Consensus of the Fragile X Clinical & Research Consortium on Clinical Practices

Physical Problems in Fragile X Syndrome

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Introduction

Fragile X syndrome (FXS) is a medical disorder caused by a mutation in the FMR-1 gene. Its systemic effects are most noticeable in the cognitive behavioral domain, but multiple associated physical problems mostly related to loose connective tissue can occur. These include hypotonia, hyperflexibility, flat feet, recurrent ear infections and mitral valve prolapse. Seizures, precocious puberty and ophthalmic issues can also be present.

At this time there is no definitive specific treatment for these problems. Management is therefore largely empiric and, depending upon the individual, may include drug and/or other modalities but typically involves the combined efforts of a multidisciplinary team including ideally, psychology, developmental and behavioral pediatrics, neurology, speech and occupational therapy, neurology, psychiatry and genetics.

Diagnosis/Recognition

Diagnosis of FXS is the key to management. The disorder should be tested for in every child (male or female) with unexplained intellectual disability as well as in the offspring of premutation and full mutation carrier mothers, and considered for girls with significant processing and behavioral issues.

Following diagnosis, potential problems should be actively investigated and managed accordingly. This evaluation can be carried out systemically as, for example, via the guideline below taken from the Fragile X Healthwatch table, which includes specific recommendations for the following:

- A detailed history, actively enquiring for motor and language delays, autistic symptoms, behavioral profile, characterization of sleep, feeding, seizures, ear infections, dislocations, and in girls, relevant menstrual history.

- A detailed physical exam, specifically check for hypotonia, heart murmur, blood pressure, flexibility, pes planus, joint dislocations, hernias, scoliosis, weight, strabismus/refraction, dentition and, if applicable, signs of puberty.

- Evaluation specifically for speech and hearing; fine motor and sensory integration (occupational therapy evaluation); psychometrics (IQ, behavioral profile including evaluation for anxiety, ADHD and autism when clinically indicated)

Current Treatment Guidelines

- Cognitive deficits: Developmental & Behavioral pediatricians and psychologists should provide a working plan, ideally integrated with the early intervention service or the school's IEP (Individualized Education Program). Speech is typically delayed and speech and language pathology should be involved if there is any deficit, as assisting communication is typically a complex issue. Cognitive services may need to be coordinated with behavioral and sensory recommendations.
- Behavioral issues: Following assessment by the psychologist and occupational therapist, a plan should be devised, again ideally integrated with school services. Additional in-home support may be needed. Not infrequently, pharmacologic intervention is necessary. It should always be provided together with behavior therapy. In general medications for similar mental health concerns used in children without FXS (stimulants, alpha agonists, SSRI's, atypical antipsychotics) are also useful for children with FXS. Medications generally to be avoided include gabapentin (which appears to be unhelpful) and topamax (because of its cognitive dulling effect). A number of other medications which function as mGluR antagonists and may be specifically helpful for individuals with FXS are being currently being evaluated.
- Ear infections: Early referral to an otolaryngologist is recommended, as many children with FXS will need myringotomy tubes. The majority suffer from recurrent ear infections, for which an aggressive approach is recommended.
- Hypotonia: Evaluation and management by physiotherapy is recommended. Ideally, early intervention services will commence in infancy.
- Seizures: Typically these occur post infancy/early childhood and are often complex partial, though all types of seizures can occur. Usually they are readily managed on standard monotherapy, though care should be taken to avoid drugs which cause connective tissue hyperplasia e.g. phenytoin, as this can be disfiguring. EEG abnormalities are more common than frank seizures, and any suspicion of seizure should be evaluated by a neurologist, ideally one with experience in FXS. Medications proven to be helpful include carbamazepine and valproic acid. Good results are also occurring with newer generation AEDs.
- Autism: Applied behavior analysis therapy is recommended, likely provided in conjunction with sensory integration techniques. It is also important to note that gaze aversion is a sensory overstimulating effect in individuals with FXS, rather than a reflection of socially cued indifference.
- Connective Tissue Problems (pes planus, scoliosis, pectus excavatum, hyperflexibility): Orthotic support (and occasionally braces) are often required, as is referral to orthopedics.

- Heart murmur: Mitral valve prolapse occurs at a greater frequency in FXS from late adolescence onwards. However, if there are concerns, an echocardiogram or cardiology evaluation should be undertaken.

Common Q & A

What should I tell my patients?

Fragile X syndrome is a genetic disorder with cognitive/behavioral and systemic effects that are present in varying degrees from one individual to another. There is no cure but there are treatments that can help the symptoms and signs. Life expectancy is in the normal range though affected individuals will typically need life-long support and care. IQ for males is typically in the 50-70 range, but with areas of relative strength. Females are often in the borderline-to-normal IQ range, though some are as affected as males. Novel research treatments are currently under investigation, which may improve the outlook for the future. As the disorder is genetic, it is important to ensure that no other family members are affected or at risk for symptoms related to being a carrier (see FXTAS/FXPOI guidelines - http://www.fragilex.org/fragile-x-associated-disorders/).

What are the expected benefits/side effects of treatment?

An active approach to treatment can ensure that affected individuals will optimize their potential. In addition, affected individuals are often responsive to standard treatments, though as with all people, side effects may have an impact. Given the cognitive/behavioral aspects of the condition, side effects may present primarily as behavioral or atypical changes.

What to do in acute situations?

In general, FXS does not cause acute emergency problems. In rare cases, seizures will require emergency treatment and should be managed in the acute setting as they are with individuals without FXS. More commonly, behaviorally related problems such as aggressive outbursts or impulsive running away will precipitate a crisis situation. In such instances, the child should be taken to a familiar location with a “safe” room. This will usually allow the trauma to recede and the precipitant can be managed in a calmer manner.

Additional Resources

Alanay Y, Unal F, Turanli G, Alikasifoglu M, Alehan D, Akyol U, et al. A multidisciplinary approach to the management of individuals with fragile X syndrome. J.Intellect.Disabil.Res. 2007 Feb;51(Pt 2):151-
http://www.ncbi.nlm.nih.gov/pubmed/17217479

Hagerman RJ, Berry-Kravis E, Kaufmann WE, Ono MY, Tartaglia N, Lachiewicz A, et al. Advances in the treatment of fragile X syndrome. Pediatrics 2009 Jan;123(1):378-390.

www.fragilex.org/wp-content/uploads/2012/10/Hagerman_et_al_2008_TX_of_FXS_peds1.pdf

Fragile X Syndrome Health Watch Table -
http://www.surreyplace.on.ca/Documents/Fragile%20X%20Syndrome.pdf
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Consideration	Recommendation
1. HEENT (Head, Ears, Eyes, Nose, Throat)	
Children: Strabismus, refractive errors, recurrent otitis media and sinusitis are common	• Undertake newborn screening and auditory brainstem response (ABR). Arrange comprehensive ophthalmologic examination by 4 years of age • Visualize tympanic membranes at each visit
Adults: Strabismus, refractive errors are common	• Undertake hearing and vision screening at each visit, with particular attention to hearing loss and myopia
2. Dental	
Children & Adults: High arched palate and dental malocclusion are common	• Initiate annual dental exam
3. Cardiovascular	
Children: Mitral Valve Prolapse (MVP) is uncommon in children (≤10%), but may develop during adolescence	• Auscultate for murmur or click at each visit. If present, do ECG and echocardiogram; refer to cardiologist if indicated
Adults: MVP is common (≤80%); Aortic root dilation usually not progressive. Hypertension may be related to anxiety	• Undertake clinical exam, ECG and echocardiogram with referral to cardiologist as appropriate • Measure BP at each visit but at least annually

4. Respiratory	
Children: Obstructive sleep apnea (OSA) may be due to enlarged adenoids, hypotonia, or connective tissue dysplasia	• Ascertain sleep history for signs of OSA • Do sleep study as appropriate
Adults: Obstructive sleep apnea (OSA) may occur	• Recommendations as for children
5. Gastrointestinal	
Children: In infants, feeding problems are common with recurrent emesis associated with Gastroesophageal Reflux in >30% of infants	• Refer for assessment of gastroesophageal reflux disease (GERD). Thickened feedings and upright positioning may be adequate treatment
6. Genitourinary	
Children: Inguinal hernia is relatively common in males. Macroorchidism generally develops in late childhood/early adolescence. Persistent ureteral reflux may occur	• Assess for inguinal hernia beginning at age 1 year • Macroorchidism can be measured with an orchidometer and reassure parents that it does not require treatment • Evaluate recurrent urinary tract infections (UTI) with cystourethrogram and renal ultrasound and refer to nephrology or urology as needed • Consider renal etiology for persistent hypertension
Adults: Inguinal hernia is relatively common in males. Macroorchidism persists	• Assess periodically for inguinal hernia • Macroorchidism does not require treatment
7. Sexual function	
Adults: Males and females are fertile	• Consider discussion of recurrence risk and reproductive options as a basis for referral to a genetics clinic. Make such a referral even if FXS is only suspected so that molecular testing can be undertaken in person concerned and relevant family members

8. Musculoskeletal	
Children: Hyperextensible joints and pes planus are common. Scoliosis, clubfoot, joint dislocation (particularly congenital hip) may also occur	• Undertake physical exam at birth and then every 4 months • Elicit history of dislocations • Make orthopedics referral as dictated by clinical findings • Consider physiotherapy referral, orthotics
Adults: Hyperextensible joints and pes planus are common. Scoliosis, joint dislocation may also occur	• Assess at regular physical exam • Make orthopedics referral as dictated by clinical findings • Consider physiotherapy referral, orthotics
9. Neurology	
Children: ± 20% have epilepsy (may include generalized tonic-clonic seizures, staring spells, partial motor seizures and temporal lobe seizures)	• Ascertain history of seizures which usually present in early childhood • Arrange EEG if seizures are suspected from medical history • Obtain neurology consult as dictated by clinical findings
Adults: Seizures occasionally persist into adulthood	• Assess for atypical seizures if suspicious symptoms exist or intellectual function decreases • Arrange EEG if seizures are suspected from medical history • Obtain neurology consult as dictated by clinical findings
11. Endocrine	
Children: Precocious puberty may occur	• Include attention in clinical examination to signs of precocious puberty in females. Refer to endocrinologist for consideration of use of gonadotropin agonist to block precocious puberty • Note presence of macroorchidism and reassure parents
Adults:	• Ascertain history with attention to menstruation, anxiety, depression and mood lability. If PMS symptoms are severe enough, consider a serotonin agent to stabilize mood

Author note: This guideline was authored by Jonathan Picker, MD, PhD, and Carol Delahunty, MD, and was and reviewed and edited by consortium members both within and external to its Clinical Practices Committee. It has been approved by and represents the current consensus of the members of the Fragile X Clinical & Research Consortium.

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The Fragile X Clinical & Research Consortium *was founded in 2006 and exists to improve the delivery of clinical services to families impacted by any Fragile X-associated Disorder and to develop a research infrastructure for advancing the development and implementation of new and improved treatments. Please contact the* ***National Fragile X Foundation*** *for more information. (800-688-8765 or www.fragilex.org)*