

# Fragile X Syndrome: Medical Considerations and Stomatological Aspects for Dental Treatment

Cristhiane Olívia Ferreira Do Amaral<sup>1\*</sup>, Nilzete Santana Silva<sup>2</sup>, Alexsander Guedes<sup>3</sup>, Mariana Olívia Ferreira Do Amaral<sup>4</sup>, Eliane Cristina Gava Pizi<sup>5</sup>, Fabiana Gouveia Straioto<sup>6</sup>

<sup>1</sup>Professor, Faculty of Dentistry, University of Oeste Paulista  
Presidente Prudente, State of São Paulo, Brazil

<sup>2</sup>Dentistry participant in the Special Program for Scientific Initiation (PEIC/SPSI), University of Western Sao Paulo  
Presidente Prudente, State of São Paulo, Brazil

<sup>3</sup>Dentistry participant in the Special Program for Scientific Initiation (PEIC/SPSI), University of Western Sao Paulo  
Presidente Prudente, State of São Paulo, Brazil

<sup>4</sup>Graduate student, Medical School, University of West São Paulo  
Presidente Prudente, Sao Paulo, Brazil.

<sup>5</sup>Department of Dentistics, Dental School, University of Western Sao Paulo  
Presidente Prudente, Sao Paulo, Brazil

<sup>6</sup>Department of Prosthodontics and Geriatric Dentistry, Dental School, University of Western Sao Paulo  
Presidente Prudente, Sao Paulo, Brazil

\*Corresponding author's email: [crisamaral \[AT\] unoeste.br](mailto:crisamaral@unoeste.br)

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**ABSTRACT----** *The objective of this study was to carry out a literature review in order to elucidate general and oral physical aspects, behavioral disorders, medical considerations and discuss considerations about the dental approach in individuals with Fragile X Syndrome (FXS) as well as to provide surgeons dentists with greater care clarification towards these patients. A literature review has been carried out in the following databases: Virtual Health Library (VHL) – MEDLINE– PubMed, SciELO and in the Capes database Journals. The descriptors used were: Fragile X Syndrome, Oral Health, Systemic Condition, Behavioral Disorders. The main phenotypic characteristics found in the literature were: prominent ears, elongated face, strabismus, hyperextensible joints, macrorchidism, mitral valve prolapse, seizures. Fragile X Syndrome oral characteristics are: mandibular prognathism, atresic and deep palate, enamel hypoplasia, malocclusion, presence of biofilm due to unestablished hygiene habits, caries, calculus and gingivitis. Cognitive deficit, autism spectrum disorder, anxiety disorder and hyperactivity are behaviors found in FXS which bring difficulties for these patients to undergo a dental approach. The dental surgeon must be up-to-date and aware of the medical and behavioral conditions of FXS individuals and, thus, offer an adequate and safe dental approach. Systemic, behavioral and oral abnormalities require an initial dental treatment planning.*

**Keywords---** Fragile X Syndrome, Oral Health, Systemic Condition, Behavioral Disorders

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## 1. INTRODUCTION

Fragile X syndrome is a genetic disorder (FXS) which causes hereditary mental retardation. It mainly affects men, it presents a characteristic phenotype and it is transmitted mainly by women [1]. The name of this syndrome comes from a narrowing of the distal end of the X chromosome (Xq27.3) that appears in the karyotype of affected individuals, and which was called a “fragile site” [1].

Carriers of this syndrome present, as main physiological and bodily characteristics the presence of prominent ears, elongated face, strabismus, hyperextensible joints, macrorchidism, mitral valve prolapse, seizures, flat feet, muscular

hypotonia, enlarged testicles with post-pubertal age. , in addition to psychological alterations such as learning difficulties, hyperactivity, anxiety, autistic behavior, impaired social interaction and shyness [2-5] . Regarding the oral characteristics of this syndrome, it can be observed the presence of mandibular prognathism, macroglossia , atretic and deep palate , cleft palate, supernumerary teeth, impacted teeth, congenital absence of teeth 6 , enamel hypoplasia, malocclusion, presence of biofilm, caries, calculus and gingivitis and unestablished hygiene habits [5] .

Taking these characteristics into account, the dental surgeon plays a very important role in controlling the prevention and oral health of patients with special needs, keeping parents informed about the importance of oral health 4 . For a correct clinical care and follow-up of these patients, the presence and performance of a specialized multidisciplinary team is essential, in order to provide a life as close as possible to the normal reality [7] . Therefore, professionals must be empowered with a specific degree of knowledge, once it is known that repeated inefficiency during these patients'care is caused by lack of knowledge and preparation of professionals along with inadequate information concerning oral health conditions and dental needs [8] .

These patients make continuous use of controlled drugs, present difficulties in manually removing the dental biofilm as well as inadequate eating habits, which generates a higher prevalence in the development of oral diseases [6] . It is the responsibility of the dental surgeon to carry out an adequate anamnesis, in which the professional will be able to perceive the dental aspects that involve the family, desires and expectations regarding the treatment, as well as any experiences that may not have pleased or traumatized the patient [9]. Therefore, the dental surgeon must have correct training in the care of a patient with fragile X syndrome, as it is common for patients to present systemic diseases that can modify the dental treatment plan, such as heart disease and seizures, also related to behavioral difficulties during clinical care as autistic and hyperactive characteristics. The aim of this manuscript was to carry out a literature review in order to elucidate general physical, oral and behavioral aspects and medical considerations. Furthermore discuss the dental approach in Fragile X Syndrome (FXS) individuals leading to greater dentist care clarification regarding these patients.

## **2. METHODOLOGY**

The present research was developed through documental analysis of bibliographic production obtained from the following databases: Virtual Health Library (VHL), MEDLINE, PubMed , SciELO and from the Capes database Journals Among the search strategies used, the following descriptors were included: Fragile X Syndrome, Oral Health, Systemic Condition, Behavioral Disorders . The article selection criteria were determined according to the objective of the present study. Articles published as: original research, case reports and literature review were included as well as research that addressed topics related to Medicine, systemic condition, dentistry and oral health of Fragile X Syndrome. After analyzing the studies, 30 references were selected from 2010 on.

## **3. LITERATURE REVIEW**

The Fragile X Syndrome (FXS) is one of the main forms of intellectual alterations and autism spectrum disorder, and patients with this syndrome can present serious alterations related to behavior such as hyperactivity, anxiety, impulsivity, seizures in addition to low social development [9] . It is a hereditary disease triggered by the silencing of a gene called FMR1, whose function is to codify the Fragile X Mental Retardation Protein (FMRP), which is involved in the process of RNA metabolism [10] . FMRP plays an important role in gene expression and, as mentioned, regulates the production of RNA messenger in the process of gene translation, related to the transmission of synaptic neural connections [9]. It is believed that the failure in maintaining balance in these processes occurring in the inhibitory and excitatory neuronal circuits may be the origin and explanation of the various clinical exposures of FXS [9] .

The prevalence of this syndrome is controversial in the literature; it is reported by most authors with a prevalence of one in 6,000 to 8,000 women and one in 4,000 men. Other studies have reported a worldwide prevalence of FXS of 1:2000 in men and 1:4000 in women [11,12] . However , Wadell et al., 2013 [12] state that the estimates of the prevalence of the disease are approximately 1:3600 births. The lack of information on this syndrome and the high cost of diagnosing it make it difficult to find the prevalence of FXS in Brazil. There are few studies in the country, in which there is an estimated frequency of 8% of men and 4% of women with mental disabilities having the syndrome [3] .

About 30% of girls and 90% of boys affected by SXF present changes related to behavioral disorders related to the autism spectrum (ASD), in addition, anxiety disorders can be seen in about 70 to 80% of patients with this syndrome. It was also highlighted that about 90% of the children with autism presented developmental delay, and as already mentioned, about 50-60% present autism spectrum disorder [13] .

The physical, systemic and behavioral FXS characteristics are not so specific, therefore, the diagnosis of this pathology is carried out through laboratory tests in order to detect alterations related to the FMRP protein, which, as mentioned, relates with the syndrome etiology and the verification of the main phenotypic characteristics, which may slightly increase the clinical diagnosis so that, later on, the molecular tests of the FMRP protein can be carried out. There are proven alterations

at family levels, such as learning difficulties, intellectual disability, movement disorders and primary ovarian insufficiency, which may be warnings of a protein mutation related to FXS resulting from its family origin [14]. Currently, the test of choice for diagnosing FXS per *American College guidelines of Medical Genetics* are molecular DNA tests, *Southern blot test*, polymerase chain reaction (PCR), or even by the cytogenetic technique [15].

The dental care of these patients is rarely reported in the literature, however Amaral et al report that their dental needs were not well resolved due to the lack of oral hygiene, which are intensified by their salivary characteristics, use of medications, environment and socio-economic condition that trigger oral diseases [3,16].

Patients often present an intellectual deficit, associated with a peculiar profile of cognitive, behavioral and emotional dysfunction. The literature review suggests that when male patients presenting intellectual deficits are observed, the hypothesis of FXS should be considered even when the cause of intellectual deficits is unknown [14].

Characteristics that can compromise dental care must be observed as well as intellectual deficits along with other behavioral characteristics such as ASD, attention deficit hyperactivity disorder and anxiety disorder are associated with the FMR1 gene [17]. Muscular hypotonia and connective tissue dysplasia, which can sometimes cause mitral valve prolapse, are often present, should also be observed [18]. Patients with a family history of intellectual disability and a diagnosis of low intelligence quotient (IQ) of unknown etiology, combined with some of the behavioral characteristics, can also be considered as a SXF suspect [13,18].

Exactly how FXS leads to delayed neuropsychomotor development is not known. In a normal condition, the FMR-1 (*Fragile Mental Retardation 1*) gene, located in the subterminal portion of the long arm of the X chromosome (Xq27.3), produces the FMRP (*Fragile X Mental Retardation - Protein*), this protein is expressed in a variety of tissues, being more abundant in neurons. Individuals affected by SXF present a disorder in the FMR-1 gene conditioned by the increase in the number of unstable CGG trinucleotide repeats (Cytosine-Guanine-Guanine), whose consequence is a low or no production of the FMRP protein. The absence of this protein encoded by this gene determines the FXS phenotype [13].

CGG trinucleotide repetition in the FMR-1 gene vary in the population. According to the number of CGG repeats, the alleles are divided into 4 types: normal stable with 6 to 55 repeats; intermediate or *gray zone* with 41 to 60 repetitions, with the possibility or not of transmitting the instability to its offspring; premutation with 55 to 200 repeats, which are clinically “normal”, are more likely to transmit the expansion to their offspring and are only detected by direct molecular analysis, and may also be associated with other disorders; and complete mutation with more than 200 repetitions, in which individuals present the clinical characteristics of the disorder [19].

Premutation statistics indicate that 1 in 250 women and 1 in 700 men carry the premutation. Due to the great phenotypic variability of patients with FXS, it is estimated that 65% of cases, especially in the pediatric population, have not been diagnosed, even in specialized genetics centers in developed countries [20]. The characteristics of women with a complete mutation are milder, and it is common to find girls with the syndrome, however, they are clinically normal or almost normal, with learning and/or behavioral difficulties being the cause of most consultations, since the intellectual prognosis depends on the percentage of affected cells [21].

The identification of families in which the alleles are segregating in the form of premutation is important for better guidance in genetic counseling, as the premutation can pass through several generations until it becomes a complete mutation and an affected child appears. Carriers of the full mutation are fertile. However, men and women with delayed neuropsychomotor development rarely reproduce, due to their social and cognitive limitations [16].

The difference in phenotype between men and women with FXS is due to the fact that men have only one X chromosome, while women have two X chromosomes. In women, FMRP protein production is maintained at higher levels compared to men due to the presence of the unaffected X chromosome, which results in less damage to neurological development [22].

FXS, the pharmacological treatment under development for fragile X syndrome (FXS) is complicated by a number of biological and behavioral factors. The interaction between the causal relationship between these biological factors and behavioral presentation is unclear, making stratification of patients in clinical trials difficult. The field of FXS treatment research is moving towards pharmacological trials of treatment at the earliest possible age, in an effort to correct deficits in synaptic plasticity in early child development, for early intervention. Furthermore, progress in clinical trials and development of molecular biomarkers are becoming priorities in this field [23].

There is a need to disseminate information about SXF not only to families, mainly to health professionals, as well. The knowledge of the clinical characteristics associated with the syndrome is of great importance for the dental surgeon, in order to guide him in the dental treatment and in the prevention of problems arising from the syndrome [3,16].

#### 4. DISCUSSION

In the current literature there are few considerations about the oral aspects of SXF, therefore, the planning of dental care for this specific disease, **is crucial**. Based on the information presented, it was verified that it is important to disclose information related to the characteristics of SXF, not only for families and for health professionals in general, as well.

As presented, FXS is the main cause of hereditary mental retardation, in addition to being the second genetic cause related to intellectual deficit [18]. Regarding the SXF medical treatment there is a need for continuous monitoring to observe the intellectual development of these patients in relation to their intelligence potential. On the other hand, children with this syndrome and a higher socioeconomic level, have shown a greater capacity for adaptation and behavioral improvement [24].

Numerically, Salceno-Arrelano et al., 2020 [13] demonstrated in their work that more than 90% of children affected by SXF have developmental delay and between 50-60% are diagnosed with ASD, and throughout life, individuals with SXF often display anxious and hyperactive behaviors (ADHD), in addition to hyperphagia and aggression. In the same study, a relationship between SXF, ADHD and ASD was demonstrated, with 2% of the syndromes presenting some of these alterations, being the same regarded as symptoms resulting from SXF. Systemically between 15-20% have seizures, this symptom being the most prevalent in autistic individuals, 30% present obesity, gastrointestinal disorders (such as gastroesophageal reflux) and sleep disorders, as well as strabismus and otitis. Salcedo, also highlighted the presence of a long face (83% more commonly found in adults), macrocephaly (50-81%), prominent ears (75%), joint hypermobility (50-70% in children), macroorchidism. in adolescence in 95%), prominent jaw (80% in adults) and flat feet (29-69%). These data converge with those presented in the literature review of this present work [13].

With reference to dental treatment, it was demonstrated that the use of sedation reduced the burden of anxiety related to the patient and his family, which can provide more comfort and tranquility during the treatment. The dental surgeon who performs the care of patients with special needs may face situations where the dental approach must be adapted to their needs in order to provide adequate and good quality care [20].

The studies also highlighted the importance of identifying and diagnosing SXF carriers, and an early diagnosis is of utmost importance, taking into account the anguish of parents and the importance of initiating intervention and treatment earlier, either for therapeutic or educational means [25,26].

Regarding oral alterations relevant to SXF patients, Amaral et al [3] reported the presence of deep palate, hypoplasia of dental enamel, presence of poor hygiene and, consequently, calculus and dental caries, in addition to mandibular prognathism, malocclusion, gingivitis and macroglossia. Muzzi et al [14], relate the malocclusion present in these individuals as being a result of habits that patients exercise, such as thumb sucking and not being due to a craniofacial alteration, however this same author corroborates the previous one, stating that the presence of a high, arched palate may be a FXS-related peculiarity. In addition to the main alterations already mentioned, this last study verified alterations related to limited mouth opening and excessive presence of choking. Furthermore, it is important to highlight that the drug therapy performed by these patients can present systemic impacts, as well as facial changes, since the drugs used to treat this syndrome can interact with the drugs indicated for dental treatment [14]. Finally, precaution is a must when these patients are submitted to general anesthesia, due to heart problems and joint hypersensitivity that can make it difficult to position the patient during the surgical procedure [3,16].

Concerning the characteristics related to SXF, it is observed the difficulty of dental care of these patients, as they present several behavioral changes such as cognitive deficits, autism, hyperactivity and anxiety, which may require the performance of a multidisciplinary team for better care [3, 27-29]. Because of this, patients who have alterations related to mental development can be considered a high-risk group for the development of dental caries [16]. The prevalence of dental caries in the population affected by SXF was verified, correlating oral health with unsatisfactory salivary parameters, poor oral hygiene, low socioeconomic levels, in addition to the high presence of *S. mutans* bacteria in their saliva [16].

These patients, as reported in this review, have several changes at the systemic level inherent to FXS, making a multidisciplinary approach together with the dental approach indispensable in order to restore their general health [20,26,27,30]. Thus, the dental surgeon must be knowledgeable of this disease. The aim of this work was to demonstrate the most relevant dental and systemic characteristics and dental approach as well regarding the dental care planning. The dentist can refer these patients to the medical doctor who can establish an early diagnosis, limiting the harm to the affected child.

## 5. CONCLUSION

The main phenotypic characteristics found in the literature were: prominent ears, elongated face, strabismus, hyperextensible joints, macroorchidism, mitral valve prolapse, seizures. The oral characteristics in SXF are: mandibular prognathism, atresic and deep palate, enamel hypoplasia, malocclusion, presence of biofilm due to unestablished hygiene habits, caries, calculus and gingivitis. Cognitive deficit, autism spectrum disorder, anxiety disorder and hyperactivity are behaviors found in SXF that make it difficult for these patients to have a dental approach. The dental surgeon must be knowledgeable and aware of the medical and behavioral conditions of individuals with FXS and, thus, provide a proper and safe dental approach. Systemic, behavioral and oral abnormalities require an initial planning for the dental treatment.

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