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CHAPTER 14

Fragile X Syndrome and Fragile X–Associated Disorders

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Fragile X syndrome (FXS) and fragile X–associated disorders (FXDs) include a broad spectrum of problems, including intellectual disability (ID) and learning disabilities; emotional problems; fragile X–associated primary ovarian insufficiency (FXPOI); and an aging syndrome associated with tremor, ataxia, and dementia, called the fragile X–associated tremor/ataxia syndrome (FXTAS). These disorders are caused by genetic mutations in the fragile X mental retardation 1 (FMR1) gene, which was discovered in 1991 (Verkerk et al., 1991). Those with FXS have a full mutation (>200 cytosine–guanine–guanine [CGG] repeats) on the front end of FMR1 leading to silencing or methylation of the gene, such that little or no FMR1 messenger RNA (mRNA) is transcribed, and subsequently little or no FMR1 protein (FMRP) is translated. It is the lack or deficiency of FMRP that leads to the physical, behavioral and cognitive deficits of FXS. In carriers with a premutation (55–200 CGG repeats), there is too much mRNA produced, two to eight times the normal level. This extra level of mRNA causes a gain of function in carriers. The resulting phenotypes include neurodevelopmental problems in some boys, such as attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorders (ASDs); FXPOI in 20% of adult females; and FXTAS in 10% of older females and 40% of older males.

Significant advances over the last decade concerning the neurobiology of FXS have led to new treatments for FXS (Hagerman et al., 2009). FMRP, which is missing in FXS, is an RNA transport protein inhibiting the translation of many other mRNAs that occur in the neuron and are important for synaptic plasticity and learning (Bassell & Warren, 2008). In FXS there is enhanced translation of many proteins throughout the brain (Qin, Kang, Burlin, Jiang, & Smith, 2005), and one of the consequences is upregulation of the metabotropic glutamate receptor 5 (mGluR5) pathway, leading to weakening or long-term depression (LTD) of synaptic connections (Bear, Huber, & Warren, 2004). This finding has led to new treatments for FXS, specifically mGluR5 antagonists that have been shown to reverse the LTD and weak synaptic connections in the animal models for FXS (de Vrij et al., 2008; McBride et al., 2005; Yan, Rammal, Tranfaglia, & Bauchwitz, 2005). The new trials of mGluR5 antagonists in humans with FXS have included use of fenobam, which even in a single dose appeared to be promising in the treatment of adults with FXS (Berry-Kravis

et al., 2009). FXS is the most common inherited form of ID and the most common single gene associated with ASDs. It is now leading the way for new targeted treatments for neurodevelopmental disorders (Hagerman et al., 2009). The mGluR5 antagonists are likely to be helpful for other causes of ASDs besides FXS.

Prevalence

Numerous studies have been done to determine the prevalence of both the premutation and the full mutation in the general population (Song, Barton, Sleightholme, Yao, & Fry-Smith, 2003). The premutation is more common, and it occurs in approximately 1 in 130–250 women and 1 in 250–810 males (Dombrowski et al., 2002; Fernandez-Carvajal et al., 2009; P. J. Hagerman, 2008). The full-mutation allele occurs in approximately 1 in 2,500 in the general population (P. J. Hagerman, 2008), but FXS is only recognized in 1 in 3,600 (Crawford et al., 2002). Some individuals with FXS are high-functioning and present with only learning problems or emotional problems and not ID, particularly females with the full mutation (Angkustsiri, Wirojanan, Deprey, Gane, & Hagerman, 2008). Approximately 2–3% of males with ID of unknown etiology have FXS (Slaney et al., 1995). In addition, 2–6% of individuals with ASDs have FXS (Hagerman, Rivera, & Hagerman, 2008b), so fragile X DNA testing should be carried out in all children or adults who present with ID or ASDs of unknown etiology.

FXS occurs in all racial and ethnic groups that have been studied (Sherman, 2002). A relatively high prevalence of both the premutation and the full mutation occurs in Finland, Israel, and Tunisia, suggesting a *founder effect*—that is, the presence of a carrier in the original founding population for these areas (Eichler & Nelson, 1996; Pesso et al., 2000; Song et al., 2003; Zhong et al., 1996).

Inheritance

The expansion from a premutation to a full mutation only occurs when the FMR1 gene is passed on to the next generation through a female. When the gene passes from a male with the premutation, he will pass on the premutation to all of his daughters because the sperm in males with FXS has only the premutation (Reyniers et al., 1993). Therefore, whether a male has a full mutation, a mosaic pattern (premutation in some cells and full mutation in others), or a premutation, he will only pass the premutation on to all of his daughters. A female, however, can pass either the premutation or the full mutation on to her children. The greater the CGG repeat number in a carrier female, the greater the chance of expansion to a full mutation in the next generation (Nolin et al., 2003). If a female has more than 100 CGG repeats, and she passes the X chromosome with the mutation on to her child, it will expand to a full mutation 100% of the time in the next generation. Since females have two X chromosomes, the risk of passing the mutation on to the next generation is 50% with each pregnancy. A carrier mother can therefore have affected daughters with FXS, daughters with the premutation, affected sons with FXS, sons with the premutation, and/or normal children without the fragile X mutation (McConkie-Rosell et al., 2007).

In contrast, a male will pass on the premutation to only his daughters but none of his sons. His sons will receive the Y chromosome and therefore will be unaffected by FXS or by the carrier state. Daughters who receive the mutation from their fathers have a high risk of producing children with FXS in the next generation. Therefore, once the diagnosis of FXS or the premutation is made, it is essential to have genetic counseling (McConkie-Rosell et al., 2007). All individuals in the family who are at risk to have the premutation or the full mutation should have fragile X DNA testing, which can be ordered by any physician and is usually covered by insurance.

It is imperative for affected families to understand the inheritance pattern of FXS. Family members should be well informed of the dynamics of inheritance, so that relatives will understand their risk for involvement from either the premutation or the full mutation. Figure 14.1 shows a family pedigree that demonstrates the change in CGG repeats through four generations and the types of clinical features in each generation

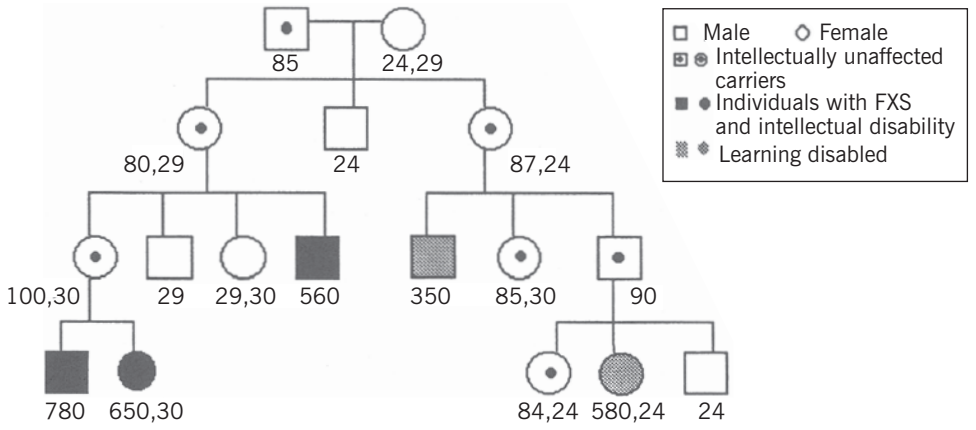

FIGURE 14.1. A pedigree of a family affected by FXS. The numbers represent the CGG repeat numbers at *FMR1* in each X chromosome. Note that the male with 350 repeats has an unmethylated full mutation; he does not have intellectual disability (ID), but does have learning disabilities. The female with 650 repeats has a full mutation and has ID, whereas the female with 580 repeats also has a full mutation, but has learning disabilities rather than ID.

that can be related to the premutation and the full mutation. Involvement in individuals with the full mutation is covered in detail below, followed by a briefer description of premutation involvement.

Physical, Behavioral, and Cognitive Phenotypes of Full-Mutation Involvement

Physical Phenotype

Young children with FXS usually present with language and motor delays, hypotonia, and hyperactivity. The typical physical features of FXS may not be present in early childhood, so it is important not to dismiss a diagnosis of FXS solely because of a lack of these physical features (see Figure 14.2). Physical features of FXS include prominent ears, long face, hyperextensible finger joints, double-jointed thumbs, flat feet, soft skin, and a high-arched palate (Hagerman, 2002b). Most of these features can be seen in the general population, and children with FXS do not typically look dysmorphic or unusual. On occasion, ears can be dramatically prominent, with cupping in the upper part of the pinnae. Females with the full mutation are less likely than males to present with typical physical features of FXS. For males, macroorchidism (large testicles) is also part of the physical phenotype, but it is usually not present until adolescence (Lachiewicz & Dawson, 1994). In adolescence or adulthood, the testicular volume may be two to three times normal size, although this is also not always recognized in a physical examination (Hagerman, 2002b). The degree of physical involvement and cognitive involvement in FXS correlates with the level of FMRP that is present in the blood (Loesch et al., 2004). Typical physical features of FXS are outlined in Table 14.1.

Many of the physical features in FXS are considered part of a connective tissue dysplasia (Hagerman, 2002b). The high frequency of otitis media difficulties in early childhood is probably related to the connective tissue problems, in that the eustachian tube is easily collapsible, trapping fluid in the middle ear. The connective tissue problems on occasion lead to other medical complications, such as hernias, scoliosis, and mitral valve prolapse (Hagerman, 2002b).

Growth abnormalities also may occur in FXS. Young patients often have a large head circumference, and those with FXS and autism have larger heads in early childhood than those with FXS but no autism do (Chiu et al., 2007). In puberty, however, the growth velocity may be slowed, and short stature is not uncommon in adulthood (Loesch, Huggins, & Hoang, 1995).

FIGURE 14.2. These siblings all have the full mutation of FXS. Although they do not display typical physical features of FXS, they do present with characteristic behavioral features of FXS (see text). Photograph used by permission of the children's parents.

TABLE 14.1. Typical Physical and Behavioral Features of FXS

Physical features	Behavioral features
Long ears	Poor eye contact
Prominent ears	Tactile defensiveness
Long face	Hand flapping
Single palmar crease	Hand biting
Cardiac murmur or click	Perseveration
	Hyperactivity
Hand calluses	Diagnosis of attention-deficit/hyperactivity disorder (ADHD)
Flat feet	
Hyperextensible finger joints	Verbal or physical outbursts
Double-jointed thumbs	Tantrums
High-arched palate	Shyness or social anxiety

Behavioral Phenotype

Behavioral features of FXS include an extremely short attention span, impulsivity, and hyperactivity, as well as hypersensitivity to visual, auditory, tactile, and olfactory stimuli (Miller et al., 1999; Roberts et al., 2001). Children with FXS often have difficulty in crowds and with loud noises because their hypersensitivity and hyperarousal often lead to tantrums or aggression. They may also overreact to some smells with a gagging or vomiting response. In addition, children with FXS may experience tactile defensiveness to such an extent that they pull away from light touch. Tags in clothes or firm textures of materials can be irritating to them. The extra stimuli associated with transitions—even going from the car into the house—can lead to behavior outbursts for children with FXS. Behavioral interventions and therapy, as described below, can be helpful in alleviating or calming the intensity of some of these behaviors.

Perseveration is a typical communicative and behavioral feature in children with FXS. Children may repeat a certain activity (e.g., stacking toys, spinning objects, flushing the toilet, or watching the same video) over and over again. Perseveration is also present in speech—not only in repeating the same phrase, but in talking about the same subject continually. Mumbling, echolalia, cluttered speech, and self-talk (i.e., carrying on a conversation with oneself, often using different vocal tones) are all commonly seen in individuals with FXS (Abbeduto & Hagerman, 1997; Hagerman, 2002b).

Autistic-like features are also common in children with FXS, including hand flapping, hand biting, toe walking, poor eye contact, tactile sensitivity, shyness, and social anxiety. Full autism—that is, autistic disorder as defined by the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, text revision (DSM-IV-TR) and documented

by standardized autism diagnostic measures such as the Autism Diagnostic Observation Schedule (ADOS)—occurs in 30% of boys with FXS, and DSM-IV-TR defined pervasive developmental disorder not otherwise specified (PDD-NOS) occurs in an additional 30% (Harris et al., 2008). Those with autism and FXS together have lower IQs than those with FXS without autism, but the severity of autism does not correlate with the level of FMRP once the IQ is controlled (Loesch et al., 2007). Autism is common in FXS, and it should be assessed in the evaluation of children with FXS because if it is present appropriate educational interventions should be carried out (including applied behavior analysis interventions, such as the Denver model or pivotal response training (Rogers & Vismara, 2008). Children with FXS are at high risk for autism because the absence or deficiency of FMRP leads to dysregulation of many proteins that are known to be associated with autism through their action in synaptic plasticity, or through dysregulation of the gamma-aminobutyric acid (GABA) and glutamate systems in the brain (Belmonte & Bourgeron, 2006). This dysregulation leads to an imbalance of inhibitory and stimulatory systems, problems with connectivity in the brain, weak synaptic connections, and growth abnormalities; some of these are related to protein tyrosine phosphatase (PTEN) dysregulation, which occurs in the absence of FMRP (Belmonte & Bourgeron, 2006; Chonchaiya et al., 2009; Hagerman, Rivera, & Hagerman, 2008).

Cognitive and Neuroanatomical Phenotypes

The majority of males with FXS have ID, with IQs lower than 70 (Bennetto & Pennington, 2002); females are less affected by FXS because they have two X chromosomes, and although the full mutation may be present on one of the X chromosomes, the other is normal and is producing FMRP. All females inactivate one of their X chromosomes, and an activation ratio, which can be calculated from the DNA studies, represents the percentage of cells with the normal X chromosome as the active chromosome. The activation ratio correlates with IQ in females and with the level of FMRP (Tassone et al., 1999). Approximately 50–70% of females with the full mutation have intellectual deficits in the borderline or mild-ID range (de Vries et al., 1996). Females with normal IQs but with the full mutation usually demonstrate learning disabilities, including attentional and organizational problems and math difficulties. Approximately 70% of women with the full mutation who do not have an IQ deficit have problems in executive functioning, which relate to their difficulty with organization and attention (Cornish, Turk, & Hagerman, 2008). Their behavior is often impulsive, and they can be tangential in their speech, as well as mood-labile. Young girls and boys with the full mutation usually demonstrate significant shyness and social anxiety, which often interferes with social interactions and can predispose them to ASDs (Cordiero et al., unpublished raw data). On occasion the social withdrawal and anxiety may lead to quieter language and even selective mutism in school, but usually not at home (Hagerman, Hills, Scharfenaker, & Lewis, 1999).

Studies of neuroanatomical changes in FXS have helped to increase our understanding of the neurobehavioral phenotype of FXS (Reiss & Dant, 2003). In general, certain parts of the brain are generally larger in patients with FXS than in age- and IQ-matched controls. These areas include the caudate and the thalamus, although the amygdala is not enlarged, at least in younger boys with FXS (Hazlett et al., 2009). The brains of young children with idiopathic autism without FXS have a very different neuroanatomical structure from the brains of those with FXS either with or without autism. Boys with autism have a larger amygdala and a smaller caudate than boys with FXS (Hazlett et al., 2009). These findings demonstrate that the genetic etiology for autism is more important for determining brain structure than the behavioral phenotype of autism. The enlarged caudate in FXS may relate to the problems with executive functioning and ADHD that are common in these children.

Phenotypic Illustrations

Case 1

Case 1, a boy age 4 years, 3 months, was diagnosed with FXS by FMR1 DNA testing. He has a full mutation that is fully methylated. He was born after a normal pregnancy, and his birthweight was 8 pounds, 14 ounces.

He did well in the newborn period, although his suck was poor, he was hypotonic, and his developmental milestones were mildly delayed. He sat at 10 months and walked at 15 months. At present he does not yet speak in phrases, but can use approximately 10–15 words. He began to hand-flap and bite his hands in his first year. His father called him "little butterfly" because of his hand flapping. He also chews excessively on things such as his shirt collar, has poor eye contact, and has problems with perseveration. He is easily overstimulated and has a high activity level, as well as impulsivity and distractibility. In addition, tantrums are a problem for him, although he is not physically aggressive. He has difficulty with transitions and becomes easily overwhelmed on a daily basis.

Like many children with FXS, this boy has had recurrent otitis media infections. Pressure-equalizing (PE) tubes were used to help alleviate this problem. His height is at the 75th percentile for his age, and both his weight and head circumference are at the 95th percentile for his age. He has visually prominent ears as well as ear cupping, but his face is not long. He has a high-arched palate, along with hyperextensible joints and double-jointed thumbs. In addition, his hands display a single palmar crease. His cardiac examination is normal, with no click or murmur, and he has flat feet.

His cognitive abilities were assessed several years ago with the Bayley Scales of Infant Development and the Vineland Adaptive Behavior Scales. On the Bayley, he is performing at a developmental level between 23 and 25 months. His mother describes him as difficult to motivate; she notes that he mainly enjoys watching videos and/or eating. On the Vineland, his Adaptive Behavior Composite score is 51, which is typical of a child 21–22 months of age. His other Vineland scores are as follows: Communication, 52; Daily Living Skills, 55; Socialization, 66; and Motor Skills, 49. He has not yet been able to complete the Kaufman Assessment Battery for Children (K-ABC) because of significant attention and concentration problems in addition to language deficits.

Case 2

Case 2 is a boy age 4 years, 6 months who has FXS and autism. DNA testing demonstrates a full mutation that is fully methylated, and he has no detectable FMRP in peripheral blood. His mother had a normal pregnancy, and she was delivered by cesarean section; his birthweight was 9 pounds, 5 ounces. He sat at 7 months, crawled at 11 months, walked at 21 months, and began speaking in two-word phrases at 3 years. He had significant reflux in the newborn period and was a very colicky baby. His parents noticed that his behavior was unusual even in the first year. He would frequently arch his back and focus on ceiling fans; he displayed hand flapping and poor eye contact, as well as tactile defensiveness. When he was diagnosed with autism, he was qualified to receive appropriate autism preschool services, as well as speech–language and occupational therapy. It was not until he was older than 3 years, well after his autism diagnosis was made, that he was found to also have FXS.

This boy is hyperactive with a very short attention span; he has tantrums, but these are not aggressive episodes. He has difficulty with transitions and anxiety on a daily basis. Although some of his autistic behavior has improved with therapy, he continues to seek self-stimulatory input and perseverates in spinning and twirling objects. In the past on the Vineland Adaptive Behavior Scales, his Adaptive Behavior Composite score is 54, with an age equivalent of 24 months. His other scores are as follows: Communication, 65; Daily Living Skills, 54; Socialization, 65; and Motor Skills, 51. His total score on the ADOS is 15, which is well into the autism range.

As noted above, he is already receiving special education and various therapies. He also spends part of the school day integrated into a regular kindergarten, where he is assisted by an aide. Mainstreaming him into the normal classroom is beneficial for him because he can learn from and imitate other children who are performing at a typical level. He has outgrown some of his autistic tendencies, and his interest in others and socialization skills have improved over time. However, he continues to be anxious, easily overwhelmed, and overstimulated, and he utilizes approach–withdrawal behavior in most of his social interactions.

His medical history includes a history of sinusitis and recurrent otitis media infections, with more than 20 infections beginning at 6 months of age. He has not had

hernias or joint dislocations, and his only surgery was for PE tubes because of the recurrent otitis media infections. He originally had a history of staring spells occurring a couple of times a week, and he was unresponsive to his name during these spells. An electroencephalogram was carried out and he was found to have spike wave discharges in the frontal and parietal areas, although no seizures were documented. Once he was started on valproic acid, his staring spells stopped, and he became more socially responsive.

His physical examination demonstrates a height at the 50th percentile, weight at the 75th percentile, and head circumference at the 98th percentile for his age. His forehead and ears are prominent, but his face is not long. He has a high-arched palate, hyperextensible joints, and flat feet, but does not have double-jointed thumbs, a single palmar crease, or hand calluses. Cardiac exam shows a normal rhythm, without murmur or click. His testicular volume is 3 ml bilaterally, which is normal for his age.

Molecular–Clinical Correlations and Adult Outcome

As described earlier, the majority of males with FXS present with ID, although approximately 13% have IQs above 70 (Bennetto & Pennington, 2002; Hagerman, Hull, et al., 1994). This number may increase when younger children are examined. Freund, Peebles, Aylward, and Reiss (1995) found that approximately 50% of preschool boys with FXS had intellectual functioning in the typical or borderline range. Children with FXS may present with normal or near-normal expressive vocabulary abilities, and they also do well on visual matching tasks, so their initial IQ may look fairly good. However, IQ usually declines with age as more demands are made in reasoning. Significant IQ decline typically occurs in the majority of males and in about 30% of females with the full mutation (Bennetto & Pennington, 2002; Wright-Talamante et al., 1996). A few males are able to maintain IQs in the normal or borderline range in adolescence and adulthood. These individuals usually have variant DNA patterns and are producing a significant level of FMRP. For high-functioning males, a typical pattern is a full mutation that is completely or almost completely unmethylated (Loesch, Huggins, & Hagerman, 2004). In addition, individuals with a mosaic pattern (i.e., some cells with the premutation and other cells with the full mutation) may also be high-functioning, particularly if a high percentage of cells demonstrate the premutation (Tassone et al., 1999). The higher the FMRP level, the more likely the patient is to maintain an IQ in the borderline or normal range. Studies have shown that the average IQ in adulthood for a male with the full mutation that is fully methylated is 41; the average IQ for a mosaic male is 60; and the average IQ for patients with a lack of methylation, or at least 50% of the mutation unmethylated, is 88 (Merenstein et al., 1996). Therefore, it appears that the level of FMRP produced by the gene correlates with an improved prognosis in adulthood (Tassone et al., 1999).

Premutation Involvement

Individuals with the premutation typically have IQs in the average range, and they were previously thought to be completely unaffected by the premutation. However, some children with the premutation were found to have cognitive deficits or autism, particularly boys; these findings led to further investigation of the molecular findings in those with the premutation who had problems (Tassone, Hagerman, Taylor, Mills, et al., 2000). Some of these individuals were found to have lower levels of FMRP, but the most striking and unexpected finding was elevation of the FMR1 mRNA level from two to eight times normal (Tassone, Hagerman, Taylor, Gane, et al., 2000). At the same time of this discovery, several grandfathers with the premutation were found to have a similar phenotype of tremor with action and ataxia leading to frequent falls (Hagerman et al., 2001). Further studies demonstrated that this phenotype of tremor and ataxia was seen in approximately 40% of male carriers who were older than 50 years, and that the prevalence increased with age (Jacquemont et al., 2004). This condition was found to be associated with the premutation and a toxicity to the neurons, leading to the formation of intranuclear inclusions in neurons and astrocytes, in addition to brain atrophy

and white matter disease in the periventricular and subcortical regions and in the middle cerebellar peduncles (Adams et al., 2007; Jacquemont et al., 2003). This condition has been named the fragile X–associated tremor/ataxia syndrome (FXTAS), but it also includes executive function deficits, cognitive decline in all, dementia in some, and a neuropathy in most. The inclusions appear to be caused by the RNA toxicity of the premutation, but their formation may be a protective mechanism of the cell to handle the protein dysregulation that occurs in cells with the premutation (Greco et al., 2006). Various proteins become dysregulated with the toxicity of the premutation, including lamin A/C, alpha B crystallin, heat shock proteins, and ubiquitin, and they all are also sequestered in the inclusions of FXTAS (Arocena et al., 2005). Inclusions also occur in the peripheral nervous system, including autonomic ganglia throughout the body, such as pericardial ganglia, periadrenal ganglia, and myenteric plexus ganglia in the gastrointestinal system (Gokden, Al-Hinti, & Harik, 2009). This suggests that RNA toxicity affects the peripheral nervous system, leading to various types of autonomic dysfunction: impotence (which is common even before the onset of tremor and ataxia), orthostatic hypotension, hypertension, and even cardiac arrhythmias (Coffey et al., 2008; Jacquemont et al., 2003). Inclusions can also occur in the thyroid gland and in the Leidig cells of the testicles, which make testosterone (Greco et al., 2007; Louis, Moskowitz, Friez, Amaya, & Vonsattel, 2006). Testosterone deficiency is common in men with FXTAS, and thyroid dysfunction is also common, particularly in women with FXTAS (Coffey et al., 2008).

FXTAS can also occur in about 10% of women with the premutation who are older than 50 years, but dementia is rare because women are relatively protected by the second X chromosome (Coffey et al., 2008; Rodriguez-Revenga et al., 2009). Women with the premutation, however, have a higher rate of autoimmune problems (including fibromyalgia and thyroid disease) than age-matched controls without the premutation have (Coffey et al., 2008; Rodriguez-Revenga et al., 2009). In addition, about 3–4% of women with the premutation may also suffer from multiple sclerosis, and sometimes this can occur together with FXTAS (Greco et al., 2008).

An additional unique phenotype seen only in the premutation and not in the full mutation is primary ovarian insufficiency or FXPOI. Approximately 20% of women with the premutation will experience cessation of their menses before age 40, although a small percentage may become pregnant later (Sullivan et al., 2005). This is thought to relate to RNA toxicity in the ovum or in the cells that support the ovum, and it is more common with higher CGG repeat numbers in the premutation range (Sullivan et al., 2005; Wittenberger et al., 2007). In addition, women with the premutation have higher rates of depression and anxiety than the general population (Roberts et al., 2009). In individuals with FXTAS, inclusions occur throughout the limbic system, so it is likely that emotional problems in carriers are related to RNA toxicity in the limbic system.

Within the last decade, several children with the premutation have been found to have learning deficits; emotional problems such as anxiety; social deficits and ASDs; or even ID (Aziz et al., 2003; Farzin et al., 2006; Tassone, Hagerman, Taylor, Mills, et al., 2000). Although this finding led to the identification of elevated FMR1 mRNA in premutation carriers, the focus has been on the aging problems in carriers and FXTAS (P. J. Hagerman & Hagerman, 2004). However, now we know that the premutation can also cause neurodevelopmental problems, particularly in males with the premutation, because they only have one X chromosome and are not protected by the second X. Although most individuals with the premutation usually have IQs in the average range, ADHD and ASDs are not uncommon in males (Clifford et al., 2007; Farzin et al., 2006).

Case 3

Case 3 is a 12-year-old boy who was diagnosed as carrying the premutation at 8 years of age, when DNA testing demonstrated a CGG repeat number of 79. His mother had a normal pregnancy; she delivered at full term; and the birthweight was 6 pounds, 4 ounces. He did well in the newborn period and exhibited normal developmental milestones, including sitting at 6 months, walk-

ing at 11 months, riding a tricycle at 3 years of age, and riding a bicycle by 7 years of age. His coordination has been quite good, and he has played soccer and other sports, but he has had mild difficulty with handwriting and drawing. In the language area, he said words in the first year and sentences by 2 years of age. However, he was noted to be hyperactive as a toddler, and this persisted into his school years; his significant attentional problems and impulsivity led to a diagnosis of ADHD. He has also suffered from tantrums, which began at 3 years of age but became worse at age 9 and into adolescence. His mother is a premutation carrier with 70 repeats; her father (the boy's grandfather) suffers from tremor and ataxia in addition to mild dementia, and he has been recently diagnosed with FXTAS. He lives in an apartment attached to the main house, and Case 3's mother is stressed with the caretaking needs of her father.

As treatment for his ADHD, Case 3 was started on Concerta at 27 mg a day at age 8. He is now on 36 mg a day with a good response and normal growth parameters. His behavior has not included hand flapping or hand biting, but he had approximately one tantrum per week in middle childhood, and he has shown more significant problems with aggressive behavior both at home and at school within the last year. His mother has remarried during the last year, and he dislikes his stepfather. A more detailed psychological evaluation was recently carried out because of his history of both verbal and physical aggression. His emotional assessment demonstrated severe problems with anger, anxiety, mood instability, and dysthymia. It also revealed obsessive thinking focused on violent ideation. His aggressive ideation toward his stepfather was severe, and intensive counseling was initiated, in addition to a positive behavioral program in school.

Cognitive testing at age 8 years, 10 months with the K-ABC yielded an overall Mental Processing Composite score of 100, a Sequential Processing score of 108, and a Simultaneous Processing score of 95. Cognitive testing at 12 years of age with the third edition of the Wechsler Intelligence Scale for Children yielded a Full Scale IQ of 103, a Verbal IQ of 99, and a Performance IQ of 107.

Because Case 3's recent evaluation revealed not only severe ADHD but aggression and violent ideation, he was started on aripiprazole (Abilify—2 mg at bedtime, with a gradual increase to 4 mg), an atypical antipsychotic. This medication has helped to stabilize his mood, reduce his anxiety, further improve his ADHD symptoms, and decrease his aggression. He was also started in weekly counseling to help his aggression, anxiety, and dysthymia. Sertraline was subsequently started after the positive effects of the aripiprazole were noted, and it has further improved his mood, anxiety, and obsessive ideation.

Recent molecular testing for Case 3 demonstrated the presence of a premutation at 66 repeats that was completely unmethylated in 85% of his cells. However, it also showed an additional light smear in the full-mutation range with 230 repeats, and this was present in 15% of his cells and was methylated. Subsequent FMRP levels demonstrated that 70% of his lymphocytes stained positive for FMRP (Tassone et al., 1999). Case 3 is therefore a mosaic male with FXS; his cognitive abilities are in the average range, but he has significant emotional and behavioral problems, including ADHD, violent ideation, mood instability, and dysthymia. In addition, his FMR1 RNA level is 3.8 times normal, so he is also at risk for RNA toxicity. In essence, he has a "double hit"—that is, a mild decrease in FMRP levels that gives him some features of FXS, as well as elevated mRNA levels that may add to his psychopathology and perhaps to his ADHD and his social problems. My colleagues and I have never seen a patient with FXS develop FXTAS, and it is likely that the lowered level of FMRP can protect individuals from FXTAS.

Assessment Issues: Who Requires FMR1 DNA Testing?

Children and adults with FXS or premutation involvement may often present with other diagnoses. These may include an ASD, such as PDD-NOS, autism, or Asperger syndrome; schizotypal personality disorder; or other diagnoses with specific etiologies, such as Tourette syndrome, Pierre Robin sequence, Soto syndrome, or even

Prader–Willi syndrome. Tics are seen in approximately 20% of patients with FXS, and abrupt mood swings and ADHD are common in those with the full mutation and in those affected by the premutation, as they are in Tourette syndrome. Children with Tourette syndrome do not usually demonstrate the cognitive deficits that are present in FXS, however. The large head circumference in childhood frequently causes FXS to be confused with Soto syndrome or cerebral gigantism. Approximately 5% of patients with FXS can have a cleft palate, which can be confused with other clefting syndromes, including Pierre Robin sequence. As previously discussed, autism and other ASDs also overlap with FXS. Obsessive–compulsive behavior is often seen in FXS, and occasionally the obsessive behavior may focus on eating, which can lead to obesity and a phenotype similar to Prader–Willi syndrome. This is called the Prader–Willi phenotype (PWP) in FXS, and it is associated with obesity, hyperphagia, delayed puberty, and often a small phallus. This PWP is not associated with a 15q deletion that is causal to Prader–Willi syndrome. However, recently a down-regulation of cytoplasmic FMR1-interacting protein (CYFIP1), a sister protein that binds to FMRP and whose gene is located at the 15q region, was documented in individuals with the PWP compared to controls (Nowicki et al., 2007). The CYFIP1 level in individuals with the PWP was much lower than that of controls, and the level was also much lower than that seen in individuals with FXS without the PWP (Nowicki et al., 2007). Why CYFIP1 is down-regulated in the PWP is not known, but those with the PWP also have a higher ASD rate than is seen in FXS without the PWP (Nowicki et al., 2007).

It is important to consider fragile X testing in all individuals who have ID or ASDs, when the etiology for these problems is unknown. In addition, if there is a family history of ID, the chance that this could be due to FXS increases dramatically. As noted earlier, FXS causes 30% of X-linked ID, and in general FXS is the most common inherited form of ID or ASD known.

Not all children with hyperactivity should be tested for FXS. However, if a hyperactive child has cognitive deficits or typical physical features associated with FXS, has a family history consistent with FXDs, or exhibits autistic-like features (e.g., hand flapping, hand biting, or poor eye contact), then the diagnosis of FXS or premutation involvement should be strongly considered, and DNA testing should be carried out. Similarly, not all children with learning disabilities need to be tested for FXS. However, if a learning disability involves math deficits (particularly in a female), and it is combined with shyness, social anxiety, or physical features related to FXS and/or with a family history of ID or consistent with an FXD, then this child should be tested for fragile X mutations. In addition, patients who have selective mutism or schizotypal personality disorder and other features consistent with FXS or FXDs should be tested.

An FXS or FXD diagnosis is important from two perspectives. First, it allows genetic counseling to be given to multiple family members who may be carriers of fragile X or affected by FXS. In addition, a diagnosis of FXS or FXD helps in the development of treatment programs, including the various interventions described below.

Treatment

There is no cure for FXS or FXDs, but various interventions and treatments are helpful for affected children and adults. For FXS the treatment team should include multiple professionals, including a special education teacher, a speech–language pathologist, an occupational therapist, a physician, and a psychologist (Braden, 2000; Hagerman, 2002a; Hagerman et al., 2009; Scharfenaker, O'Connor, Stackhouse, & Noble, 2002).

Medical Follow-Up and Psychopharmacology

The medical treatment of FXS includes vigorous intervention for recurrent otitis media infections, which can further exacerbate the language delays in FXS (Hagerman, Altshul-Stark, & McBogg, 1987). In addition, approximately 20% of patients have seizures; these can further interfere with normal development and academic progress, and they require treatment (Hagerman, 2002a; Hagerman et al., 2009). Other medical problems associated with loose connective tissue include rare hernias, rare joint dislocations,

mitral valve prolapse, sinus infections, and gastroesophageal reflux. Medical interventions for these problems have been discussed elsewhere (Hagerman, 2002a).

Medical interventions can be most helpful for the behavior problems that are usually present in FXS. For the preschool child, tantrums and hyperarousal are common difficulties, in addition to a short attention span. Stimulant medications (see below) may benefit some preschool children, but may exacerbate behavioral problems in others (Berry-Kravis & Potanos, 2004; Hagerman et al., 2009; Hagerman, Murphy, & Wittenberger, 1988). Additional medications, including clonidine (Catapres), guanfacine (Tenex), and aripiprazole (Abilify), can also help ADHD symptoms (Hagerman et al., 2009). Abilify is an atypical antipsychotic that appears to be helpful in low doses for the majority of children and adults with FXS, not only for improving attention but also for stabilizing mood and improving anxiety and aggression (Hagerman et al., 2009). Currently a controlled trial is taking place in Indiana to test the efficacy of Abilify in the treatment of FXS.

For the treatment of moodiness, aggression, anxiety and obsessive–compulsive behavior, the selective serotonin reuptake inhibitors (SSRIs) have been remarkably helpful in FXS (Berry-Kravis & Potanos, 2004; Hagerman, Fulton, et al., 1994, 2009). The SSRIs include fluoxetine (Prozac), sertraline (Zoloft), paroxetine (Paxil), citalopram (Celexa), escitalpram (Lexapro), and fluvoxamine (Luvox). They are relatively safe and easy to monitor because they do not require regular blood work or electrocardiograms. The side effects include diarrhea, agitation, hyperactivity, sleep disturbances, abdominal pain, and the rare occurrence of mania. They are commonly used in adolescence and adulthood, and limited experience is available regarding their use in childhood. Controlled studies are needed to document their efficacy, specifically in FXS.

The most exciting aspect of treatment in FXS is the development of targeted treatments that can reverse the neurobiological abnormalities documented over the last few years. As noted at the beginning of this chapter, the absence or deficiency of FMRP leads to up-regulation downstream in the mGluR5 pathway. This pathway normally leads to LTD of synaptic plasticity, so that synaptic connections are weakened. FMRP is the inhibitor of this pathway; therefore, in the absence of FMRP there is enhanced LTD, which is thought to lead to the ID in FXS (Bear et al., 2004). Therefore, the use of mGluR5 antagonists should block this effect, and this has been proven in the mouse and *Drosophila* models of FXS (de Vrij et al., 2008; Dolen & Bear, 2008; McBride et al., 2005). Now treatment with mGluR5 antagonists has begun to be studied in patients with FXS, and preliminary positive responses have been seen in a single-dose trial of fenobam (Berry-Kravis et al., 2009). Lithium also down-regulates the mGluR5 system, and an open trial of lithium in individuals with FXS demonstrated positive behavioral effects, with some signs of improved cognition as well (Berry-Kravis et al., 2008).

Another new targeted treatment in FXS is minocycline, which lowers the level of matrix metalloproteinase (MMP9), one of a family of proteins important for synaptic plasticity. MMP9 levels are high in the absence of FMRP, and treatment of the knockout mouse model of FXS with 1 month of minocycline at birth improved synaptic connections and also improved behavior and cognition (Bilousova et al., 2009). Therefore, human trials are being initiated in children with FXS, although in children younger than 8 years minocycline can lead to the graying of teeth. Long-term minocycline treatment can lead to graying or darkening of other tissues, including skin, at any age. In addition, pseudotumor cerebri or increased intracranial pressure, as well as drug-induced lupus, can occur as a rare side effect of minocycline treatment. Further studies, including a controlled trial, are needed before minocycline can be broadly recommended for treatment of children with FXS. This new age of targeted treatments in FXS should lead to exciting benefits from treatment in cognition and behavior. It should also encourage more widespread screening efforts, including newborn screening.

Treatment of premutation involvement includes treatment of ADHD with stimulants, and treatment of the emotional problems (including anxiety and depression) with SSRIs (Bourgeois et al., 2009; Hagerman, Hall, et al., 2008). Treatment of FXPOI may include the use of hormone replacement therapy

(Wittenberger et al., 2007). Treatment of the tremor, the ataxia, and the pain problems associated with neuropathy in patients with FXTAS is more complicated; a recent review has been published on this topic (Hagerman et al., 2008a).

Speech–Language and Occupational Therapy

All children who are significantly affected by FXS can benefit from speech–language therapy and occupational therapy (Scharfenaker et al., 2002; Schopmeyer & Lowe, 1992). Speech and language deficits in FXS include auditory processing problems, cluttering, mumbling, poor pragmatics, motor dyspraxia, and difficulties with abstract reasoning. Speech–language therapy can focus on each of these deficits. Even in a child without ID, deficits in higher linguistic skills and pragmatics may exist. Strengths in the language area include memory and imitation skills, a fine sense of humor, and empathy in social interactions if there is no ASD. The memory strengths and the imitation skills can be well utilized in a therapy intervention program (Scharfenaker et al., 2002).

Sensory integration occupational therapy can also be helpful for children with FXS. Physical calming techniques, such as brushing of the arms and legs, joint compression, and deep back rubs, can be helpful in decreasing hyperarousal behavior or aggression. In addition to sensory integration therapy, a focus on fine and gross motor coordination and on motor planning is helpful in therapy. Hypotonia also improves with time and with intervention.

Additional techniques can be used to improve oral strength and verbalizations. PROMPT therapy has been studied in young children with ASDs but without FXS (Rogers et al., 2006), and anecdotal information suggests that it is also beneficial for children with FXS. For jaw and mouth strength, several approaches are suggested. For instance, introducing a variety of textured foods can help decrease oral sensitivity. Bagels, fruit leather, and chewy candy are excellent at improving oral function. Simple games, such as playing tug of war with a wet washcloth during bathtime, can also promote increased jaw strength (Scharfenaker et al., 2002). Other methods can be used for stimulating verbal expression, including the use of rhythm, movement, dancing, and singing. The combination of speech–language therapy with occupational therapy can be helpful, particularly for less verbal children with FXS (Scharfenaker et al., 2002). Therapies can be even more effective when they are implemented at home as well as in school.

The use of augmentative and alternative communication can be successful for children with FXS who are nonverbal. Many different methods of communication can be used to augment a child's speech production or provide an alternative to speech (Beukelman & Mirenda, 1992; Greiss-Hess et al., 2009), and an evaluation can determine which of these may be useful. For instance, some children may use signs and gestures to communicate with others. Pointing to pictures, or using the Picture Exchange Communication System, can also be a useful form of communication and choice making. Parents and teachers can create picture books or cards to help a child communicate his or her needs (e.g., the child can point to a picture of a glass of water when he or she is thirsty). For choice making, the child can choose between pictures of two things or activities (e.g., pictures of going outside or of playing in the house). More complicated picture boards can also be successful in generating expressive language. For instance, the child can select pictures that represent the words "I," "want," and "hug," to generate the sentence "I want [a] hug." Finally, speech output devices may be used to help a child communicate his or her needs through synthesized or digitized speech (Hagerman, 1999).

Computer-Based Interventions

Computer technology is a useful adjunct to the educational experience for children with FXS. They usually enjoy working on computers, and they show talent in this area. Computers can be utilized to enhance attention and build vocabulary skills, in addition to improving written language output. Adaptive peripherals, such as an expanded keyboard or IntelliKeys, can be useful in helping children with FXS to use a computer (IntelliTools, Inc., 1996).

The use of both visual and auditory feedback computer technology is most beneficial

for children with FXS. Computers can help sustain attention in some children with FXS who are otherwise easily distracted in standard learning environments. There is such a wide variety of software available in different topics of learning that it is important to evaluate a child's cognitive level and visual–spatial, memory, motor, and language skills, in order to match a beneficial program to the child (Braden, 2002; Greiss-Hess et al., 2009; Scharfenaker et al., 2002). Some helpful programs include IntelliTalk from IntelliTools, which is a talking word processor that can speak letters, words, sentences, and a combination of all three (IntelliTools, Inc., 1996); and Co-Writer from Don Johnston, Inc., which is a combination of a dictionary and software that uses artificial intelligence to predict what a person wants to say (Greiss-Hess et al., 2009). Programs such as Co-Writer were initially established to aid people with physical limitations, but children with learning and cognitive disabilities have also benefited tremendously from these programs.

Behavioral and Educational Interventions

The use of behavioral intervention techniques, including structure and positive behavioral reinforcement, is beneficial for children with FXS. Several references outline behavioral interventions for children with FXS (Braden, 2000; Chonchaiya et al., 2009; Hills-Epstein, Riley, & Sobesky, 2002). A controlled trial of a sleep intervention in children with FXS was also beneficial (Weiskop, Richdale, & Matthews, 2005).

Children with FXS can be often educated in an inclusion setting in the regular classroom (Spiridigliozzi et al., 1994). If cognitive deficits or behavioral problems are significant, then an aide or paraprofessional can be utilized in the classroom to modify assignments or to give extra explanation to the child with FXS (and perhaps others who need it). An inclusion setting helps to improve social skills, since the child imitates the typical and appropriate behavior of the other children. Education in a segregated program exclusively with children who have special needs can be problematic, particularly if all of the other children are lower-functioning, since the child with FXS will imitate the behaviors and language of the lower-functioning children. Therefore, an inclusion setting is recommended for a child with FXS whenever possible, so that the other children in the class can model appropriate behavior for the child with FXS.

An emerging area of intervention in those with FXS is in the first year of life, as newborn screening becomes more widespread. Rogers and Vismara (2008) have reviewed early intervention efforts for young children with autism, and such interventions, including the Early Start Denver model, can be utilized in toddlers with FXS (Vismara & Rogers, 2008). As targeted treatments are shown to be safe in young children, they should also be combined with intensive early interventions to correct the central nervous system deficits in FXS and guide more normal development.

Conclusions

The broad spectrum of involvement in FXS requires a variety of interventions specific to each individual. Although there are similar physical, cognitive, and behavioral characteristics among children with FXS and FXDs, there is no set curriculum that will be effective for every child. For instance, some children who are premutation carriers may not require medical or educational intervention, whereas others may benefit from medication to help with anxiety or ADHD, or from tutoring to help with school difficulties. Children who are affected by FXS usually benefit from special education support, speech–language and occupational therapy, and medication; however, there is no set formula as to the extent of therapy or the specific medications that will be most helpful for each individual child. For this reason, it is essential for every child with FXS to be seen by a physician and a team of professionals who are familiar with FXS and can create an appropriate program for the child. A list of Fragile X clinical and research centers from throughout the United States and Canada is now expanding internationally and can be found on the website for the National Fragile X Foundation (*www.fragilex.org*). Once a family knows of the FXS or FXD diagnosis, it is helpful for the family to contact the National Fragile X Foundation, which has

a network of parent support groups and resource centers around the country and internationally. The toll-free phone number of the National Fragile X Foundation is 800-688-8765. The National Fragile X Foundation can also provide educational information in papers, books, videos, and conferences for both parents and professionals.

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