PERIODONTITIS IN MARFAN SYNDROME: A CASE REPORT
Endodontic-periodontal lesions: from diagnosis to treatment

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RESUMO

A Síndrome de Marfan é uma doença autossômica dominante do tecido conjuntivo, caracterizada por alterações nos sistemas cardiovascular, esquelético e ocular, e que pode aumentar a suscetibilidade à doença periodontal.

Esse relato de caso descreve dados periodontais clínicos, microbiológicos e imunológicos de um paciente de 28 anos, gênero masculino, com diagnóstico clínico de Síndrome de Marfan. Neste caso, as principais alterações estão nos sistemas esquelético e ocular. A principal alteração intraoral é a presença de palato profundo e prognatismo mandibular. No exame clínico periodontal, a média do nível clínico de inserção foi de 2,35 mm e índice de sangramento à sondagem de 30%. O tratamento periodontal foi executado em uma sessão de debridamento e orientação de higiene oral, sob antibioticoterapia profilática. Na reavaliação, o paciente apresentou melhora nos parâmetros clínicos periodontais. O relato de caso apresenta um paciente com alterações leves, que afetam a saúde bucal. Em casos de Síndrome de Marfan, a manutenção da saúde periodontal é essencial para um bom prognóstico da saúde bucal.


INTRODUCTION

Marfan syndrome (MFS1, MIM # 154700) (Mckusick, 2000) is an autosomal dominant systemic disorder of the connective tissue, caused by a mutation of a gene encoding for the glycoprotein fibrillin-1 (FBN1) in chromosome 15q21 with a prevalence of 1 in 5,000 individuals (Dietz, 1991). Fibrillin-1, a component of the extracellular matrix, is essential for biogenesis and maintenance of elastic fibers. The mutation affects the elastics system fibers, which provide elasticity and resistance to expand forces (Shiga et al., 2008). The normal fibrillin-1 binds to Transforming growth factor (TGF)-β, inactivating its activity in extracellular matrix. Recently, it was suggested that mutated fibrillin-1 results in excess activation of TGF-β signaling, which weakens the tissues and may cause the features of Marfan syndrome (Suda et al., 2009). The alteration affects mainly the skeletal, cardiovascular and ocular systems (Dietz, 1991; Mckusick, 2000).

The diagnosis of the syndrome is based on a molecular genetic test and the clinical specific criteria of Ghent Marfan Nosology (Yang et al., 2012). In Marfan syndrome cases the patient is typically tall, has long and thin fingers, and the anterior chest is concave. The laxity of ligaments results in scoliosis, hiperextensibility, ectopia lens and dilatation of ascending aorta. Marfan syndrome has a wide range of clinical expressions (Gao et al., 2010), but the most serious complications are the defects of the aorta (De Coster et al., 2002). The inner layers of the aorta may be ruptured causing bleeding. In addition, some cases of Marfan syndrome are affected by mitral valve prolapsed (Judge et al., 2011).

Furthermore, this genetic disorder may cause structural and cellular defects of the periodontal tissues. The defect of elastic system fibers, such as Fibrillin-1, which are distributed throughout the periodontal ligament, can make the Marfansyndrome patient more susceptible to
periodontal disease (Shiga et al., 2008; Suda et al., 2009). We report here a mild case of Marfan syndrome presenting slight chronic periodontitis; and the clinical, microbiological and immunological parameters before and after periodontal treatment.

**CASE REPORT**

**Clinical Presentation**

A 28 years old male diagnosed with Marfan syndrome since 2008 was referred to periodontal treatment to the Department of Stomatology at the Dental School, of the University of São Paulo. Written and signed informed consent was obtained from the patient for publication of this case report and any accompanying images. According to the rules of the Ethics Committee of the School of Dentistry of the University of São Paulo (FOUSP), ethical clearance is not required for case reports.

The patient was born after a full-term pregnancy to a 36 year old mother. His mother related that his birth weight was around 3.5 kg, and no history of taking any prescriptions during pregnancy. None of his two sisters were affected. The patient showed skeletal involvement, as tall stature (1.74 m, 67 kg) with long and slim limbs and fingers, muscular hypotonia (figure 1), and ocular disorders (glaucoma) since he was born. Hypertension was under control of beta-blocker (Atenolol 25 mg/ day - Medley, Campinas, Brazil). Hypothyroidism was diagnosed two years ago, and he was taking levothyroxine (Levotiroxina sódica 50 mcg/day - Ache, Guarulhos, Brazil). No clinically diagnosed aorta complications were found in the present case.

**Intraoral findings**

The intraoral examination revealed high arched and narrow palate, and malocclusion associated with mandibular prognathism (figure 2). The periodontal examination (Florida Probe System, Florida Probe Corporation – Gainesville, USA) showed 30% bleeding on probing, 31% visible plaque index, and 6% of periodontal sites with probing depths greater than 3.5 mm (see periodontal chart 1 – figure 3), presenting a localized chronic periodontitis with slight severity (Table 1, figures 4 and 5).

**TABLE 1. CLINICAL PARAMETERS OF THE PERIODONTAL SITES BEFORE AND AFTER PERIODONTAL TREATMENT.**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD (mm)</td>
<td>2.38 ± 0.81</td>
<td>2.33 ± 0.73</td>
</tr>
<tr>
<td>CAL (mm)</td>
<td>2.38 ± 0.90</td>
<td>2.24 ± 0.71</td>
</tr>
</tbody>
</table>

SD, standard deviation; PD, probing depth; CAL, clinical attachment level

**Table**: Initial periodontal chart.

**Figure 1.** Extraoral exam. Note slim and long limbs and fingers.

**Figure 2.** Intraoral exam. Note mandibular prognathism, high arched and narrow palate.

**Figure 3.** Initial periodontal chart.
Microbiological analysis

The presence and quantification of periodontal pathogens (Socransky & Haffajee, 2002) – Porphyromonas gingivalis (P. gingivalis), Tannerella forsythia (T. forsythia), Treponema denticola (T. denticola) - were determined by real-time polymerase chain reaction (qPCR). Subgingival plaque was collected from 8 sites, with a sterile paper point #30 (Tanari, São Paulo, Brazil) after supragingival plaque removal. The paper points were stored in a sterile microtube (Axigen, Union City, USA) at -80°C. Before the DNA extraction from the subgingival plaque sample, 200μl of phosphate-buffered saline was added to the microtubes which were kept under agitation during 12 hours. DNA was extracted from all samples using a tissue kit (QiaAmp DNA mini kit, Qiagen, Hilden, Germany) according to manufacturer’s instructions. Primers and probes were selected using a software and based on species-specific highly conserved regions from 16S ribosomal RNA gene of each species evaluated (Table 2). Ten-fold serial dilution (10¹ – 10¹⁰) of positive plasmid controls for the target species were run in triplicate by real-time PCR (7500 Fast PCR System - Applied Biosystems, Foster City, USA) to obtain standard curves. Samples were assayed in triplicate in 20 μl reaction mixture containing 2μl template DNA, 10μl TaqMan Universal Fast PCR master mix (Applied Biosystems, Foster City, USA), 0.5 μl 200-nM forward primer and reverse primer, 0.5 μl 200-nM probe, 6.5 μl sterilized deoxyribonuclease- and ribonuclease-free water. The cycling conditions were: 95°C for 20 seconds, followed by 40 cycles at 95°C for 3 seconds and 60°C for 30 seconds each (Rodrigues et al., 2012).

<table>
<thead>
<tr>
<th>Bacteria species*</th>
<th>Sequences (5'-3')</th>
<th>Strain</th>
<th>Accession numbers</th>
</tr>
</thead>
<tbody>
<tr>
<td>P. gingivalis</td>
<td>ACC TTA CCC GGG ATT GAA ATG</td>
<td>ATCC 49417</td>
<td>AF118634</td>
</tr>
<tr>
<td>Sense</td>
<td>CAA CCA TGC AGC ACC TAC ATA GAA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>anti-sense</td>
<td>ATG ACT GAT GAT GGT GAA AAC CGT CTT CCC TTC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T. denticola</td>
<td>CCG AAT GTG CTC ATT TAC ATA AAG GT</td>
<td>ATCC 33521</td>
<td>AJ277354</td>
</tr>
<tr>
<td>Sense</td>
<td>GAT ACC CAT CGT TGC CTT GGT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>anti-sense</td>
<td>TGA GTA ACG CGT ATG TAA CCT GCC CGC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T. forsythia</td>
<td>AGC GAT GGT AGC AAT ACC TGT C</td>
<td>ATCC 43037</td>
<td>AM039448</td>
</tr>
<tr>
<td>Sense</td>
<td>TTC GCC GGG TTA TCC CTC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>anti-sense</td>
<td>CCG CGA CGT GAA ATG GTA TCC CTC</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Immunological analysis at the gingival crevicular fluid (GCF)

Eight sites with the deepest probing depths were chosen from the patient with Marfansyndrome. First, supragingival plaque was carefully removed, and periodontal sites were isolated. Then, the periopaper strips (Periopaper Collection Strip, Oraflow, Plainview, NY, USA) were introduced one at a time into the gingival sulcus or periodontal pocket and removed after 30 seconds. GCF samples were discarded for further analysis if they were visibly contaminated with blood. The individual volume of GCF samples was determined by a moisture meter (Periotron 6000, IDE Interstate, Amityville, NY, USA) and the strips were stored at -40°C.

In order to determine GCF levels of interleukin (IL)-6, IL-8, tumor necrosis factor (TNF)-α, Matrix metalloproteinases (MMP)-1, MMP-2, MMP-8, MMP-13, hepatocyte growth factor (HGF), and vascular endothelial growth factor (VEGF), samples were assayed in duplicate in a Bio-Plex cytokine assay kit (Human VersaMAP multiplex development system; R&D Systems, Minneapolis, MN) was used. The assay was read on the Bio-Plex suspension array system, and the data were analyzed with the Bio-Plex Manager software, version 4.0.

Quality of life

A Short Form Survey Instrument (SF-36)(Xenouli et al., 2016) was applied in order to evaluate the patient’s own perception of quality of life, in relation to physical health and emotional health.

Case Management

Periodontal treatment was performed in one session and consisted of oral hygiene instructions and scaling and root planning (AAP, 2001) which was performed with prophylactic antibiotic premedication (Wilson et al., 2007), as well as periodontal probing, plaque and crevicular fluid sampling, and endodontic treatment of the first superior left pre-molar. The revaluation was performed 45 days after periodontal treatment (AAP, 2001). The clinical outcomes are presented in periodontal chart 2 (figure 6), which demonstrated an improvement of all clinical parameters.

The microbiological analysis showed lower levels of periodontal pathogens at baseline, and they were reduced after periodontal treatment in only 50% of the periodontal sites (Table 3). P. gingivalis was not identified in any analyzed periodontal site.

<table>
<thead>
<tr>
<th>site</th>
<th>PPD (mm)</th>
<th>CAL (mm)</th>
<th>BOP</th>
<th>T. forsythia before</th>
<th>T. forsythia after</th>
<th>P. gingivalis before</th>
<th>P. gingivalis after</th>
<th>T. denticola before</th>
<th>T. denticola after</th>
</tr>
</thead>
<tbody>
<tr>
<td>16MB</td>
<td>2</td>
<td>2</td>
<td>present</td>
<td>23,93</td>
<td>51,62</td>
<td>0</td>
<td>0</td>
<td>5,05</td>
<td>0</td>
</tr>
<tr>
<td>24MB</td>
<td>5</td>
<td>5</td>
<td>present</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>12MB</td>
<td>2</td>
<td>2</td>
<td>absent</td>
<td>5,97</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>10,65</td>
<td>0</td>
</tr>
<tr>
<td>27MB</td>
<td>2</td>
<td>2</td>
<td>absent</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>26DP</td>
<td>4</td>
<td>4</td>
<td>present</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>47MB</td>
<td>2</td>
<td>1</td>
<td>absent</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>45DB</td>
<td>1</td>
<td>1</td>
<td>present</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>34ML</td>
<td>3</td>
<td>2</td>
<td>present</td>
<td>637,92</td>
<td>1039,8</td>
<td>0</td>
<td>0</td>
<td>435,72</td>
<td>2207,46</td>
</tr>
</tbody>
</table>

M= mesio, B= buccal, D= distal, L= lingual. BOP = bleeding on probing.
The immunological parameters did not show significant differences after periodontal treatment (Table 4). There was a trend, not statistically significant, for increased levels of IL-8, TNF-α, and MMP-2 after periodontal treatment.

In accordance to the applied Short Form Survey Instrument (36-SF) (Xenouli et al., 2016), compared to general population his physical health summary score was considered below average (score 40), and his mental health was about average (score 55). Physically, his pain was considered worse compared to general population, functioning was better than most and performance was slightly worse. Emotionally, his was considered bothered less than most and performance at work was limited less.

**DISCUSSION**

In Marfan syndrome the mutation of the gene encoding for fibrillin-1 generates an alteration in the synthesis of a glycoprotein which is responsible for the formation of the connective tissue matrix, and elastic system fibers.

This case report presents a young man with Marfan syndrome with skeletal and ocular complications. The patient’s worst condition was the visual deficiency, due to glaucoma. This alteration was verified since he was a baby, and was reported to impair his daily life activities. The patient has been followed-up by an ophthalmologist and cardiologist since the diagnosis, five years ago. The cardiologist prescribed a beta-blocker (Atenolol) for continuous use, in order to decrease heart frequency and the force of heart beat. Furthermore, he prescribed antibiotic prophylaxis, with amoxicillin, previous to any dental intervention. Moreover, in accordance to the applied Short Form Survey Instrument (36-SF) (Xenouli et al., 2016), overall his health was a little worse than general population, and his participation in social activities was more limited, but his energy level was higher.

With regards to the intraoral aspect, the major oral manifestation presented was the high arched palate associated to mandibular prognathism, correlated to others features of orthognathic abnormalities (Westling et al., 1998; Straub et al., 2002; Grollmus et al., 2007; Utreja & Evans, 2009; Ganesh et al., 2012). This is a common feature of the syndrome, as well as dental caries. Patients with Marfan syndrome show higher rate of caries, root and pulp abnormality, and gingivitis, when compared with healthy patients (De Coster et al., 2002). The progression of periodontal disease in Marfan syndrome patients seems to be in accordance to presence of bacterial plaque, as a chronic disease. Only one case report showed a patient with severe periodontitis that was associated to other risk factors to periodontal breakdown as cigarette smoking and poor oral hygiene (Straub et al., 2002). Dental mobility is probably due to periodontitis, and not attributed to a primary condition of the syndrome, since the effects of dysfunctions of the elastic system fibers in the periodontal ligament are still obscure (Suda et al., 2009). This observation is correlated to the present case report, which showed supragingival calculus and 31% visible plaque, presenting T. denticola and T. forsythia in 3 of 8 sites analyzed before periodontal treatment and absence of P. gingivalis in all sites before and after treatment.

**TABLE 4. IMMUNOLOGICAL PARAMETERS OF THE PERIODONTAL SITES BEFORE AND AFTER PERIODONTAL TREATMENT (MEAN ± SD)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before</th>
<th>After</th>
<th>P (value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-6 [pg/ml]</td>
<td>0.98 ± 1.23</td>
<td>0.83 ± 0.67</td>
<td>0.84</td>
</tr>
<tr>
<td>IL-8 [pg/ml]</td>
<td>278.81 ± 312.10</td>
<td>474.38 ± 586.91</td>
<td>0.46</td>
</tr>
<tr>
<td>TNF-α [pg/ml]</td>
<td>3.40 ± 2.31</td>
<td>3.96 ± 2.48</td>
<td>0.53</td>
</tr>
<tr>
<td>MMP-1 [pg/ml]</td>
<td>63.63 ± 74.70</td>
<td>37.92 ± 40.22</td>
<td>0.25</td>
</tr>
<tr>
<td>MMP-2 [pg/ml]</td>
<td>89.97 ± 72.31</td>
<td>108.31 ± 24.88</td>
<td>0.38</td>
</tr>
<tr>
<td>MMP-8 [pg/ml]</td>
<td>30055 ± 43953</td>
<td>21097 ± 7170.6</td>
<td>0.84</td>
</tr>
<tr>
<td>MMP-13 [pg/ml]</td>
<td>85.80 ± 54.15</td>
<td>27.33 ± 18.17</td>
<td>0.37</td>
</tr>
<tr>
<td>HGF [pg/ml]</td>
<td>13.12 ± 11.84</td>
<td>8.11 ± 7.24</td>
<td>0.38</td>
</tr>
<tr>
<td>VEGF [pg/ml]</td>
<td>24.86 ± 16.19</td>
<td>34.05 ± 6.72</td>
<td>0.09</td>
</tr>
</tbody>
</table>

SD (standard deviation)
*Statistically different (95% confidence interval)
healthy rats (Suda et al., 2013). Therefore, there is plausibility for increased susceptibility to periodontal disease in Marfan syndrome patients, since the microbial challenge is present. And further, the regulation of MMP-1 may be altered in Marfan patients, as demonstrated in an in vitro study (Gao et al., 2010).

The major attention in the management of this case was the special care that should be taken during periodontal exam, periodontal and endodontic treatment. The cardiologist prescribed antibiotic prophylaxis (2 g of amoxicillin one hour before any intervention), in order to prevent bacteremia. This protocol was in accordance to the guidelines of the Marfan National Foundation American Institution, which provides information and support to Marfan syndrome patients. The patient showed improved clinical periodontal parameters after treatment: gingival index reduced from 30% to 10%. The plaque index did not improve even after the professional hygiene instructions, since the patient presented difficulties of his self-performed mechanical plaque control, probably due to his visual deficiency. High priority in periodontal treatment should be given in Marfan syndrome cases, since their genetic predisposition to heart problems, may be worsened by the inflammation in the periodontal tissues.

Furthermore, serious visual deficiency due to glaucoma has detrimental effects on the quality of life of these patients. In addition to depression, introverted personality and isolation can be reported in Marfan syndrome cases, probably because of the constant challenges in their lives.

CONCLUSION

In conclusion, the progress in diagnosis and therapy of this genetic disorder increase life expectancy and any health preventive actions prevention action should be taken in order to improve the quality of life of Marfan syndrome patients.

ABSTRACT

Marfan syndrome is an autosomal dominant disorder of connective tissue characterized by alteration in cardiovascular, skeletal and ocular system, and may increase the susceptibility of periodontal disease.

This case report describes the clinical, microbiological and immunological periodontal findings in a 28 year old male patient with a clinical diagnosis of Marfan syndrome. The major alterations of the case were in ocular and skeletal system. The major oral alterations were the high arched and narrow palate, and mandibular prognathism. At periodontal examination, an average clinical attachment level loss of 2.35 mm and 30% of bleeding on probing were found. The periodontal treatment
was performed, in one session of periodontal debridement with prophylactic antibiotic premedication and oral hygiene instructions. At the revaluation, the patient showed improved clinical parameters.

This case report presented a patient with mild features of a genetic disorder which affects oral health. The maintenance of periodontal health in Marfan syndrome cases is essential for a favorable prognosis of oral health.

**UNITERMS:** Marfan syndrome, periodontal disease, connective tissue disorder.

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