



## Stomatological aspects in fragile X syndrome cases. Literature review and clinical case presentation

### *Aspectos estomatológicos en el síndrome del X frágil. Revisión de la literatura y presentación de un caso clínico*

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#### ABSTRACT

Fragile X syndrome (FXS) is a genetic anomaly caused by excessive replication in the CGG nucleotide sequence which elicits severe physiological and physical anomalies which impair the child's intellectual development. Moreover, FXS constitutes, after Down's syndrome, the second most frequent genetic cause for mental retardation. Due to epidemiological transition, attention deficit disorders as well as hyperactivity are confused in the clinical diagnosis; this might lead to a situation where FXS might be under-diagnosed. In the realm of stomatological practice, behavior disorders are most important since communication can be considered the cornerstone of behavior management. The present study purports the aim of encouraging the clinician to look further into patients afflicted with mental retardation, TDA and hyperactivity to find FXS since under-diagnosis impairs treatment, is specific and genetic counseling for these patients is of the utmost importance.

**Key words:** Fragile X syndrome, clinical and stomatological characteristics, under-diagnosis.

**Palabras clave:** Síndrome X frágil, características clínicas estomatológicas, subdiagnóstico.

#### RESUMEN

El síndrome de X frágil (SXF) es una anomalía genética causada por la replicación excesiva en la secuencia del nucleótido CGG que ocasiona anomalías físicas y psicológicas importantes, las cuales repercuten en el desarrollo intelectual del niño, además de que es la segunda causa genética más importante de retraso mental después del síndrome de Down; en ocasiones, y debido a la transición epidemiológica los trastornos de déficit de atención así como la hiperactividad, son confusos en el diagnóstico clínico y puede ser que el SXF sea subdiagnosticado. En la práctica estomatológica los trastornos del comportamiento son de suma importancia ya que la piedra angular en el manejo de la conducta es la comunicación. Este trabajo está destinado a estimular al clínico para que busque más en los pacientes con retraso mental, trastorno por déficit de atención (TDA) e hiperactividad para encontrar el SXF, ya que el subdiagnóstico complica tratamiento, el cual es específico y el consejo genético es importante en estos pacientes.

#### INTRODUCTION

Fragile X Chromosome (FXS) or Martin-Bell syndrome is responsible for about a third of all mental retardation cases. This condition encompasses physical, behavioral and cognitive alterations,<sup>1</sup> it generally ranges from moderate to severe; it is linked to the X chromosome in males and a tenth of these cases it is found in females. This condition affects approximately 1 in 2,000 males and 1 in 4,000 females.<sup>2</sup> It is recessively inherited and linked to chromosome X; this indicates that boys will probably be more affected than girls. Both parents must be mutation-carriers for the disease to appear. The affliction is caused by mutation of a gene located at q27.3 of the long arm of X chromosome, with increase in the number of repetitions of the CGG nucleotide sequence. A healthy patient might exhibit 6-54 repetitions, FXS patients exhibit 1,000 to 2,000.<sup>2-4</sup> They produce a fragile or weak area in this chromosome, thus derives the name of the

disease. Another anomaly caused by the FX syndrome is abnormal methylation of the Xq27.3 region, rich in nucleotids of cytidine phosphate guanosine, which block expression of adjacent genes.<sup>2</sup>

#### Clinical characteristics

Affected subjects exhibit mental retardation and in males, a characteristic phenotype (large

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ears, elongated face, prominent lower jaw and post-pubertal macroorchidism). Many patients also present macrocephaly and anomalies of the connective tissue, with joint hyperlaxity, specially finger joints.<sup>5</sup> Expression of these characteristics is variable, the most frequent fact is moderate to severe mental retardation;<sup>6</sup> afflicted subjects suffer fundamental difficulties for mathematical calculations, recent memory and movement coordination. Visual contact is very difficult with these patients.<sup>7</sup> They are hyperactive, especially during childhood, and exhibit behavior and social relations problems, as well as autistic traits.<sup>8</sup>

#### **FXS-related anomalies**

- Macrocephaly
- Macrotia
- Cardiovascular alterations ( mitral valve prolapse)<sup>9</sup>
- Fingerprint anomalies
- Elongated face, large testicles<sup>4,10</sup>
- Intra-oral manifestations which vary in frequency and characteristics
  - Bruxism
  - Prominent jaw (although there are cases presenting Pierre Robin sequence)
  - Vertical facial growth
  - Gingivitis and periodontitis,<sup>5</sup> some authors mention idiopathic gingival hyperplasia related to fragile X<sup>10</sup>

#### **Behavioral manifestations**

In young girls, manifestation can be frequent tantrums, attention deficits, language retardation. These symptoms can be present from the moment the patient is 2 to 3 years of age; nevertheless, behavioral phenotype characteristics, as well as physical phenotype have not been documented in young girls.<sup>11</sup>

Boys are apparently healthy at birth, disease manifestations begin from the first year onwards, they are present with greater intensity as the boy's development advances, and they increase when the child reaches two to four years. The following characteristics are most frequently found:

- Psycho-motor development delay of the child, especially language development.
- In the psychic and behavioral sphere:
- Hyperactive behavior, timidity (aversion to visual contact),<sup>11,12</sup> repetitive speech, learning difficulties, difficulties to relate to other people.

- Tendency to possible autism.
- Connective tissue anomalies with joint hyperlaxity.

#### **Convulsive crises in FXS**

This syndrome is the main hereditary cause of cognitive deterioration and the main monogenetic impairment associated to autism and convulsive crises. These crises resolve after childhood, for this reason it is also known as childhood benign focal epilepsy, also known as Rolandic epilepsy.<sup>13</sup> Subjects thus afflicted exhibit hyperactivity and aggressive behavior in males and timidity and isolation in females.<sup>14</sup>

#### **Behavior management**

Behavior management characteristic traits in these patients are: autism, hyperactivity, sometimes even self-mutilation. Moreover, in rare occasions, there can be FXS children with normal intelligence.<sup>5</sup>

To this date, there is no specific treatment for Fragile X Chromosome Syndrome. Efforts, up to date, target education and training so that afflicted children might perform at the highest possible level. Specific educational approaches have been developed bearing in mind the fact that this disease is common.<sup>9</sup>

Although, to this date, there is no specific remedial treatment, benefits obtained with individualized early stimulation in these children cannot be overlooked. This stimulation is to be performed by a multi-disciplinary team composed of pediatricians, speech therapists, psychologists, physiotherapists, psychopedagogues, stomatologists, among others, which might modify behavior and language problems, enabling thus incorporation of the children into different social activities, and work according to their skills and abilities, securing thus better quality of life both for patients as well as their parents.

#### **CLINICAL CASE PRESENTATION**

9 year old female patient, without pathological history, in a stable familial environment. The patient informed about being afflicted with intermittent, medium-intensity pain, as well as pain elicited during mastication in tooth 64. The patient exhibited caries in various degrees in the rest of teeth.

#### **Clinical examination**

Clinical examination revealed the following: elongated face, copper-colored hair and eyelashes,

hypertelorism, disproportionate ears, wide brow, wide nasal septum, Dennie's lines, lip dryness, angular cheilitis (*Figure 1*). Arms and fingers hyperflexion could also be observed (*Figure 2*). The following could be intra-orally observed: mixed dentition, plaque, caries of varied degrees, anterior tooth crowding, loss of space due to extraction of teeth 74, 84 and 85, as well as oral rehabilitation treatment involving chrome-steel crowns which were perforated due to excursive, compulsive movements of the mandible (bruxism), a lingual arch used as space maintainer, presence of caries. This treatment, as the mother reported, was performed by a pediatric dentist. Horizontal and vertical overbite could equally be observed, as well as transverse collapse of upper and lower jaw and mandibular retrusion (mouth breather).

#### Panoramic X-ray

Radiographic analysis revealed partial anodontia of premolars, supernumerary teeth, tooth resorption due to unsuitable canine eruption guide, presence of a lower space maintainer, crown restorations in primary teeth. Cephalometric analysis revealed mesio-facial

pattern, class III malocclusion due to lower molars, severe skeletal class II due to mandible and palate (*Figure 3*).

#### Treatment area

The aim of the rehabilitating treatment was to withdraw the fixed appliances, eliminate infection foci in the mouth, and correct maxillary discrepancy. The patient was required to simultaneously attend treatment with the otolaryngologist at the final stages of the orthodontics treatment.

#### Cognitive characteristics

The patient exhibited passive behavior. Behavior management technique was tell-show-do with positive reinforcement, sometimes repetition of instructions. The patient, although avoiding direct gaze, was cooperative. Very seldom did she complain of discomfort during operative or extraction procedures. Contrary to other children, in the waiting room she only asked for a toy and remained then almost static, she did not show signs of impatience, did not ask any questions, and sometimes fluttered her hands.



**Figure 1.** Extra oral view. Prominent forehead (macrocephaly) with low nasal bridge, low-implanted ears with syndrome-characteristic prominence, gingival smile and growth with class II tendency.



**Figure 2.**

Hyperlaxity. X Fragile characteristic condition, not as important as in Ehlers Danlos, which must be differentiated from it.

**DISCUSSION**

**Key points to avoid FXS under-diagnosis**

Fragile X syndrome (FXS) is the most frequent cause of monogenetic, familial mental retardation (MR). It shows incidence of 1 in 4,000 males and 1 in 8,000 females. This syndrome is transmitted as a dominant x-linked trait, with incomplete penetrance (80% in males, 30% in females). It is caused by an amplification of the repeated CGG in

the non-transcribed region towards 5' of the FMR1 gene promoter located at the FRAXA locus of the chromosome X, in Xq27,3.<sup>15</sup> Butler et al proposed conducting clinical diagnosis through 15 points, out of which 11 were of stomatological background.<sup>16,17</sup> (Table I). In these patients, a behavioral management must be designed which might allow to establish effective communication with the patient.<sup>18</sup> There are few recorded cases in hospitals and clinics, since very often, these cases are not diagnosed as being FXS.

**CONCLUSIONS**

FXS timely diagnosis is of the utmost importance, since, within epidemiological transition, many patients arriving to the dental office are afflicted with Attention Deficit Disorders and hyperactivity, attributed to current social and cultural changes. Nevertheless, chromosopathies are increasingly becoming more frequent within the realm of pediatric population. It is important to emit a correct diagnosis, since under-diagnosed patients could «pass» for normal children, and therefore, be the subject of prolonged efforts to correct behavioral and physical disorders, which would be deemed to failure, since the reasons for those alterations are not environmental, but genetic. Once the diagnosis has been established, all necessary measures must be adopted in order to perform restorative, orthopedic, and surgical treatments, bearing in mind the fact that prognosis and evolution are guarded, since we are in the presence of a special patient.



**Figure 3.** Intra-oral characteristics. X fragile patients are frequently associated with intra-oral high number of caries, due to poor hygiene and dental malposition caused by craniofacial anomalies with which they are afflicted.

**Table I.** Clinical screening of Dx FXS<sup>16</sup> and stomatological consequences.

Characteristics	Stomatological background	Stomatological considerations
1. Delay of mental psychomotor retardment	Yes	Special management modified position of dental chair
2. Big ears	No	-----
3. Macroorchidism	No	-----
4. Prognathism	Yes	Orthopedic orthodontic treatment
5. Familial history of mental retardation	Yes	Identified in medical history
6. Hyperactivity	Yes	Difficult behavior management
7. Familial history of language delays	Yes	Identified in medical history
8. Articular hyperextension	Yes	TMJ hyperlaxitude
9. Attention deficit	Yes	Difficult behavior management
10. Speech disorders	Yes	Communication difficulties
11. Hand fluterring	No	-----
12. Elongated face	Yes	Vertical growth, dolichocephalic
13. Simian ridge	No	-----
14. Hand biting	Yes	Self-mutilation disorder with teeth
15. Avoids eye contact	Yes	Management in dental chair

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