, mitral and tricuspid prolapse, massive ascending aortic aneurysms and descending) changes. Death occurs in hours or days after birth for heart failure.

Children Marfan

Sporadic cases were diagnosed at age 11.4 ± 3.95 years and familial cases at the age of 7.3 ± 5.23 years. The appearance of extracardiac manifestations shows age variation, with arachnodactyly present from birth, feet-plans from 2-3 years, and high-arched palate with 3-4 years of age, for example. Cardiovascular lesions are present in 55% of cases, all asymptomatic, predominating aortic dilatation in 42% of syndromic patients. Manifestations are also associated with delayed walking (probably linked with joint hypermobility), and disorders of learning [4,12].

Classic Marfan

It is the most common and recognized presentation of MS. The latest criteria for diagnosis of the syndrome should be made in accordance with the revised diagnostic criteria, known as the Ghent nosology [13] based on genetic familiar history and failure of various organs and affected systems [1,4]. The major criteria consist are clinical characteristics, including long limbs, scoliosis, pectus carinatum, pectus excavatum, lens subluxation, expansion and/or dissection of the ascending aorta, aortic regurgitation and dural ectasia.

Table 1. Major manifestations of differents types of Marfan's Syndrome.

	Major Manifestations
Neonatal Marfan	Several manifestations in hour or days after birth. Cardiomegaly and severe tricuspid insufficiency
Children Marfan	Severe manifestations under the age of 16 years. Arachmodactyly (present from birth), feet-plans (2-3 years), high-arches palate (3-4 years).
Classic marfan	Major criteria: Long limbs, scoliosis, pectus carinatum or excavatum, lens subluxation, expansion and/or dissection of the ascending thoracic aorta, aortic regurgitation. Minor criteria: Dolichocephaly, retrognathism, mitral valve prolapse, recurrent herrias.

The minor criteria are present in the syndrome and are often seen in the general population, including joint hypermobility,

high palate, dolichocephaly, retrognathism, flat cornea, mitral valve prolapse, dilatation or dissection of the thoracic aorta, spontaneous pneumothorax and recurrent hernias (Table 1). In the presence of non-significant genetic family history are necessary two organs/systems with greater discretion and a commitment of a third organ/system in order to characterize the syndrome. However, in the presence of positive genetic family history, we need an organ/system with greater commitment and the commitment of a second organ / system [1,4].

Oral Manifestations and Dental Treatment

The oral manifestations of Marfan syndrome, although not specific, can be identified during a routine intraoral examination and may present a wide variation of commitment, similar to the ones found in the whole body. Although they are considered minor features for diagnosis of the syndrome, oral changes are important in clinical practice for determining treatment needs to improve the functions of chewing, breathing, phonation and swallowing [1,14].

Orofacial defects are more prevalent, as constriction of the maxilla and deep palate, with concomitant dental crowding and anterior open and posterior cross bite that are important in an orthodontic approach. Those patients are usually dolicocephalic with Angle's type II of malocclusion. The maxillary constriction can influence the increase in nasal resistance, which can cause severe obstructive sleep apnea, prevalent in those patients, usually bucal respirators [15,16]. The looseness of the capsular ligaments and muscles contribute to dysfunction of habitual movements or subluxation of the temporomandibular joint. Developmental abnormalities can also be evident and the most common are supernumerary teeth. Rare cases of dental congenital absence or incomplete development, crown dysplasia, enamel hypoplasia, dentinogenesis imperfecta and multiple odontogenic cysts have also been reported. There is no evidence showing there is more prevalence of tooth decay in patients with this syndrome, while there is disagreement on the propensity to periodontal diseases [1,17] (Table 2).

SM patients have varying degrees of high obstructive respiratory disorders. Cistulli and Sullivan [18] observed higher incidence of snoring and obstructive sleep apnea in patients with the syndrome, in case-control studies. These authors observed increased collapsibility of the upper airways of patients with MS. It is highlighted that the biotype of the syndrome patient - thin, tall, lanky young - differs from the typical patient with obstructive apnea -overweight, with short neck and middle-aged.

Also was observed high frequency of cephalometric changes, such as retraction of the maxilla and mandible, increased mandibular angle and excessive facial height [13]. These changes proved to be still significantly related to high rates of obstructive apnea. They argued, however, that not deeply know the etiology of craniofacial changes of MS, which may be the same derived from genetic modification, as well as growth changes similar to those of patients with chronic nasal obstruction and mouth breathing (dolichocephaly).

Bauss et al. [19] evaluated the prevalence of signs and symptoms of temporomandibular disorders (TMD) through questionnaires, clinical examination and magnetic resonance. There was a prevalence of 51.6% of temporomandibular symptoms, being more described subluxation.

The treatment of patients with Marfan syndrome, do not differ from the treatment of a healthy individual. The identification of patients with MS, as well as the determination of organs and/or compromised systems, prior to dental treatment is important due to the high risk of complications, especially cardiovascular, such as infectious endocarditis.

Table 2. Major Craniofacial features of Marfan Sundrome.

Craniofacial Manifestations or MS
Dolichocephaly
Transverse maxillary deficiency
Upper palate high and deep
Mandibuklar prognathism
Jaw retrognathia
cross bite
Crowding and dental deductions
Narrow teeth
Tempomandibular disorders Subluxations of the mandibular condyle Recurrent dislocation of the jaw

Antibiotic prophylaxis may be required before extractions and placement or removal of orthodontic bands, as well as other invasive procedures to reduce the risk of subsequent bacteremia and endocarditis [20].

Rigorous maintenance of oral hygiene is also highly relevant to minimize the need for scaling and root planing. Marfan syndrome individuals may need orthodontic treatment to correct malocclusion associated to orofacial anomalies. The growth and development of the craniofacial complex tends to highlight facial features of a growing child. Moreover, orthognathic surgery may be indicated in patients with severe abnormalities. Surgical procedures can be performed as long as the proper precautions are taken, see the systemic manifestations of the syndrome [1,20]. The challenge to the orthodontist is to establish a proper relationship of the jaws along with retention and stability.

Conclusion

Marfan syndrome has several systemic manifestations, where the maxillofacial complex changes are as minor criteria that can support diagnosis. Dental treatment of these patients is mainly focused on the resolution of orthopedic disorders, which include features like dolichocephaly, upper deep palate and occurrence of obstructive apnea. It is important to know the systemic features that accompany the syndrome to enable safe and proper treatment.

References

1. Achint Utreja, Carla a. Evans. Marfan Syndrome- An orthodontic perspective. *Angle Orthodontist*. 2009; 79.
2. Robbins, Stanley L. Patologia estrutural e funcional. 2005; 7th ed.
3. Judge and Dietz. Marfan's syndrome. *Lancet*. 2005.
4. Oliva N, Regina Moreno A,M. Isabel Toledo G, Andrea Montecinos Oa, Juan Molina P et.al. Marfan Syndrome. *Revista médica de Chile*. 2006; **134**: 1455-1464.
5. Fusar-Poli P, Klersy C, Stramesi F, Callegari A, Arbustini E, et.al. Determinants of quality of life in Marfans Syndrome. *Psychosomatics*. 2008; **49**: 243-248.
6. Salamanca Gómez, Fábio. Nuevos hallazgos moleculares en el síndrome de Marfan. *Gac. Méd Méx*. 2008; **144**: 349-350.
7. Marque V, Kieffer P, Gayraud B, Lartaud-Idjouadiene I, Ramirez F, et al. Aortic wall mechanics and composition in a transgenic mouse model of Marfan syndrome. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2001; **21**: 1184-1189.
8. Barreto MM, Bressane RC, Menguer RK, Silveira SM, Alberti TZ, et.al. *Síndrome de Marfan*. 2002; 1-74.
9. Ha, Seo JM, Lee SH, Kang JW, Goo HW, et.al. Imaging of Marfan Syndrome: Multisystemic manifestations. *Radiographics*. 2007; **27**: 989-1004.
10. Robinson PN, Godfrey M. The molecular genetics of Marfan syndrome and related microfibrilopathies. *Journal of Medical Genetics*. 2000; **37**: 9-25.
11. Knecht S de, Yntema JL, Hamel BCJ, Cruysberg JRM. Neonatal Marfan syndrome : a case report. *European Journal of Pediatrics*. 1996; **155**: 741-742.
12. Lipscomb KJ, Clayton-Smith J, Harris R. Evolving phenotype of Marfan's Syndrome. *Archives of Disease in Childhood*. 1997; **76**: 41-46.
13. Loeys BL, Dietz HC, Braverman AC, et al. The revised Ghent nosology for the Marfan syndrome. *Journal of Medical Genetics*. 2010; **47**: 476-485.
14. De Paepe A, Devereux RB, Dietz HC, Hennekam RC, Pyeritz RE. Revised Diagnostic Criteria for the Marfan's Syndrome. *American Journal of Medical Genetics*. 1996; **62**: 417-426.
15. Peter A. Cistulli, Glenn N. Richards, Richard G. Palmisano, Gunnar Unger, Michael Berthon-Jones, et al. Influence of Maxillary Constriction on Nasal Resistance and Sleep Apnea Severity in Patients with Marfan's Syndrome. *Chest*. 1996; **110**: 1184-1188.
16. Peter A. Cistulli, Helen Gotsopoulos, Colin E. Sullivan. Relationship between Craniofacial Abnormalities and Sleep-Disordered Breathing in Marfan's Syndrome. *Chest*. 2001; **120**: 1455-1460.
17. Nualart Grollmus, Zacy Carola, Morales Chavez, Mariana Carolina, Silvestre Donat, Francisco Javier. Periodontal disease associated to systemic genetic disorders. *Medicina Oral Patologia Oral y Cirugia Bucal*. 2007; 12.
18. Cistulli, PA. Influence of Maxillary Constriction on Nasal Resistance and Sleep Apnea Severity in Patient's with Marfan's Syndrome. *Chest*. 1996; **110**: 1184-188.
19. Bauss O. et al. Temporomandibular Joint Dysfunction in Marfan Syndrome. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology*. 2004; **97**: 592-598.
20. Baraldi CE, De Paris MF, Wanyce MR. The Marfan syndrome and their dental aspects: case report and literature review. *Rev Fac Odontol Porto Alegre*. 2008; **49**: 36-39.