Fragile X Syndrome

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Introduction

Background

Fragile X syndrome, also termed Martin-Bell syndrome or marker X syndrome, is the most common cause of inherited mental retardation and is the second most common cause of genetically associated mental deficiencies after trisomy 21. In 1943, Martin and Bell investigated a family with multiple male members who had mental retardation.[1] They were able to link the cognitive disorders to an unidentified mode of X-linked inheritance. In 1969, Lubs discovered excessive genetic material that extended beyond the long arm of the X chromosome in affected males and in their unaffected female relatives.[2] These results were impossible to reproduce until the importance of the folate-deficient thymidine-deficient medium, which was used in the initial studies to culture lymphocytes, was realized.

Since the 1960s and early 1970s, progress toward mapping the gene has been steady and rewarding, and the precise genetic defect that causes fragile X syndrome has been characterized. Advances in molecular genetics have provided reliable diagnostic testing. Clinically, patients with fragile X syndrome have an array of physical, cognitive, and neurobehavioral features.

Pathophysiology

Cognitive, behavioral, and neuropsychological difficulties characterize the syndrome. These signs are especially important in alerting physicians, parents, and teachers to deficits exhibited by preschool-aged children and elementary school–aged children. This group represents the age at which the diagnosis of fragile X syndrome is often made or considered.

Problems include mild-to-moderate autisticlike behavior (most notably, hand flapping and avoidance of eye contact), shyness, sensory integration difficulties, attention deficits, hyperactivity, impulsivity, attention deficit disorder (ADD), attention deficit hyperactivity disorder (ADHD), depressed affect, anxiety, mental retardation (intelligence quotient [IQ] is typically 35-70), mathematical learning disabilities,[3,4] aggressive tendencies, deficiency in abstract thinking, developmental delays after reaching early milestones (especially speech and language delays), and decreasing IQ with increasing age.

The wide range of these abnormalities is partially related to each individual's environment, maternal psychopathology, and available educational and therapeutic opportunities, especially in affected males. Patients with high-functioning home environments and appropriate education services demonstrate higher IQs and improved behavioral outcomes.

In addition, physical signs are associated with fragile X syndrome; however, these signs are more obvious during adolescence or after puberty and rarely result in disabilities. In addition to the cognitive, behavioral, and neuropsychological findings, the organ systems most frequently involved include the craniofacial, genital, and musculoskeletal systems.

Fragile X-associated tremor/ataxia syndrome (FXTAS) has been reported in 33-40% of men older than 50 years and, less frequently (4-8%), in older women with premutations in the fragile X mental retardation (*FMR1*) gene. Full

mutations of this gene result in fragile X syndrome. Clinical features of FXTAS include cerebellar ataxia, neuropathy, autonomic dysfunction, severe intention tremor, and other signs of neurodegeneration, such as brain atrophy, memory loss and dementia, anxiety, and irritability. Premature ovarian failure is reported in 25% of women with premutations; this represents a 30-fold increase compared with the general population. Recent associations between women with premutations and autoimmune diseases (hypothyroidism and fibromyalgia) have been reported.

Frequency

United States

Conservative estimates report that fragile X syndrome affects approximately 1 in 4000 males and 1 in 8000 females. The prevalence of female carrier status has been estimated to be as high as 1 in 130-250 population; the prevalence of male carrier status is estimated to be 1 in 250-800 population. As many as 10% of cases of previously undiagnosed mental retardation in males and 3% of cases of previously undiagnosed mental retardation in females are attributed to fragile X syndrome.

International

Exact frequency is unknown. However, data collected from England and Australia are comparable to data from the United States.

Mortality/Morbidity

Aside from the morbidity associated with mental retardation and cognitive, behavioral, and neuropsychological problems, the morbidity and mortality associated with fragile X syndrome are unremarkable. Life span is generally unaffected by the disorder.

Race

Fragile X syndrome has been described in all racial and ethnic groups. The overall frequency in other countries is slightly lower than in the United States. Whether this is related to racial or ethnic diversity or to diagnostic technology is unclear.

Sex

Females carry the gene abnormality 2-4 times more often than males; however, only about one third of females who carry the abnormal gene demonstrate decreased intelligence. Females with the disorder are more likely to have less impairment and less obvious physical characteristics. Males with the disorder are more likely to be sensitive to environmental factors.

The pattern of inheritance most closely resembles X-linked dominance with variable penetrance. Occasionally, females are severely affected because of the complex genetics of the disorder.

Age

Fragile X syndrome is an inherited disorder and is present at birth.

If the mental retardation is discovered during a prenatal or family history, diagnosis is typically made at a younger age. If the physician is intimately acquainted with the patient's family, providers may be alerted to possible maternal carrier states in mothers who display cognitive impairment. Therefore, developmental delays in children are appreciated earlier.

As patients complete puberty, the characteristic craniofacial features, in addition to the cognitive, behavioral, and

neuropsychological disabilities, alert physicians to the possibility of a genetic disorder.

Despite provider education and fragile X syndrome advocates, the average age of diagnosis for males (35-37 mo) and fully-mutated females (41.6 mo) remained unchanged between 2001 and 2007.[5]

Clinical

History

Significant family, developmental, cognitive, and neuropsychological histories are keys to diagnosis. Unusual musculoskeletal anomalies, feeding difficulties, and recurrent nonspecific medical problems are infrequently reported.

- Family history
  - Screening and diagnosis in utero or during infancy is usually the result of a family history that features multiple male relatives with mental retardation.
  - Other clues to the diagnosis include a mother with learning disabilities, mental retardation, or both or family members with ataxia and tremors.
  - Female infertility secondary to premature ovarian failure and increased rates of dizygotic twinning have recently been discovered to be more common in fragile X carriers and may provide another clue to the diagnosis.
- Developmental history
  - During infancy, developmental milestones are achieved as expected or are slightly delayed.
  - However, after the first year of life, delays in speech and language are notable, and fine motor skills are impaired.
  - As the patient matures, perseveration and echolalia may dominate speech patterns. Expressive language ability, short-term memory, and attempts at problem solving are significantly impaired.
- Cognitive history
  - Intelligence quotient (IQ) frequently indicates mild-to-severe mental retardation (20-70). Females and less-affected males may have IQs that approach 80.
  - IQ may be higher in childhood than in adulthood because of slowing mental development and difficulties with IQ test taking rather than loss of intellect.
  - IQ in patients with premutations can be normal or slightly decreased.
- Neuropsychological history
  - Patients have many neuropsychological features, including depression and anxiety.
  - Autisticlike behavior (especially poor eye contact and hand biting or hand flapping) is present in 16-30% of patients with fragile X syndrome. However, even patients with autisticlike behavior may have social conversation abilities. Molecular investigation for fragile X syndrome is the single laboratory test proven to aid in definitively diagnosing infantile autism.
  - Universal behavioral features of males with fragile X syndrome are similar to those observed in patients with attention deficit hyperactivity disorder (ADHD), including aggressive tendencies and attention deficits.
  - Approximately 20% of male patients and 5% of female patients have a seizure disorder, with nearly one

half of those having persistent seizures that require anticonvulsant therapy. The onset of seizures is typically at age 6-24 months. The seizure type most often diagnosed is complex partial seizure. Additionally, simple febrile partial seizures and generalized tonic-clonic seizures may be present.

- Many children have difficulty when routines are altered.
- Some people with fragile X syndrome display features of obsessive-compulsive disorder, sensory integration disorder, or both.

- Musculoskeletal features: Features include pes planus, pectus excavatum, joint laxity, scoliosis, and joint dislocation.
- Feeding difficulties: Affected individuals may manifest symptoms of reflux, vomiting, or both and, rarely, failure to gain weight during infancy and childhood. A minority of patients with fragile X syndrome demonstrate a Prader-Willi phenotype, which includes obesity due to severe hyperphagia.
- Recurrent nonspecific medical problems
  - Patients may have recurrent sinusitis, otitis media, and decreased visual acuity.
  - During the history taking, ask about apnea.[6]

Physical

The phenotype of fragile X syndrome is difficult to diagnose in prepubertal children. Most physical examination findings are notable only after onset of puberty.

- Growth
  - Childhood growth is marked by an early growth spurt. However, adult height is often average or slightly below average.
  - A study by Lachiewicz et al (2000) reported 3 statistically significant phenotypic characteristics of young males with fragile X syndrome compared with young males with other developmental delays.[7] These characteristics included the presence of a hallucal crease (a single crease between the first and second toes), sensitivity to touch, and the inability to touch the tongue to the lips.
- Craniofacial: Adolescent and adult patients have a long, thin face with prominent ears, facial asymmetry, a head circumference higher than the 50th percentile, and a prominent forehead and jaw.
- Mouth: The mouth has dental overcrowding and a high-arched palate.
- Ears: Ears are typically large and may protrude.
- Eyes: Strabismus is frequently noted.
- Extremities: Hands and feet manifest nonspecific findings, including hyperextensible finger joints, hand calluses, double-jointed thumbs, a single palmar crease, and pes planus.
- Back and chest: Pectus excavatum and scoliosis are frequent findings.
- Genitals: Macroorchidism is universal in adult males. In unaffected males, average testicular volume is 17 mL; in patients with fragile X syndrome, testicular volume is more than 25 mL and can be as high as 120 mL.
- Cardiac: A heart murmur or click consistent with mitral valve prolapse is often auscultated and requires

consultation with a cardiologist.

Causes

The genetic defect is dynamic and lies at the distal end of the long arm of the X chromosome. Careful examination of the karyotype of affected individuals' lymphocytes, cultured in a folate-depleted and thymidine-depleted medium, reveals a constriction followed by a thin strand of genetic material that extends beyond the long arm at the highly conserved band Xq27.3. This constriction and thin strand produce the appearance of a fragile portion of the X chromosome, leading to the term fragile X.

- The function of the band Xq27.3, which is also termed the fragile X mental retardation-1 (*FMR1*) gene, is to synthesize fragile X mental retardation protein (FMRP), a regulatory protein that binds messenger RNA (mRNA) in neurons and dendrites.[8] In patients with a full mutation in the *FMR1* gene, FMRP is not manufactured because of hypermethylation of *FMR1*, and brain development is impaired primarily because of abnormal synapse connections. Additionally, mutations in the *FMR1* gene lead to excessive activity of the metabotropic glutamate receptor 5 (mGluR5), which results in many fragile X syndrome symptoms. FMRP is present in other tissues; however, its role is less understood.
- Once identified and sequenced, the gene was discovered to contain a repeating base pair triplet (CGG) expansion, which is responsible for fragile X syndrome.
- Unaffected individuals have 5-54 CGG repeats in the first exon at the 5' end of band Xq27.3. A span of 55-200 repeats is known as a premutation, whereas more than 200 repeats is a full mutation. Full mutation results in hypermethylation of the cysteine bases and restricts protein binding, leading to gene inactivation. Mosaic patterns are common. The number of repeats is unstable from generation to generation, making the pattern of inheritance difficult to predict. In addition, the degree of methylation is directly proportional to the signs and symptoms of fragile X syndrome.
- Males with a full mutation have fragile X syndrome. Mothers of all males with fragile X syndrome have premutation or fragile X syndrome. Males with fragile X syndrome pass a premutation to their daughters because sperm cells are mosaics. Sons are unaffected because they receive the Y chromosome from their fathers.
- Half of females with the full mutation on a single X chromosome are unaffected because of inactivation of the other X chromosome. The other half of females have fragile X syndrome, although with less severe mental retardation than males with the disorder. These affected females can pass the gene to their children.
- Males with a premutation are usually unaffected to mildly affected and transmit the premutation to their daughters. The mutation is stable; thus, the CGG triplets are not increased. Sons of affected males are unaffected because they receive the Y chromosome from their fathers.
- Females with a premutation are usually unaffected to mildly affected. Unlike their male counterparts, the CGG triplets are unstable and increase in size during oogenesis. If the number of repeats exceeds 200 and the oocyte is fertilized, a male child will have fragile X syndrome, and a female child will have a 50% chance of having fragile X syndrome. The number of repeats is directly proportional to the risk of the disorder in an offspring.
- Although most patients with fragile X syndrome have a CGG triplet expansion, few patients have a point mutation in the *FMR1* gene or a deletion of the gene.[9]

Differential Diagnoses

Attention Deficit Hyperactivity Disorder
Ehlers-Danlos Syndrome
Marfan Syndrome
Pervasive Developmental Disorder
Pervasive Developmental Disorder: Autism
Pervasive Developmental Disorder: Rett Syndrome

Other Problems to Be Considered

Learning disabilities
Lujan syndrome

Workup

Imaging Studies

- Radiography of the spine is recommended in patients with fragile X syndrome to evaluate for scoliosis.
- Echocardiography is recommended to exclude mitral valve prolapse.

Other Tests

- Cytogenetics
    - Cytogenetic testing for fragile X syndrome is not as sensitive as molecular testing, with a false-negative result rate of approximately 20%. Thus, DNA testing for fragile X syndrome is recommended.
    - Karyotyping may reveal other chromosomal anomalies, and both a standard karyotype and DNA testing are suggested when a possible diagnosis of fragile X syndrome is considered.
- Molecular genetics: The criterion standard diagnostic test involves molecular genetic techniques. The exact number of CGG triplet repeats can be determined. Southern blot and polymerase chain reaction (PCR) are the 2 methods of genetic analysis that are currently available.
    - Southern blot analysis provides a more accurate estimation of the number of CGG triplet repeats if a full mutation is present (with a large CGG expansion). It can also be used to evaluate the degree of methylation at the CGG repeat site.
    - PCR is faster, requires a minimal sample, and is less expensive than Southern blot analysis. Additionally, PCR more accurately estimates the number of CGG triplet repeats if a premutation is present (with small-to-moderate increases in CGG repeats). Recent success with fluorescent methylation-specific PCR and GeneScan analysis may further expand diagnostic options.
- A comprehensive developmental evaluation by a speech and language therapist, physical therapist, and occupational therapist is recommended to assess weaknesses and to identify areas in which improvement is needed most. As the patient matures, repeat evaluation may be necessary.
- Ophthalmology examinations are required.
- Routine auditory examinations are advised; otolaryngology referral for chronic otitis media and evaluation for pressure equalization (PE) tube placement are recommended.

Treatment

Medical Care

- Workup and diagnosis of fragile X syndrome can be done on an outpatient basis.
- Routine care involves treating the medical problems that these patients commonly experience, including gastroesophageal reflux, sinusitis, and otitis media.
- During infant and early childhood healthcare maintenance visits, focus examination on possible hip dislocations, hernias, and hypotonia.

Consultations

- Genetic specialist
- Speech and language therapist
- Occupational and physical therapist
- Behavioral intervention/modification team: Specific areas of focus include social eye contact and stress reduction training.
- Special education professional: Consultation with a special education professional is appropriate to assess the level of cognitive functioning, attention deficit hyperactivity disorder (ADHD) symptoms, and aggressiveness and to initiate sensory integration therapy for behavior problems.
- Psychology or behavioral specialist: This consultation is important to assist families with methods for decreasing negative behavior. Additionally, some patients with fragile X syndrome benefit from social skills–oriented therapy and individual counseling.
- Neurologist: Consult a neurologist if seizures persist.
- Cardiologist
- Otolaryngologist: Patients with chronic sinusitis and chronic otitis media require an evaluation by an otolaryngologist.
- Ophthalmologist: An ophthalmologic referral is important for patients with strabismus.
- Gastroenterologist
- Orthopedic surgeon
    - An orthopedic surgeon frequently assesses patients for abnormal gait caused by pes planus, which is managed with orthotic inserts or orthopedic shoes.
    - Although scoliosis is rarely severe enough to warrant orthopedic surgical intervention, the degree of scoliosis should be assessed with spinal imaging. Referral to an orthopedic surgeon is required if the curvature is significant.
- Nutritionist: For patients with the Prader-Willi syndrome phenotype, consider referral to a nutritionist. Other consultations include experts in Prader-Willi syndrome to guide an exercise program, to assist with environmental solutions (eg, locking cabinets), and to educate about specific Prader-Willi interventions (Food Security and Red, Yellow, Green Dietary Programs).

Diet

- A special diet is indicated in infants with significant gastroesophageal reflux. In these patients, thickened feeds may decrease the incidence of reflux; otherwise, no special diet is indicated.

Activity

- No limitations of activity are indicated.

Medication

- The results of folic acid supplementation to curb the inattention and aggressiveness in prepubertal males are controversial; thus, folic acid supplementation is currently not the standard of care in fragile X syndrome. No effect has been observed in adults treated with folic acid.
- Trials of medications, such as fenobam, that act as mGluR5 antagonists are underway. Excess mGluR5 signaling occurs when FMRP is decreased or absent. Therefore, downregulation of mGluR5 may improve outcomes in patients with fragile X syndrome. Lithium also inhibits mGluR5 signaling (as well as other pathways) and may benefit patients with fragile X syndrome.

Follow-up

Further Outpatient Care

- Routine outpatient care and immunization schedule are indicated in patients with fragile X syndrome.
- Family counseling assists with behavior modification strategies.

Inpatient & Outpatient Medications

- Stimulants (eg, methylphenidate, dextroamphetamine) have been used in fragile X syndrome patients for attention deficit disorder (ADD) and attention deficit hyperactivity disorder (ADHD) in the doses prescribed for patients with typical ADHD. Responses vary, but 70% of patients experience some improvement in their behavior. For patients younger than 5 years, alpha-adrenergic receptor agonists (clonidine and guanfacine) may be used to improve behavioral difficulties. Clonidine may be preferred in patients with sleep disorders.
- Patients with anxiety may benefit from selective serotonin reuptake inhibitors (SSRIs). Fluoxetine is advised for patients with social anxiety, selective mutism, and autism but should be avoided in patients with impulsivity and other activating symptoms.
- Most patients with fragile X syndrome and seizure disorders are treated with a single antiepileptic medication. Phenobarbital, phenytoin, and gabapentin should be avoided. First-line agents include carbamazepine and valproic acid. Other options for patients who do not respond to or cannot tolerate carbamazepine or valproic acid include lamotrigine, oxcarbazepine, zonisamide, and levetiracetam; however, levetiracetam occasionally worsens irritability and aggression.
- Antireflux, sleep (eg, trazodone, melatonin), and mood-stabilizing medications (risperidone and aripiprazole) are useful in patients with these symptoms.

Complications

- Scoliosis
- Mitral valve prolapse (most frequently encountered cardiac defect)

Prognosis

- Life expectancy is normal.

Patient Education

- Family members should attempt behavior modification techniques and be involved with a counselor to assist with appropriate modes of discipline.
- Adult patients should reside in the least restrictive environment that is safely acceptable to foster independent living.
- Patients should receive special education classes that are appropriate for cognitive ability. Work programs should be sought for patients who are trainable.
- Early childhood intervention for children with significant developmental delays is essential, especially in patients with speech and cognitive delays.
- For more information by mail, send a request to the following address:

  The National Fragile X Foundation
  PO Box 37
  Walnut Creek, CA 94597

- For further information, visit the Fraxa Research Foundation Web site or the National Fragile X Foundation Web site.

Miscellaneous

Special Concerns

- Because fragile X syndrome is underdiagnosed, has a high prevalence, and is inheritable, preconceptual and antenatal molecular genetic screening is encouraged for women.
- Obstetricians and primary care providers should recommend screening in high-risk cases. Additionally, a geneticist, genetic counselor, or both should be available to provide accurate information to families if screening findings are positive for fragile X mutations.
- Southern blot analysis, polymerase chain reaction (PCR), and immunocytochemical testing are used for diagnosing maternal, preimplantation, and fetal premutations; full mutations; and associated proteins.
- Fetal testing involving chorion villus sampling or amniocentesis may be performed and incurs the risks inherent to these procedures.
- Recommending prepregnancy or prenatal fragile X syndrome screening to women with a family history of fragile X syndrome or mental retardation and to women with learning difficulties, mental retardation, or both is advisable. All women who are known carriers of the premutation or full mutation should be offered prenatal testing.

- Genetic counseling is important for women who have premutations and full mutations or who are carrying an affected child.
- Fragile X syndrome testing should be considered for women with premature ovarian failure, for older adults with ataxia or tremor that could be associated with fragile X-associated tremor/ataxia syndrome (FXTAS), and in children with autism, autism-spectrum disorder, or mental retardation.
- Some states are considering adding fragile X syndrome to their newborn screening programs.
- Public awareness about fragile X syndrome is increasing thanks to media attention, including an article in *Time Magazine* on June 26, 2008.

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Keywords

fragile X syndrome, marker X syndrome, Martin-Bell syndrome, retardation, mental retardation, mental deficiency, folate-deficient thymidine-deficient medium, FRAXA, X-linked mental retardation, fragile X-associated tremor/ataxia syndrome, FXTAS, cerebellar ataxia, autonomic dysfunction, severe tremor, neurodegeneration, memory loss, anxiety, irritability, autistic-like behavior, autisticlike behavior, cognitive disorders, neurobehavioral disorders, premature ovarian

failure, attention deficits, depressed affect, aggressive tendencies, abstract thinking deficiency, developmental delays, echolalia, pes planus, pectus excavatum, joint laxity, scoliosis, joint dislocation, recurrent sinusitis, otitis media, decreased visual acuity, apnea, macroorchidism

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