the Child Dental Patient with

Fragile X syndrome

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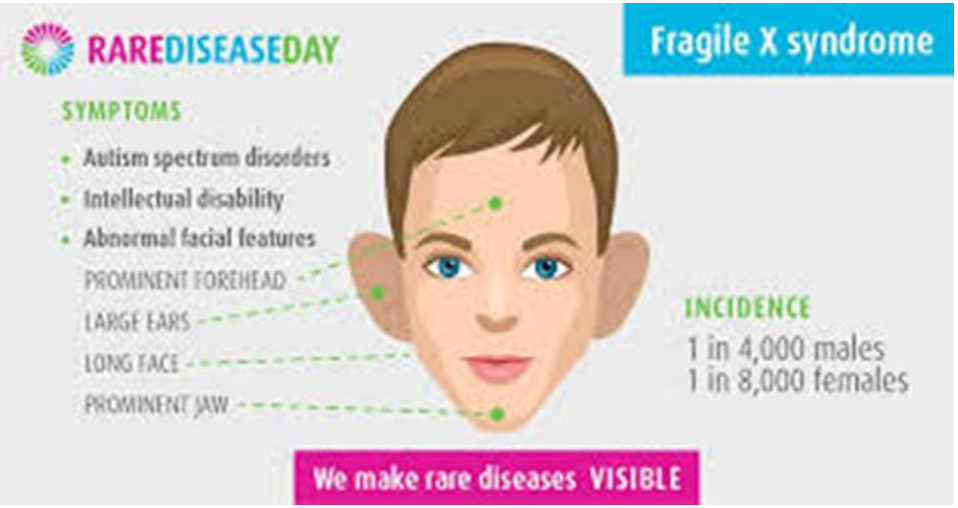
Fragile X syndrome (FXS): Definition and general clinical overview



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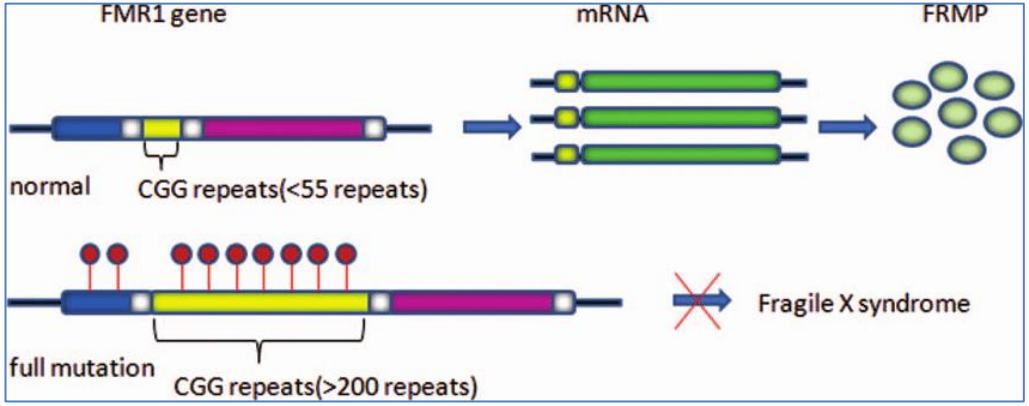
- FXS = **leading inherited form of intellectual disability and autism spectrum disorder.**
- Usually not diagnosed until 8–9 years of age; clinical manifestations are greatly attenuated in childhood.

- FXS may be suspected in both sexes, and includes a **variable clinical phenotype**.
- Patients can present with:
  - severe behavioural alterations, including hyperactivity, impulsivity and anxiety
  - poor language development
  - seizures.

Epidemiology

- FXS may be suspected in both sexes, and includes a variable clinical phenotype.
- A recent meta-analysis (molecular genetic testing of *FMR1*) estimated prevalence of the full mutation as 14:100,000 males.
- The prevalence of females with FXS is presumed to be approximately one half the male prevalence due to reduced penetrance.
- Higher prevalence for the premutation: 345:100,000 males and 677:100,000 females.

Genetics



- The FXS designation is related to a fragile region of the gene, which is located at the distal portion (Xq27.3) of the X-chromosome long arm.
- In 1991, the gene responsible for FXS, *FMR1*, was identified as a trinucleotide repeat disorder.
- The vast majority of cases of fragile X syndrome are caused by the expansion to over 200 copies of a CGG repeat in the 5′-untranslated region of *FMR1* that shuts off transcription of the gene.
- The unstable alleles that give rise to full mutations are called premutations and are associated with phenotypes distinct from FXS.
- FMRP has a central role in gene expression and regulates the translation of potentially hundreds of mRNAs, many of which are involved in the development and maintenance of neuronal synaptic connections.

Genetic diagnosis

- A **checklist of phenotypic criteria** has been established in order to identify individuals with undiagnosed developmental delay who would be appropriate candidates for FXS molecular testing. The **behavioral phenotype** may be helpful in suggesting the diagnosis of FXS.

> *"Any child (male or female) with delay of speech, language, or motor development of unknown etiology should be considered for fragile X testing, especially in the presence of a family history of intellectual disability and a consistent physical and behavioral phenotype, and the absence of structural abnormalities of the brain or other birth defects"*.

- If a positive FXS test is discovered, the proband and family should be referred for **genetic counseling** and cascade testing of family members at risk of carrying a full mutation or permutation.

Proband = the first person in a family to receive genetic counseling and/or testing for suspected hereditary risk.

Medical issues

- Individuals with FXS usually do not have significant medical issues:
  - recurrent otitis media (60%) and recurrent sinusitis are common during childhood
  - joint laxity with hyperextensibility of finger joints and flat feet may be present and usually improve with age
  - gastroesophageal reflux disease occurs in a third of young infants with FXS, and may present with irritability or recurrent emesis
  - mitral valve prolapse
  - sleep disorders
  - seizures and EEG findings consistent with epilepsy are common during childhood (incidence: 13 - 18% in boys, 5% in girls).

FXS - Intellectual disability

- Cognitive deficits:
  - problems with working and short-term memory,
  - executive function,
  - mathematic and visuospatial abilities.

- Average IQ in **adult men** with completely methylated **full mutation**: ~ 40.

- **Females** with **full mutation**:
  - much more mildly affected than males, particularly in terms of cognitive functioning,
  - usually normal/borderline IQ (70% of cases QI<70),
  - higher risk for emotional problems associated with learning disabilities.

- Most individuals with the **premutation**:
  - normal intelligence,
  - males are prone to attentional problems, executive dysfunction, social deficits, and obsessive-compulsive behavior.

Behavioral aspects

- **Behavior is a prominent issue** in males and some females with FXS of all ages.
- **Autism spectrum disorder (ASD)** - in 50%-70% of individuals with FXS; tends to be associated with more severe behavioral issues and an increased rate of seizures.
- Autistic-like features include:
  - hand flapping, hand biting
  - gaze avoidance (poor eye contact)
  - tactile defensiveness
  - perseverative speech
  - hyperarousal to sensory stimuli
  - attention-deficit/hyperactivity disorder (ADHD) symptoms.

Behavioral aspects

- **Anxiety and mood disorders**, hyperactivity, impulsivity, and aggressive behavior can also be present and often disabling.

- Emotional and behavioral characteristics in females with FXS are usually variable. Females with the full mutation are prone to social anxiety, shyness, social avoidance, withdrawal, language deficits, mood lability and depression.

- Anxiety and irritable/aggressive behavior may increase during or after puberty.

Physical features

- Only a subset of affected individuals have typical physical features of FXS, which include:
  - macroorchidism that is apparent just prior to puberty
  - excessive softness and smoothness of the skin
  - widened fingertips
  - connective tissue dysplasia: joint hypermobility and flat feet.
- These connective tissue disorders lead to **cardiac anomalies** such as heart valve alterations, particularly mitral valve prolapse, which gives rise to heart murmurs.

Facial characteristics

- Can include:
  - elongated, narrow face
  - hypoplasia of the middle third of the face
  - mandibular protrusion
  - prominent ears that often project away from the head
  - a large forehead and prominent chin.

FRAXA Research Foundation

- Can be subtle and may become more apparent with age

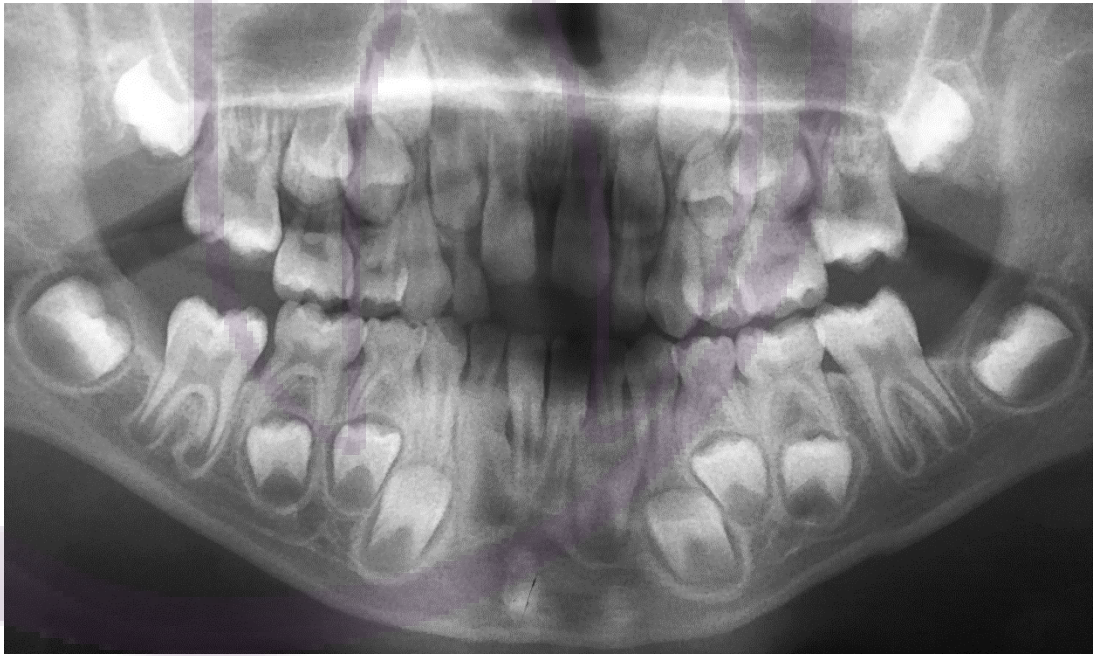
- 25 to 30% of all patients with FXS do not present the typical aspect of the syndrome.

Variable oral characteristics

- The most frequent intraoral manifestations are:
  - ogival palate, cleft palate
  - dental hypomineralization
  - abrasion of the occlusal surfaces and incisal edges
  - root malformation (taurodontism)
  - Macrodontia → severe bone-dental discrepancies
  - recurrent TMJ luxations
  - biofilm, dental caries, dental calculus and gingivitis
  - decreased salivary flow and buffering capacity
- Montes et al (2020):
  - high-arch narrow palate (71%)
  - gag reflex (45.2%)
  - bruxism (22.6%)
  - difficulties to perform oral hygiene
- Controlled drugs (e.g. anticonvulsants, anxiolytics) → hyposalivation → oral diseases

Dental anomalies

- Higher frequency of dental anomalies:
  - supernumerary deciduous teeth (2.83%)
  - rotations (2.31%)
  - oligodontia (1.82%)
  - lacerated roots (1.16%), fused roots (0.99%), and supernumerary root (0.33%) in the permanent teeth
  - Sabbagh-Haddad et al (2016): increase of the mandibular angle, accelerated eruption of upper and lower third molars and lower second molars



X fragile 7-y-old boy with mild taurodontism

Medical treatment

- Cognitive deficits, autism, hyperactivity and anxiety disorders may require **multidisciplinary management**.

- **Psychopharmacologic intervention** should be combined with other supportive strategies to maximize functioning like:
  - speech therapy
  - sensory integration occupational therapy
  - individualized educational plans
  - tailored behavioral interventions.

- In boys with FXS, the most frequently used medications are stimulants, targeted to symptoms of hyperactivity, impulsivity, and distractability.

Dental management

- In case of heart valve malformation, **antibiotic prophylaxis** is advised to prevent bacterial endocarditis before dental treatment or oral surgery.

- Important to take into account the **behavioral disorders** of children with FXS :
  - Patients should become familiarized with the environment of the dental clinic, since they become afraid in the presence of numerous external stimuli (noise, lights etc.)
  - management of anxiety (social phobia and specific phobias, anticipatory anxiety, performance anxiety, and separation anxiety) is necessary
  - the stress of dental treatment should be minimized with anxiolytic premedication (midazolam administration) or nitrous oxide inhalation sedation

- Healthcare providers could be helped by the **Fragile X Family Support Groups**.

Family support groups

EUROPEAN FRAGILE X NETWORK

The aim of the European Fragile X Network is to provide support and information to families affected by fragile X syndrome and it's associated conditions (FXPAC) among them: Fragile X-associated tremor/ataxia syndrome and Fragile X-associated primary ovarian insufficiency.

Inheritance of Fragile X

The FMR1 gene is on the X chromosome. Males have one X and one Y chromosome; females have two X chromosomes. In females with a full mutation, their other, unaffected X often compensates for the FMR1 mutation which frequently results in milder symptoms of fragile X syndrome. In males the Y chromosome cannot compensate for the effects of the fragile X mutation.

- Both males and females can be FMR1 carriers and can pass the premutation on to their children
- Male premutation carriers will pass the premutation on to all their daughters and none of their sons.
- Only premutations carried by women expand to the full mutation that causes fragile X syndrome in their children. Female premutation carriers have a 50 percent chance in each pregnancy of passing the premutation to their children of either gender. The risk of a premutation expanding to a full mutation is dependent on its number of CGG repeats.

Testing for Fragile X

Any individual who has unexplained developmental disabilities, especially when they are associated with speech and language delay or an autism spectrum disorder, should be tested for fragile X. The fragile X test, also called the FMR1 DNA test, is not the same as a chromosome analysis. However a healthcare provider may order a number of tests in a child who exhibits unexplained delays in development. The fragile X test can be arranged by your GP/family doctor, any physician or genetic counsellor. Genetic counselling is recommended for any individual or relative of someone who has a positive test result, or a relative diagnosed with any of the Fragile X-associated disorders. Your GP/family doctor can refer you to a local genetic counsellor. For more information about testing and genetic counselling visit **www.fragilex.org.uk** click on information and then on genetic testing.

About the Fragile X Society

The Fragile X Society was founded in 1990 to provide support and information to fragile X families, to raise awareness of fragile X and to encourage research into all aspects of fragile X.

The Society offers support and information through its family support workers, website, regular newsletters and other publications. It also organises annual conferences and supports research through the participation of its family members in fragile X studies.

For more information on fragile X syndrome and other topics related to fragile X, email: info@fragilex.org.uk or telephone 01371 875100

Special thanks for assistance on this leaflet to:

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Produced in cooperation with the European Fragile X Network, www.fragilex.eu

EUROPEAN FRAGILE X NETWORK

Additional copies of this leaflet available free of charge. Other leaflets in this series which explain FXTAS and FXPOI also available free of charge.

The Fragile X Society

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FXS

FRAGILE X SYNDROME

An Introduction for Families and Healthcare Providers

The Fragile X Society

A Fragile X Overview

Fragile X is associated with changes in the Fragile X gene. The gene (also known by its scientific name of "FMR1") can be normal, but it can also exhibit a "premutation" or "full mutation". When a premutation or full mutation is present, it can result in a Fragile X condition. These include:

- **Fragile X syndrome (FXS):**
  An inherited condition affecting intellectual, behavioural, language and social development. It occurs in both males and females who have a full mutation of the FMR1 gene.
- **Fragile X-associated tremor/ataxia syndrome (FXTAS):**
  An adult onset (over 50 years of age) neurological condition, more common and more severe among males, that causes tremor, memory difficulties and balance problems in those with a premutation of the FMR1 gene. (Both males and females who have a premutation are also referred to as "carriers".)
- **Fragile X-associated primary ovarian insufficiency (FXPOI):**
  A condition affecting ovarian function that can lead to infertility and early menopause. It occurs in some female carriers, who have a premutation of the FMR1 gene.

The FMR1 Gene

The FMR1 gene can undergo changes which cause these fragile X conditions. These changes affect a pattern of DNA called CGG repeats. Typically, the FMR1 gene has up to about 54 CGG repeats. A premutation in the FMR1 gene results in approximately 60–200 CGG repeats, and a full mutation in more than 200 CGG repeats.

www.fragilex.org.uk

Characteristics of Fragile X syndrome

The following physical, cognitive and behavioural characteristics of fragile X syndrome are usually more evident in males, but females can also demonstrate a range of features.

Physical features may include:

- Large/protruding ears, long face, soft skin
- Flexible joints – particularly fingers, wrists, elbows
- Low muscle tone
- Flat feet
- Large testicles (at puberty)
- Seizure disorder (epilepsy)

Behavioural, intellectual and social characteristics may include:

TODDLERS/CHILDREN

- Learning disabilities
- Speech and language delay and continuing difficulties
- Motor delay (late crawling, walking, toileting)
- Tactile defensiveness and sensory overload (high sensitivity to fabrics/clothing, loud noises, crowds, food textures and tastes, etc.)
- Overactivity, impulsivity, poor concentration/ short attention span
- Autistic-like features including dislike of eye contact, difficulty relating to other people, anxiety in social situations, insistence on familiar routines, hand flapping or hand biting
- Dislike of transitions

ADOLESCENTS/ADULTS

Extra difficulties arising in adolescents and adults may include:

- Managing independent living skills such as independent travel and using money
- Making and sustaining friendships

FEMALES

with mild or no learning disabilities may show:

- Concentration problems and particular difficulties with maths
- Social, emotional and communication difficulties related to extreme shyness and anxiety in social situations
- Oversensitivity to perceived rejection or criticism.

Their problems and difficulties need to be acknowledged so that appropriate support can be offered. Otherwise repeated failure to achieve may further increase their social anxiety and low self-esteem.

Interventions and Treatments

Research and clinical experience have shown that children with fragile X may benefit from the following treatments and interventions:

- Early intervention e.g. home based teaching schemes like portage and special needs nurseries
- Speech and language therapy, physiotherapy and occupational therapy, particularly sensory integration therapy
- Behavioural therapies
- Special education (though many children with fragile X are able to be "fully included" in an age-appropriate classroom)
- Medications for symptom-specific issues such as anxiety, ADHD, seizures, etc.

Adolescents and adults with fragile X also benefit from educational opportunities that help them acquire appropriate life skills. These programmes can begin in secondary school and extend into adulthood, and should include education and guidance in matters of employment, social activity, recreation, independent living, and sexuality.