

Fragile X syndrome: a case of mental retardation

By

Dr Muhammad Arshad

Hawkes Bay District Hospital Hastings

&

Professor Michael Fitzgerald

Henry Marsh Professor of child and adolescent psychiatry

Trinity College Dublin

"Our wealth of research strategies and technologies may soon lead to new forms of therapy and medication. Someday we may be able to prevent the mental retardation and other symptoms of Fragile X." Dr Watson (Noble prize winner 1928-)

History

Fragile X syndrome (FXS) or Martin-Bell syndrome was mentioned by Martin and Bell (1943) as the second most common X-linked form of mental retardation, and the commonest cause of autism or "autistic-like" behaviours. Herbert Lubs (1969) developed the Fragile X chromosomal test and 'Fragile site' term was coined by Frederick Hecht (1970), while Fragile X mental retardation-1-gene (FMR-1) was identified in 1991.

Prevalence

FXS is identified in each ethnic group and socioeconomic class. It is present in 1:4000 males and 1:6000 females with full mutation for Fragile X. Around 1:800 males and 1:260 females are carriers of the Fragile X premutation.

Epidemiology

Genes are made up of various lengths of DNA, which contains four chemicals: adenine (A), guanine (G), cytosine (C), and thymine (T). The gene for FXS is carried on the X chromosome and both parents can pass on the mutated gene to their children. A father with Fragile X gene will only pass it to his daughters. If the father has the altered gene on his X chromosome, but the mother's X chromosomes are normal, all of the couple's daughters would have the altered gene for Fragile X, while none of their sons would have the mutated gene.

FXS is caused by a mutation in FMR-1 gene on the X chromosome. This gene appears in three forms that are defined by the number of repeats of a pattern of DNA called CGG repeats. (Table 1)

Table 1: FMR-1 gene	Repeats of CGG
Normal gene	6-55
Permutation gene	60-200

Full mutation/FXS	>200
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Normally, FMR-1 gene produces an important protein called fragile X mental retardation protein (FMRP). Methylation of FMR1 gene in chromosome band Xq27.3 results in constriction of the X chromosome which appears fragile under microscope. When the gene is turned off, the individual does not make FMRP and the lack of this specific protein causes fragile X syndrome.

Characteristics

These fall into these categories:

Physical appearance

- Children have very soft, velvety skin
- Broad forehead, long face, long wide ears and larger head than other children
- Macroorchidism (Enlarged Testicles), twice the size of typical males.
- Prognathism, hypertelorism, high arched palate, blue eyes, thickened nasal bridge

Connective tissue

1. Double-jointedness with hyperextension of fingers or thumbs.
2. Recurrent otitis media due to floppy eustachian tube
3. Mitral valve prolapse murmur.
4. Cutis verticis gyrate as a result of thickening of the scalp skin.
5. Flat feet
6. Single palmar /simian crease or Sydney line
7. Recurrent hernia

Social behaviour

- Poor eye contact, shyness
- Hand flapping
- Social anxiety
- Interpersonal relationship difficulties, unable to adjust in new situations
- Temper tantrums, aggressive behaviour (Hagerman 2001)
- Distractibility, impulsivity, and short attention span
- Repetitive behaviour: rocking back and forth or biting themselves

Speech and language

1. Don't talk till 6-8 years of age
2. Mild stutter to severe communication problems
3. Difficulty in receiving and processing spoken information in social contexts.

Intelligence and learning

Impaired intellectual functioning affects their ability to think, reason, and learn. They have good memories for pictures and visual patterns but their main weaknesses are in thinking about abstract ideas, organizing information, planning ahead, and solving problems.

Cognitions

Up to 80% of males with FXS show mild to severe mental retardation. Persons with FXS can achieve more than would be expected based upon their IQ score.

Sensations

Infants with FXS may have bottle feeding problem, as the feel of the nipple upsets them and a touch, brief tickle, texture of clothes against the skin or hug may be overwhelming. About 90% of boys with FXS have reported sensory defensiveness and are easily distracted by slight sounds.

An intention tremor, short-term memory loss, Parkinson's-like symptoms, lower limb weakness, and impaired planning skills may progress slowly over years which may be misdiagnosed as Parkinson's disease.

Investigations

Prenatal testing Amniocentesis or chorionic villus sampling may contain large number of CGG repeats to diagnose FXS.

Tests are performed on blood, hair root and buccal mucosa. *DNA molecular tests* are the most accurate which count the number of CGG repeats in the *FMRI* gene and FXS is confirmed by:

- Southern Blot studies
- Polymerase Chain Reaction

Protein test is useful for screening large groups of people for Fragile X.

Differential diagnosis

Mental retardation, Autism, ADHD/ADD, *Cardiac murmurs, Seizures, Premature Ovarian Failure, Fragile X-associated tremor ataxia syndrome*

Treatment

There is no cure for FXS but these interventions can improve a child's quality of life.

Advice to carers

- Provide consistent daily routine in a safe quiet place.

- Use visual signs and interactive educational techniques
- Teach names of clothing and dressing skills
- Encourage the child to be active and move around.

Educational Options

Individualized Education Plan should be prepared based on child's needs/abilities and are evaluated regularly.

1. Full inclusion in a regular classroom with an aide
2. Inclusion with "pull-out" services from the regular classroom and some time in small-group
3. Full-time, special education classroom

Speech therapy to improve pronunciation of words and sentences.

Occupational therapy to adjust conditions to suit a person's needs.

Physical therapy to improve motor control, posture and balance.

Behaviour therapy to minimize symptoms, modify behaviour and teach ways to calm down.

Medication

FXS has no medical cure but various symptoms are treated with drugs as in table 2:

Table 2: Symptoms	Medications
Seizure Mood instability	Carbamazepine, Valproic acid, Lithium, Gabapentin, Lamotrigine, Topiramate, Phenobarbital, primidone, And Phenytoin
ADHD	Methylphenidate, dexamethamphetamine, Clonidine
Aggression Obsessive-compulsive disorder	Fluoxetine, Sertraline, Risperidone, Olanzapine
Sleep disturbances	Melatonin

Future

Gene repair, gene reactivation, and gene therapy may induce certain brain chemicals to repair defective *FMR1* gene or prevent or reverse methylation. Protein replacement (FMRP) may be available in pill or injection form to relieve symptoms of FXS. Fragile X at this time.

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