Fragile X Syndrome: An Update and Review for the Primary Pediatrician

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Summary: Fragile X syndrome (FXS) is the most common inherited cause of mental retardation. Since the initial identification of the responsible gene more than a decade ago, substantial progress has been made in both the clinical aspects of the disorder and its mechanistic basis; hence, it is important for primary care physicians to be familiar with these advances when providing anticipatory guidance. Timely diagnosis allows children to receive early intervention services and families to receive genetic counseling. Here the current state of knowledge is reviewed and a framework is provided for early recognition and diagnosis, along with counseling and treatment implications for the children and family members. Clin Pediatr. 2005;44:371-381

Introduction

Fragile X syndrome (FXS) occurs in both males and females and can cause intellectual and cognitive deficits ranging from subtle learning disabilities and a normal IQ to severe mental retardation and autistic behaviors. In addition to mental impairment, FXS is characterized by a group of symptoms, which may include specific physical features, distinctive behavior patterns, defective speech and language, and cognitive deficits. Appropriate management of individuals with FXS requires multidisciplinary efforts from a geneticist and a developmenta pediatrician, along with individualized educational planning. The primary care physician should be able to recognize the presenting signs and symptoms of FXS, and once the diagnosis is confirmed, be able to serve as a valuable source of support and advocacy for the family.

History

Although we recognize today more than 70 different syndromic forms of X-linked mental retardation (XLMR) and more than 200 nonspecific forms of XLMR,1 the well-established excess of males among the mentally retarded was, for most of the previous century, thought to be due to reasons other than genetic causes. In 1943, Martin and Bell described a large family with 11 mentally retarded males and a few mildly involved females.2 Affected males had clinical features of large ears,
long and narrow face, and enlarged testicles. They believed that this pedigree suggested X-linked inheritance since males were more severely affected than females.

It was not until 1968 that Robert Lehrke, in his PhD dissertation, described genetic aspects of mental retardation and, specifically, X-linked mental retardation. He made the rather startling conclusion that "25–50% of all mental retardation is due to X-linked genes." Lehrke suggested that there are genes on the X chromosome relating to intellectual function that, if mutated, can lead to mental retardation and be transmitted in an X-linked manner.9

One year later, Herb Luborsky described a family with mental retardation over 3 generations, affecting males only. He noted that the X chromosome of the affected males and some carrier females appeared abnormal with "satellites" and called these marker X chromosomes. However, widespread replication of Luborsky's observation was not forthcoming until the 1970s, when Grant Sutherland demonstrated that the cell culture media had to be deficient in folic acid to reproducibly cause expression of the marker X chromosome.5 Since this gap in the metaphase marker X chromosome led to the appearance of the distal chromosomal material barely being held by the remainder of the chromosome, the chromosome observed in this disorder was thought to be "fragile." Hence, the name FXS was used to describe this type of XLMR manifesting a fragile site or marker on the distal long arm of the X chromosome. Until 1991, when the FMR1 gene was cloned, this cytogenetic manifestation of the fragile X site became the diagnostic test for FXS. Indeed, the original Martin and Bell family from 1943 was subsequently found to demonstrate the fragile site at Xq27.3.6

Genetics and Etiology

The diagnosis of FXS was originally made by visualizing the folate-sensitive fragile site at Xq27.3 (FRAXA) induced by culturing the cells in folate-deficient media. This technique, while believed to be reasonably effective in a well-experienced laboratory, still had a high false-positive rate and suffered from being of only limited usefulness for carrier detection. In 1991, Verkerk et al. discovered the gene for FXS, designated FMR1 (fragile X mental retardation-1). This genetic breakthrough revealed that FXS is caused by abnormal expansion of a trinucleotide repeat in the FMR1 gene.

The mutation causing FXS is an expansion of this CGG-trinucleotide repeat, which is inherited in an unstable fashion in fragile X families and displays intergenerational expansions.8 Expansion of CGG repeat results in methylation of the adjacent CpG island, shutting down transcription of the FMR1 gene. Genetically, what distinguishes individuals with the common mutation responsible for FXS from those who have the normal FMR1 gene is the CGG repeat size. Normal individuals have 6–40 CGG repeats, with 30 being the average number. In the general population, the normal number of repeats is typically transmitted from parents to offspring in a stable manner. Carriers of "intermediate" alleles have 41–60 repeats, and "premutation" carriers have 61–200 repeats, although the boundaries are not definite.

Individuals with the full mutation have > 200 CGG repeats, resulting in the absence of the FMR1 protein (FMRP), which is responsible for the symptoms of FXS.8 All males with the full mutation show clinical manifestation of FXS; however, up to 40% of patients with the full mutation are mosaics with a limited number of cells containing variable length full or premutation alleles.9 Premutation carriers are generally unaffected intellectually and behaviorally and do not express the cytogenetic fragile site but may be affected by a neurologic disorder called fragile X-associated tremor/ataxia syndrome (FXTAS) and/or premature ovarian failure.

Direct deoxyribonucleic acid (DNA)-based testing that determines the size of the fragile X CGG repeat is considered diagnostic with 99% sensitivity and 100% specificity.8 These tests are also applicable for prenatal diagnosis in amniotic fluid cells and chorionic villus samples (CVS). Utilizing direct DNA analysis, a very specific piece of DNA within the FMR1 gene is identified. The most widely accepted method for DNA-based testing for the full mutation is the Southern blot. Methylation status is important for distinguishing between borderline premutation and full mutation. It also reveals the degree of methylation of full mutation in males and females. Polymerase chain reaction (PCR) is not commonly utilized since the DNA fragment with the expanded repeat does not amplify and becomes problematic for females and individuals with repeat-size mosaicism. However, PCR analysis can be critical in assigning carrier status.
Principles of X-linked Inheritance

Females have 2 X chromosomes, males have 1 X and 1 Y chromosome. The \textit{FMR-1} gene is located on the X chromosome. All female carriers of fragile X are at risk to have children affected by FXS. A carrier female has a 50\% chance of passing the X chromosome with the fragile X mutation to each of her children, although not all of these children may be affected. Sons of a carrier mother are at risk to inherit the mutation and will, in the majority of cases, be affected by FXS. Since the trinucleotide repeat expands upon transmission from females to their offspring, males with the full mutation inherit their X chromosome with the expanded gene from their carrier mother, and will, in the majority of cases, be affected by FXS.\textsuperscript{10}

In the case of a carrier father, all of his daughters will be carriers since he gives each of his daughters only his X chromosome, and upon transmission from males to females, the trinucleotide repeat changes only slightly in size. All of his sons receive his Y chromosome and are not at risk to be affected by the fragile X mutation.\textsuperscript{10}

In the mid-1980s, it was revealed that 9\% of brothers of carrier males have FXS, 40\% of their grandsons, and 50\% of their great-grandsons have the syndrome. Daughters of carrier males are never affected with the disorder, but their sons can be affected. This complicated pattern of inheritance was known as the "Sherman paradox" in which the brothers of carrier males are less likely to be affected than the sons of their daughters.\textsuperscript{11} The discovery of expansion of CGG triplet repeats located in the 5'-untranslated region of \textit{FMR-1} gene explains the "Sherman paradox." The sex of the parent and the number of CGG repeats influence the likelihood of repeat expansion.

Premutation Males

Males with the premutation form of the gene will pass on the premutation to all their daughters but none to their sons.\textsuperscript{12} Expansion to full mutation has not been observed during male-to-female transmission. The daughters of males with less than 90 repeats may show a small expansion over their father's CGG repeat number, typically remaining within the premutation range. Daughters of males with 80-99 repeats may either show expansion (44\%) or contraction (34\%), and daughters of males with greater than 100 repeats are more likely to contract (67\%). The contraction in these daughters ranges from 2 to 20 CGGs, with a mean of 10, whereas the range of expansions was 2-54, with a mean of 18. All daughters, regardless of CGG repeat contraction, are FXS carriers and are at risk for having FXS offspring.\textsuperscript{12}

Premutation Females

The premutation form in females is unstable across generations. Unlike premutation males, the premutation may expand to a full mutation when a female transmits it to her offspring. The probability of expansion to the full mutation in offspring increases as the repeat size in the mother increases. Female premutation carriers with more than 90 CGG repeats have a high (97.3\%) risk of the gene expanding to the full mutation (>200 repeats). The full mutation occurs in 13.4\% of fragile X offspring from mothers with 56-59 repeats, 20.6\% with mothers with 60-69 repeats, 57.5\% with mothers with 70-79 repeats, and in 72.9\% with mothers with 80-89 repeats.\textsuperscript{12}

Understanding the FXS inheritance pattern is important since the CGG repeat number changes with transmission through generations. For instance, a mother of a boy with FXS is at risk for having other children with FXS. Her unaffected daughter may have the premutation or full mutation form of the gene, which may be subsequently transmitted to the next generation. Although a son may be unaffected, he is still at risk for carrying a fragile X premutation, which all of his daughters would inherit. Although the daughter is a carrier and unaffected, she can still have an affected son with FXS as well as an unaffected carrier son. His daughters would be obligate carriers. Family members must be aware of this inheritance pattern and receive testing to determine if they are carriers. It is important to trace the premutation back as far as possible in previous generations to determine which side of the family is at risk to have affected children, and to monitor older premutation carriers for FXAS.

Incidence

The initial prevalence rate of 1 in 1,000 was based on cytogenetic data, which have proven to be less accurate than expected. With the introduction of molecular testing, Turner et al.\textsuperscript{13} reexamined males identified as being fragile X positive by using Southern Blot testing, and the prevalence was estimated to be 1 in 4,000. Based on the prevalence of the full mutation among the general population (approximately 1 in 3,500 to 4,000) and the fact that only females can transmit the full mutation to their offspring, the expected prevalence of the full
mutation in females is approximately 1 in 8,000 to 9,000 in the general population.\textsuperscript{14} The prevalence of premutations in females is 1 in 246 to 468 and 1 in 1,100 in males.\textsuperscript{14-16} A screening study in a US public school special education programs revealed that approximately 1 in 400 males receiving special education were affected by FXS.\textsuperscript{10}

Suspecting the Diagnosis

Although FXS is the most common inherited cause of mental retardation with reliable testing methods, genetic screening is currently not routinely offered. The detection of FXS requires observation of developmental delay over time, verification of significant delays, and specific referrals for FXS testing by a physician who suspects the disorder.\textsuperscript{17} The variability and subtlety of clinical manifestations may not be recognized in childhood. Several FXS checklists provide useful information concerning physical, developmental, and behavioral characteristics in young children who might be suspected of having FXS, but it is also important to recognize that FXS is not uniform or distinctive in expression.\textsuperscript{17}

Since physical appearances are subtle and may become more apparent with advancing age, the primary-care physician should strongly consider the diagnosis of FXS in any infant and toddler with developmental delays, particularly affecting speech, or in the setting of a maternal family history of mental retardation, developmental disabilities, or learning problems. Systemic use of standard developmental screening measures in pediatric practice may help to maximize the early identification of children with FXS or other genetic developmental disorders.\textsuperscript{18}

Individuals with full mutation FXS display a range of impairment and disabilities. Males with full mutation usually exhibit global developmental delays and mental retardation. Many have autistic spectrum disorder, with sensitivity to tactile stimulation and easy arousal by environmental stimuli. Physical characteristics may include macrocephaly, prominent forehead, loose joints, soft stretchy skin, mitral valve prolapse, and large testicles in pubertal and postpubertal males (Figure 1).\textsuperscript{17}

Females with full mutation may be more mildly affected and present with a wide spectrum from normal development to learning disabilities. They may also have some degree of mental retardation.\textsuperscript{17}

Physical Characteristics

Screening boys for FXS is challenging because many of the distinctive physical features, such as macroorchidism, do not present prepubertally. The classic triad of physical findings in the FXS consists of macroorchidism, large or prominent ears, and a long narrow face (Figures 1, 2).\textsuperscript{19-21} In general, the older the individual the more likely he will exhibit these features. One distinctive differ-
ence between adults and children is that testicular enlargement does not seem to be a useful clinical sign until the child is at least 8 years old. Other variable physical findings include hyperextensible metacarpophalangeal joints, plantar and halluxal crease, pale blue irises, and soft skin over the dorsum of the hands. Hagerman et al suggest using both physical and behavioral traits to identify prepubertal males. Typical behavioral traits include poor eye contact, tactile defensiveness, hand flapping, hand biting, and perseverative speech. Hyperactivity and a short attention span are less specific findings.

The syndrome is transmitted as an X-linked dominant trait and with reduced penetrance. Most, but not all, individuals with the full mutation will express a phenotype. Mosaic (the presence of both premutation and full mutation forms of the gene) contributes to reduced penetrance. The level of phenotypic involvement in females with full mutation depends on the FMRP production which is influenced by the X chromosome activation ratio (the percentage of cells that have the normal X as the active X). In females, only 1 X chromosome per cell is active while the other is inactivated. This occurs randomly, resulting in equal use of each X chromosome. In contrast to males, about 50% of females carrying the full mutation display characteristics of FXS due to random X inactivation and use of the normal FMR-1 gene. Unequal X inactivation in females can result in milder or more severe symptoms. The activation ratio and methylation status determine the amount of FMRP production.

Typical physical characteristics are more often present in females with full mutation than in females with premutations. Physical features are similar to those found in males such as a long face, prominent ears, high arched palate, hyperextensible finger joints, and soft skin (Figure 3).

Medical Complications

FXS individuals rarely have significant medical issues or malformations. Recurrent otitis media and recurrent sinustis are common in childhood. Joint laxity with hyperextensible metacarpophalangeal joints and pes planus may be present. Mitral valve prolapse typically develops during adolescence or adulthood. In terms of neurologic abnormalities, children with FXS of-
ten have hypotonia and motor dyspraxia. Seizures may also present in childhood and are typically well controlled with anticonvulsants.\textsuperscript{25} The cause of macroorchidism is unclear, though it does not impact fertility or sexual functioning.

Individuals with a premutation were previously believed to be unaffected. However, recent studies have revealed that such individuals can present with any of 3 distinct clinical entities: fragile X-associated tremor/ataxia syndrome (FXTAS) in older adult carriers, premature ovarian failure, and mild cognitive and/or behavioral deficits.

A subgroup of older males with the premutation develop a neurologic syndrome, which usually begins between age 50 to 70 years and is associated with a progressive intention tremor and/or ataxia manifested by balance problems, frequent falls, occasional dementias, and Parkinsonian symptoms, such as masked facies, intermittent resting tremor, and mild rigidity. This condition is termed fragile X-associated tremor/ataxia syndrome (FXTAS) and has stimulated an interest in the aging process in those with the \textit{FMR-1} mutation.\textsuperscript{26} The premutation is associated with elevated messenger RNA levels, leading to the formation of intranuclear inclusions in neurons and astrocytes in individuals with FXTAS.\textsuperscript{27} This RNA-mediated disorder is clinically distinct from FXS and caused by the production of mRNA with lengthy CGG repeats, which does not occur in normal individuals with a normal number of repeats or in FXS individuals, who do not produce \textit{FMR-1} message.\textsuperscript{28} Furthermore, symmetrical regions of increased T2 signal intensity in the middle cerebellar peduncles and adjacent cerebellar white matter are present on MRI studies.\textsuperscript{29} Female carriers with \textit{FMR-1} premutation have also presented with FXTAS, demonstrating a clinical course typical of males with FXTAS.\textsuperscript{30} However, none of these 5 females had dementia, which is seen in roughly 20\% of males with FXTAS. It is important that families with the \textit{FMR-1} mutation be evaluated for the presence of FXTAS in both male and female grandparents and in mothers who are carriers of the \textit{FMR-1} premutation. Females are likely to have subtle symptoms and present less frequently than their male counterparts.\textsuperscript{30}

Women carrying the premutation may also have an increased risk of premature ovarian failure before the age of 40, possibly as high as 21–33\%.\textsuperscript{31,32} In addition to genetic counseling, fertility counseling and awareness of osteoporosis risk with early menopause need to be discussed.

Female premutation carriers are typically unaffected intellectually or physically; yet, they have been reported to be susceptible to the psychological problems often associated with the full mutation phenotype. Depression is more likely to occur in carrier females with greater than 100 CGG repeats.\textsuperscript{33}

**Cognitive Profile**

The level of cognitive functioning exhibited by males with FXS varies, ranging from normal to borderline-normal functioning with learning disabilities to severe mental retardation. The degree of cognitive deficit in FXS correlates with the amount of FMRP produced in each individual.\textsuperscript{34} Full mutation males have a low or absent FMRP production with overall cognitive deficits, and deficient executive functioning. Males are more severely impacted cognitively than females, but both show declines in IQ scores as they age.\textsuperscript{35} Declines in cognitive ability are seen in all areas: verbal reasoning, abstract/visual ability, quantitative skills, and short-term memory. Furthermore, declines in all domains of adaptive behavior, communication, daily living skills, and socialization are also noted. The declines in cognitive and adaptive levels are not regression in abilities but reflect the fact these children acquire adaptive skills at a slower rate than other children of their age do and are unable to keep pace with their peers. Longitudinal studies emphasize the importance of early intervention to facilitate cognitive abilities and adaptive behavior skills.

Some investigators have reported strengths in verbal skills, long-term memory for learned information, and expressive and receptive vocabularies. Verbal-reasoning strengths are associated primarily with strengths in simple labeling, vocabulary, and verbal comprehension. Dykens et al.\textsuperscript{36} found that boys with FXS display difficulties with short-term memory tasks, including auditory-verbal and visual-perceptual short-term memory. These deficits are not a function of general memory or attentional deficit but appear to be specific to the type of information to be remembered (i.e., visual material that is abstract and not easily labeled).\textsuperscript{37} These deficits may impact their performance with sequential tasks and their ability to maintain attention and effort.

The level of cognitive impairment in females also relates on the amount of \textit{FMR-1} protein produced and to the X activation ratio. Females with full mutation are less cognitively impaired than
males with full mutation. Approximately 71% of females with a full mutation had IQ scores less than 85, representing borderline or mild/moderate retardation.48 One study found 25% of girls with FXS ages 1 to 18 years, had an IQ less than 70, and 28% had an IQ in the borderline range (70 to 84).9 Unlike males with FXS, female counterparts have a more variable cognitive profile. In addition, females with the full mutation had a significantly lower IQ (full scale IQ 82.7)48 than females with the premutation (full scale IQ 105.1) or their fragile X-negative sisters.9

Similar profiles of strengths and weaknesses are seen in females with FXS. Consistent weaknesses are found in both males and females for quantitative skills and short-term memory recall for visually presented abstract stimuli, whereas consistent strengths are evident for short-term memory recall of visually presented meaningful stimuli.37 Females with the full mutation perform worse than premutation or control groups on arithmetic and demonstrate strength on picture completion tasks.40 They also manifest deficits on executive functioning, spatial ability, and visual memory. Learning disabilities, especially deficits in mathematics, may be present in females with FXS.39

Language Functioning

Males with FXS show delays in language development, gaining expressive language skills more slowly than receptive language skills.41 The discrepancy between expressive and receptive language skills increases as the children get older. This finding has important implications for developing specific intervention strategies, such as focusing on strengths in receptive language as well as targeting lower expressive language skills in vocabulary, syntax, and language use.41

Speech can be rapid and dysfluent and may be characterized by “cluttering” in more highly functioning individuals.42 Cluttering is a rapid, fluctuating rate of speech with repetitions of sounds, words, and phrases, and occasional garbled, slurred, or disorganized speech. Males with FXS also exhibit a greater likelihood of atypical language during conversational interactions as evidenced by tangential language or perseverative expressions, repetitive speech, and tendency toward delayed echolalia. Sudhalter et al49 described FXS males as having tangential language consisting of off-topic questions, responses, or comments that do not appropriately relate to the current topic. Males with FXS produce significantly more tangential language than their peers because of their hyperarousal and social anxiety. FXS males also tend to perseverate by reintroducing favorite topics over and over again. Furthermore, repetitions of phonemes, words, or phrases have been noted in males with FXS.44 Such speech dysfluency reflects the effects of physiological arousal caused by hypersensitivity to social and sensory stimuli.

Children with a dual diagnosis of both FXS and autism are more impaired in expressive language and cognitive skills.46 They require intense intervention in both areas of receptive and expressive language. Receptive language can be a relative strength for children with fragile X without autism. Little work has been published on the speech and language profiles of females with FXS. Affected carrier females may present with language delay during early childhood.48

Behavioral Characteristics

A number of specific behaviors have been noted to occur more frequently in males with FXS. Boys with FXS may manifest social avoidance.47 They have high levels of avoidant behavior for novel objects and situations and tend to reject or move away from new objects. However, they do not remain socially withdrawn or avoid familiar people. Preschool-age males with FXS often display deficits in attention, hyperactivity, and greater degrees of positive mood. Other specific behavior characteristics include shyness or social anxiety, gaze aversion, and stereotypic behavior like hand flapping and hand biting.48,49 When compared to others with mental retardation, males with FXS are more inattentive, overactive, and impulsive.50 These behavioral symptoms cause many FXS children to be diagnosed with attention deficit/hyperactivity disorder (ADHD). Wolff et al50 described a characteristic mannerism in FXS upon greeting a new person. This consists of gaze aversion with head and upper body turning while shaking hands with a new person. This distinctive greeting behavior becomes apparent in those over 12 years of age.
These behavioral characteristics are significant enough to warrant a concurrent diagnosis of autism or autistic-like behavior. It is estimated that nearly 25% of children with FXS also meet the criteria for autism (based on the Childhood Autism Rating Scales (CARS)). A recent study that utilized the gold standard diagnostic tools, Autism Diagnostic Interview-Revised (ADI-R) and the Autism Diagnostic Observation Schedule (ADOS), indicated 33% of children with FXS to have autism. Boys with FXS manifest deficits in communication, socialization, and behavior, which are characteristics of autism spectrum disorder. They display word/phrase perseveration, peculiar speech rate and volume in communication; deficits in social play with peers, gaze aversion, gesturing; and unusual repetitive behavior consisting of hand flapping and rocking. One study revealed that FXS boys have a common autistic-like profile of communicatory and stereotypic disturbances, most notably echolalia, repetitive speech, and hand flapping. Individuals with both FXS and autism function at significantly lower developmental levels than nonautistic individuals with only FXS alone.

Expression of emotional and behavioral features in females with FXS is variable. Females with full mutation appear more vulnerable to social anxiety, social avoidance, withdrawal, and depression. Social avoidance among girls may be apparent by the preschool years and persist through adolescence. They may look withdrawn, embarrassed, anxious, or timid when meeting unfamiliar people. Their discomfort or avoidance behavior is severe enough to interfere with social functioning, particularly in peer relationships. Parents report higher rates of shyness compared to their fragile X negative daughters. Females with the full mutation show more social discomfort than those with the premutation or unaffected females in the same home, displaying greater tendencies for social isolation, poor eye contact with difficulties in establishing rapport with others. Females with the full mutation tend to show oddities in language and interaction and to have difficulties with goal-directed thinking and display of appropriate affect. Females with the premutation have been described as more socially sensitive and anxious than females with the full mutation.

Girls with FXS may present with characteristics of ADHD without meeting full criteria for this diagnosis. They are more vulnerable to attentional difficulties without the overactivity and impulsivity components of ADHD, and are usually diagnosed with attention deficit disorder (ADD), inattentive type.

Autistic behaviors are more commonly reported for 6- to 16-year-old girls with FXS compared to nonaffected fragile X girls. These behaviors consist of communication and social interaction deficits, and stereotypies. Unlike males with FXS, girls are usually not severely affected.

Reiss et al. reported that FXS female adults are at risk for depression and schizotypal personality disorder. This disorder presents as a pattern of interpersonal socialization deficits such as excessive social anxiety, odd behavior, odd speech, and/or inappropriate affect. This may indicate a continuum of interpersonal deficits among fragile X girls extending from early avoidance, withdrawal, and depression.

Natural History and Intervention

Individuals with FXS can take advantage of early developmental stimulation and educational programs. Since the implementation of Public Law 94-142 in 1977, all children with disabilities have a right to a free, equal, and appropriate education in the least restrictive environment from ages 3 to 22 years. Public Law 99-457 allows states the additional option of including early intervention services for infants and toddlers in the entitlement.

Affected individuals benefit from early intervention services, such as, physical therapy, speech therapy, and occupational therapy with sensory integration techniques. Those with concurrent diagnosis of autism spectrum disorder need applied behavioral therapy and specific educational and therapy approaches to address deficits in communication, socialization, and stereotypical behaviors. Males with FXS need educational and therapeutic support ranging from mainstreaming in regular classes with supplemental assistance in areas of need (speech therapy or math tutoring) to more intensive and self-contained instruction with opportunities for mainstreaming for socialization. Early intervention is appropriate and may enhance the child's developing abilities as well as prevent the emergence of problematic behaviors by introducing an early focus on developing attentional behaviors and reducing behaviors that interfere with socialization and learning.

Behavioral approaches are often useful to promote effective coping skills and reduce problematic behaviors. The child can be taught to monitor and anticipate when the situation is becoming
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too stressful, and to use self-calming techniques before manifesting inappropriate responses. A structured setting with reduced environmental or sensory stimulation that is flexible enough to meet the individual’s specific needs is also essential. For example, for individuals who are resistant to change, offer them plenty of warnings before transitions. These and other behavioral methods are best applied under the guidance of a trained behavior specialist.

In the academic arena, the cognitive profile exhibited by many individuals with FXS suggests that they may benefit from holistic teaching approaches, including sight reading rather than a phonetic approach. Math can be particularly difficult to learn, requiring a concrete, functional approach. Accentuating the child’s strengths in verbal and reading tasks can help foster positive self-esteem. As with any child, strengths and weaknesses must be assessed on an individualized basis, with decisions made on the basis of each child’s distinctive pattern of needs.

Individuals with FXS should receive regular routine pediatric care with prompt referral for medical, therapeutic, and educational consultative services. In certain cases, psychopharmacological intervention is necessary for a child with maladaptive behaviors, ADHD, or self-injurious problems. Current psychopharmacological intervention is symptom-based, and no specific therapy exists for enhancing cognitive abilities. Stimulants are typically used for hyperactivity and attentional symptoms. The alpha 2 agonists clonidine and guanfacine (Tenex®) are believed to lessen sensory input and have some efficacy in treating hyperactivity, impulsivity, and aggressive behaviors (often due to overarousal). Anxiety, compulsive, perseverative behaviors, and mood symptoms can be managed with antidepressants, such as, selective SSRIs. Risperidone (Risperdal®) is effective clinically in FXS with high response rates for aggressive behavior and other aberrant and undesired behaviors.

Prospects for Families with Fragile X Syndrome

FXS is considered to be one of the most common genetic conditions, but families impacted by this genetic disorder remain undiagnosed and are unaware of it. In a policy statement by the American College of Medical Genetics, individuals for whom testing should be considered include the following:

1. Individuals of either sex with mental retardation, developmental delay, and autism, especially if they have (a) any physical or behavioral characteristics of FXS, (b) a family history of FXS, or (c) male or female relatives with undiagnosed mental retardation.
2. Individuals seeking reproductive counseling who have (a) a family history of FXS or (b) a family history of undiagnosed mental retardation.
3. Fetuses of known carrier females.
4. Individuals with negative, inconsistent, or ambiguous fragile X test results that are discordant with their phenotype.

Since early diagnosis and intervention can lead to significant improvements, there have been several proposals to offer antenatal screening. By offering screening to all women, their carrier status for FXS becomes known to them and they can receive appropriate genetic counseling and make decisions regarding current and future pregnancies. In addition, cascade screening can start immediately, enabling other family members to know whether they are at risk for having a child with FXS. Presently, population-based, antenatal, and newborn screening is not being performed.

FXS families benefit from parental and social supports, which include referrals for genetic counseling, developmental and psychological assessment and educational assistance, and psychosocial support. Since individuals with FXS have a normal life expectancy, it is essential to look toward their future and help them achieve an optimal and productive life within the community in which they live.

Fragile X Syndrome Support Groups

The National Fragile X Foundation
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The FragileX Listserv
http://listserv.cc.cmc.edu/archives/fragilex-l.html

REFERENCES


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