

## Fragile X syndrome

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### Introduction

Fragile X syndrome (FXS) is caused by a trinucleotide (CGG)<sub>n</sub> repeat expansion in the fragile X mental retardation 1 (FMR1) gene which is located near the end of the long arm of the X chromosome. Although by now over 200 genes have been identified on the X chromosome in which a mutation leads to learning disabilities, fragile X is the most common cause of X-linked learning disabilities, representing 30% of these disorders (Sherman, 1996). Fragile X also causes learning and emotional problems without mental retardation, indicating a very broad spectrum of involvement in this disorder.

Prevalence figures for FXS are complicated, as there have been new ways of diagnosing the syndrome, and different populations have been screened for this disorder. Before the FMR1 gene was discovered in 1991 (Verkerk et al., 1991), FXS was identified through cytogenetic testing, which revealed a fragile site near the end of the long arm of the X chromosome in affected individuals. However, other mutations besides the FMR1 mutation have been discovered which lead to a fragile site at this location. Although early cytogenetic studies suggested a prevalence figure of close to 1 per 1000 in the general population, more recent DNA studies of the CGG repeat element in the FMR1 gene have demonstrated that approximately 1 in 4000 males and 1 in 6000 females in the general population have learning disabilities caused by FXS (Turner et al., 1996; de Vries et al., 1997). These studies, however, have only screened individuals with global learning disabilities. A recent report by Crawford et al. (1999) assessed almost 3000 seven- to ten-year-old children in special education classes, which included children with global and other learning difficulties. They found that 1 in 362 white students and 1 in 422 black students in special education had the fragile X mutation. When these figures are extrapolated back to the general population, assuming that all children with fragile X would be in special education classes, the overall prevalence was determined to be 1 in 3460 (whites) and 1 in 4048 (blacks). It is important to realize, however, that some

individuals, particularly females, with fragile X are relatively mildly affected, and they may not be identified as requiring special education. It is likely that approximately 1 in 2000 in the general population may be affected to some degree by the FMR1 mutation when individuals with mild learning difficulties and/or mild emotional problems are included.

Everyone carries the FMR1 gene, which produces a protein that is important for brain development. In the general population, the CGG repeat element in the FMR1 gene varies from approximately 6 to 54 repeats, with a mean of 29 to 30 repeats (Brown, 1996; Wells, Warren & Sarmiento, 1998). Individuals who have the premutation, defined as a small expansion of the CGG repeat number between 55 to 200 repeats, are carriers and are usually unaffected cognitively, although there are some exceptions to this rule as discussed below. The premutation occurs in approximately 1 in 250 females and 1 in 700 males in the general population (Rousseau et al., 1995, 1996). When the premutation is carried by a female and passed to the next generation, it will usually expand to a full mutation (more than 200 CGG repeats). The full mutation is usually methylated within the promoter region, including the CGG repeat, and is typically associated with a lack of activity of the gene, such that little or no FMR1 protein (FMRP) is produced.

Clinical involvement in fragile X is generally believed to result from a lack of FMRP. In the standard model for FMR1 expression, reduced levels of FMRP (or its absence) are thought to be due to transcriptional 'silencing' of the FMR1 gene, consequent to expansion of the CGG repeat into the full mutation range and accompanying methylation of the promoter region of the gene (Pieretti et al., 1991; Sutcliffe et al., 1992). Males with full mutation alleles that have escaped methylation generally possess detectable levels of FMRP (Smeets et al., 1995), and display a milder clinical phenotype, with specific learning disabilities in the absence of mental retardation (de Vries et al., 1996a; Hagerman, 1996b; Tassone et al., 1999). Women with full mutation alleles generally display milder clinical phenotypes, and possess higher levels of FMRP, due to the presence of some normal, active allele.

## Clinical phenotype

### Physical features

The physical phenotype of FXS is associated with a connective tissue disorder. Most individuals have soft velvet-like skin, hyperflexible joints, and somewhat prominent ears. The ear pinnae may have cupping, and the ears may appear to be prominent particularly at the tips. Finger joints can be hyperflexible, with

thumbs that can be easily dislocated (double-jointed), and the fingers may bend back to greater than 90 degrees. Feet are often flat, and the ankles may pronate inward because of flexibility in the tendons around the joints.

Approximately 25% of young children with FXS may not show these typical physical features (Hagerman, 1999). As individuals age, the face may become long and narrow and the jaw may become prominent after puberty. Joint flexibility often decreases with age; approximately 30% of adults may have hyperextensibility of the finger joints. Macro-orchidism, or large testicles, are commonly seen in adolescence and adulthood, but are usually not present in the prepubertal child. Although the testicles are large, fertility appears to be normal. Males who have full mutation alleles in their blood will only transmit premutation alleles to the next generation. All of their daughters will be premutation carriers, but none of their sons will be carriers, because they receive the Y chromosome instead of the X. Females who have the premutation or the full mutation typically pass on the full mutation to their offspring when the abnormal X chromosome is transmitted. Females with the full mutation are less likely than males to show the typical physical features, because they have two X chromosomes, and the normal X chromosome is usually active in some cells (i.e. producing FMRP), which leads to less clinical involvement. The activation ratio (AR) is defined as the percentage of cells in which the normal X chromosome is active. The greater the activation ratio, the more FMRP produced, which leads to decreased clinical involvement (Mazocco et al., 1997; Riddle et al., 1998; Tassone et al., 1999).

Additional physical features associated with fragile X include a high arched palate, a single or bridged palmar crease in the hand, a hallucal crease between the first and second toe on the sole of the foot, broad fingers and toes, and hypotonia in infancy (Hagerman, 1999).

Medical complications associated with the connective tissue abnormality in FXS include a higher incidence of inguinal or umbilical hernias, gastroesophageal reflux in infancy, an occasional joint dislocation, particularly at the shoulder, elbow or kneecap, and mitral valve prolapse secondary to a floppy mitral valve, which occurs in approximately 50% of adults with fragile X (Hagerman, 1996b). In childhood, recurrent otitis media infections, perhaps related to a collapsible eustachian tube, are a problem for over 60% of young children. Grommets (PE tubes) are often necessary to normalize hearing, which in turn leads to improvements in language and cognitive development. Ophthalmological problems including strabismus or refraction errors occur in 8–50% of affected children (King, Hagerman & Houghton, 1995; Hatton et al., 1998). These problems require treatment, and an evaluation by an ophthalmologist or optometrist is essential in early childhood. Seizures are seen in

approximately 20% of children with FXS, but they usually improve or disappear in adolescence (Musumeci et al., 1999).

### Cognitive features

Approximately 80% of males and 70% of females affected by FXS are intellectually impaired (IQ less than 70) (de Vries et al., 1996b; Hagerman, 1999). The degree of intellectual involvement can be correlated with the molecular measures, including the level of FMRP, the activation ratio, and whether the individual has a mosaic status (that is, some cells with the premutation and some cells with the full mutation, or some cells with a lack of methylation). The presence of mosaicism correlates with increased levels of FMRP, and the greater level of FMRP is correlated with higher IQ levels (Tassone et al., 1999). In a study assessing males with the FMR1 mutation, it was found that males with the full mutation in adulthood had a mean IQ of 41, whereas males with a mosaic pattern had a mean IQ of 60, and males who had more than 50% of their gene unmethylated had a mean IQ of 88 (Merenstein et al., 1996). The level of FMRP in peripheral blood leukocytes may be a useful prognostic indicator for the degree of cognitive involvement in adulthood. Recently developed measures of FMRP using immunocytochemical methods can document the percentage of lymphocytes that produce FMRP (Willemsen et al., 1997). Moreover, hair follicles have been used to detect the presence of FMRP in males and females (Willemsen et al., 1999). What is still needed, however, is a more accurate quantitative measure of actual FMRP levels in each leukocyte.

In a study of females, Performance IQ scores appeared to be more sensitive to the activity of the FMR1 gene than Verbal IQ (de Vries et al., 1996b; Riddle et al., 1998). Executive function deficits are common in females with FXS even when their IQ is in the normal range (Mazzocco, Pennington & Hagerman, 1993). Visual spatial perception problems, particularly difficulty on the Block Design and Object Assembly subtests of the Wechsler scales, are common in higher functioning females, and are also part of the global cognitive deficits found in more severely impaired males and females (Bennetto & Pennington, 1996). IQ decline is a common problem in both males and females who are significantly affected by FXS (Wright Talamante et al., 1996). Cognitive decline begins in middle childhood but becomes more significant in adolescence. If the fraction of FMRP-positive lymphocytes is greater than 50%, it is unlikely that cognitive decline will occur (Wright Talamante et al., 1996; Tassone et al., 1999).

Individuals with FXS have a number of areas of strength, including a good sense of humour, strong imitation skills, a good memory for events and

directions, and intense interests in particular areas. They also learn from their environment to a greater extent than one would predict from their overall IQ. On the Kaufman Assessment Battery for Children (KABC), the Achievement scores are almost always higher than the Mental Processing Composite scores (MPC is an IQ equivalent), with the exception of the Arithmetic scores (Kemper et al., 1986). Maths is almost always a significant deficit area even in normal IQ individuals with FXS, perhaps because of the abstract reasoning necessary for maths concepts.

## Neuropathology

Neuropathological studies in the knockout mouse and in three humans with FXS have demonstrated immature dendritic spines and a higher spine density compared with individuals without FXS (Comery et al., 1997; Irwin et al., 1999). These findings have led to the hypothesis that FMRP is essential for the normal maturation of dendritic spines and for the normal pruning process of dendritic spine connections that occur in development. A deficiency of FMRP would therefore lead to an enhanced number of dendritic spines in FXS.

Neuroimaging studies in FXS have demonstrated an enlargement of the overall brain compared to controls (Schapiro et al., 1995) and enlargement of specific regions including the caudate and the hippocampus (Reiss, Lee & Freund, 1994; Reiss et al., 1995). In addition, the posterior cerebellar vermis is decreased in patients with FXS compared to controls (Reiss et al., 1991). The reason for these changes is unknown, although the consequences can be linked to the cognitive changes that are seen. The size of the posterior cerebellar vermis in females with FXS correlates with IQ measures and executive function deficits and inversely correlates with the number of schizotypal features seen (Mostofsky et al., 1998). Two recent autopsy studies of older men with FXS (age 67 and 87 years) have demonstrated focal Purkinje cell loss in the cerebellum (Sabaratnam, 2000).

## Behaviour

Young children with fragile X usually present with language delay and hypotonia. Most children are not speaking in phrases by 2 years of age, although this usually appears between the ages of 3 and 5 years. Hyperactivity and a short attention span are typical in the pre-school period. Earlier in infancy, behaviour may be marked by irritability and a lack of typical cuddling. These problems may be related to sensory integration difficulties including avoidant

behaviour to certain touch stimuli. Usually this sensitivity to touch is overcome in early childhood such that these children will hug, but intermittently they may demonstrate a sensitivity to touch, as when their fingernails are being cut, or their hair brushed.

The sensitivity that children with FXS demonstrate to visual, tactile, auditory and olfactory stimuli is described collectively as sensory integration dysfunction (Scharfenaker et al., 1996). Recent electrodermal studies, which measure sweat response to stimuli, have shown that children with FXS are over-reactive to a wide variety of sensory stimuli, with an enhanced amplitude and poor habituation compared to controls (Belser & Sudhalter, 1995; Miller et al., 1999). The sympathetic system controls the sweat response to stimuli, and these studies document an enhanced sympathetic response. This may be the physiological basis of the hyperarousal to sensory input in children with fragile X. This enhanced response may manifest clinically as an increase in anxiety in certain situations, particularly those that involve transitions or unfamiliar surroundings. Sometimes the anxiety may result in aggression or social withdrawal. Aggression is more common in adolescence and adulthood (Merenstein et al., 1996), and may be more difficult to handle at these ages. Many of the autistic-like features that have been described in FXS, including poor eye contact, hand flapping with excitement, hand biting when angry or anxious and tactile defensiveness, may be related to sensory integration dysfunction.

Most affected individuals are interested in social interactions, but shyness and social anxiety, along with sensory integration problems, may interfere with appropriate social behaviours (Freund, Reiss & Abrams, 1993; Hagerman, 1996b; Mazzocco et al., 1997; Franke et al., 1998). Emotional perception in facial expressions in boys with FXS was comparable to controls with a similar IQ (Turk & Cornish, 1998). However, approximately 15% of children and adults with FXS meet DSM-III or DSM-IV criteria for autism because of additional deficits in social relatedness (Hagerman et al., 1986; Baumgardner et al., 1995). When younger children with FXS are evaluated for autism, the rate may increase to 25 to 33% (Turk & Graham, 1997; Bailey et al., 1998b; Rogers, Wehner & Hagerman, 2000). The highest rate of 33% was reported for pre-school children with FXS aged between two and four years (Rogers et al., 2001). The autism of children with FXS was indistinguishable from that of children who had idiopathic autism using the ADOS and the ADI measures to assess autism. However, the autistic features of many children with FXS who are diagnosed in the pre-school period, will improve after intensive therapy focused on improving their social deficits and enhancing language and motor abilities. Those children whose autism persists into adulthood may have a core

deficit in social relatedness which could reflect additional genetic factors superimposed on the FMR1 mutation. As their interest in social interactions evolves in early childhood, those with better linguistic, cognitive and imitation skills appear to do best in long-term follow-up. However, problems with shyness and social anxiety often persist, and in adulthood mild social withdrawal is very common (Kerby & Dawson, 1994).

Obsessive–compulsive behaviour is a common problem in both children and adults with FXS. In childhood, there may be intense interests in cars, sports or other objects. Perseverative behaviours and language are also common. Children often insist on watching the same video over and over again, or persevere on certain themes seen in a video or movie. Well known phrases in films and television may be incorporated into a vocal routine that is often difficult to distinguish from a complex vocal tic. As an example, when the film *The Mask* became popular, many individuals with FXS adopted words and mannerisms taken from the main character, (e.g. ‘smokin’, said with a swing of the arm).

In adolescence, obsessional thinking may be focused on individuals of the opposite sex, with intense infatuations that, on occasion, lead to aggressive behaviour when that person is present. Sexual obsessions, such as a foot fetish, are not uncommon. Effeminate behaviour can be seen in approximately 20% of males with FXS. At first it was thought that this was related to enhanced imitation abilities and movements, such as flicking the hair or effeminate hand movements, which were demonstrated in a perseverative way by males who had female caretakers or females as case managers. However, the changes in neuroanatomical structure present in FXS, including enhanced dendritic connections and enhancement in the size of the hippocampus and caudate, may be a more likely cause for effeminate behaviour. Some adult males with FXS who are higher functioning and who have effeminate behaviour describe themselves as homosexuals in adulthood. For most males with FXS, the degree of intellectual deficit interferes with their sexual identity. The majority of males with FXS who have moderate learning disabilities or who are at the lower end of the mildly intellectual disabled range, are not sexually active. Males whose cognitive deficits fall within the very mild or borderline to normal range are usually sexually active and may have either a heterosexual or homosexual preference.

The most common behavioural problem in children with FXS is attention deficit hyperactivity disorder (ADHD). Approximately 70–80% of boys with FXS have some degree of ADHD, and most have hyperactivity combined with attention and concentration difficulties (Hagerman, 1996b). The hyperactivity tends to improve with age, and usually resolves by late adolescence or adult-

hood. However, the attentional difficulties, along with impulsivity and distractibility, often persist throughout adolescence and into adulthood. ADHD symptoms can be treated effectively with stimulant medications, as described below. Hyperactivity may also be associated with the problem of hyperarousal to sensory stimuli, and this can also be addressed with medication and psychological therapies.

Girls with FXS are less likely to be overtly hyperactive, although attention and concentration problems are common and are present in 30–50% of those with the full mutation (Hagerman et al., 1992; Freund et al., 1993). Girls with FXS who are not hyperactive or impulsive are at greater risk for selective mutism, which is associated with anxiety (Hagerman et al., 1999). The shyness and social anxiety problems may cause great difficulties in school, so it is usually in this environment that a child may become less and less talkative, whisper or become mute. Academic pressures to come up with an answer when questioned by a teacher in school may eventually lead to mutism in the classroom, and this problem usually continues in the medical clinic where the child is subsequently evaluated. Usually the parents indicate that communication at home among family members is normal. Selective mutism may also occur very rarely in higher functioning males with FXS.

In general, the communication of individuals with FXS usually includes perseverative and repetitive language with the frequent use of specific statements, such as 'let's get out of here' or 'I hate you' (Sudhalter et al., 1990; Sudhalter, Scarborough & Cohen, 1991). The use of these phrases and more automatic verbalizations is very common, in addition to mumbling with a lack of eye contact. Verbal dyspraxia is common in boys with FXS (Spinelli et al., 1995). Hand mannerisms such as hand flapping or other types of stereotypies may also occur during the communication process. Because of these oddities in communication and social interaction, some adolescent and adult individuals are described as having schizotypal features, features on the spectrum of pervasive developmental disorder (PDD) or Asperger-like features (Hagerman, 1996b). Because of the close association between FXS and autism spectrum disorders including Asperger syndrome, it is important that individuals who present with these diagnoses are also assessed using the FMR1 DNA test for FXS.

## **Involvement in individuals with the premutation**

Most individuals who have the premutation (55-200 CGG repeats) have normal intellectual abilities (Reiss et al., 1993). However, they may have a limited



number of physical features typical of the syndrome, when compared to controls, such as slightly prominent ears, a prominent jaw, or a high arched palate (Riddle et al., 1998). In addition, premature menopause is seen in approximately 25% of women who carry the premutation (Schwartz et al., 1994; Vianna-Morgante et al., 1996), and twinning occurs at a rate that is three times that of the normal population (Turner et al., 1994). Several studies have assessed emotional problems, and difficulties with anxiety, mood lability or depression can be seen in approximately 20–30% of women with the premutation (Franke et al., 1996; Sobesky et al., 1996; Franke et al., 1998).

More recently, a small number of individuals with the premutation have been detected with autism, or specific learning disabilities (including in maths), ADHD problems, or mood lability (Hagerman et al., 1996; Tassone et al., 2000b). In the standard model for FMR1 expression, individuals with premutation alleles are presumed to have normal levels of mRNA and protein, since such alleles are generally not methylated. However, FMR1 mRNA levels in premutation males were recently demonstrated to be elevated relative to those of normal controls, despite normal to moderately low FMRP levels (Tassone et al., 2000a). Furthermore, elevated mRNA levels persist in the full mutation range in the absence of methylation-coupled silencing (F. Tassone et al., unpub. data). These observations, coupled with the earlier observation that the efficiency of translation of the FMR1 mRNA is decreased in the full mutation range (Feng et al., 1995), suggest that elevated message levels may be a compensatory response to impaired translation. This implies that molecular-therapeutic strategies must consider means for enhancing/activating both transcription and translation, and that enhancement of translation alone may lead to clinical improvement.

## Outcomes in adulthood

### Cognitive abilities and attainments

Most males with FXS with the full mutation are moderately intellectually impaired (Merenstein et al., 1996), but they may show strengths relative to their IQ scores in adaptive behaviour and daily living skills (Dykens et al., 1996). There are various vocational endeavours in which they may excel; many do well in the catering or restaurant trades, particularly working in food preparation or washing dishes; they may also do well in laundry, gardening and janitorial work. However, vocational training is essential in secondary school, and in the United States (US) most special education programmes will continue job training until 21 years of age. The use of a job trainer after high school to

develop specific skills in the job setting is also usually required. Individuals with moderate or severe learning disabilities will usually need a sheltered workshop setting with more limited vocational goals.

The memory skills of adults with FXS can be an advantage in the vocational setting. For instance, one adult we followed up did well at delivering mail inside of an office building, because he quickly learned the names of all of the people in the building, and he enjoyed the brief social interaction with these individuals as he delivered the mail.

Computer technology has been under-utilized in vocational training. Computer skills are typically emphasized in the US in elementary education, but not in high school or in vocational training. The ability to use computers can be a strength in many individuals with FXS and does not necessarily correlate with IQ (C. Bodine et al., unpub. data). Software programmes, such as Write Out Loud and Co:Writer, can help to improve written language output and computer technology can be used to enhance vocational endeavours. One example of this is a young man who works with his father selling plans via the computer for small construction projects, such as building a tool shed. He is able to handle the orders that come in, and can e-mail the appropriate plans to the customers. For those individuals with FXS who are socially very shy or have autistic features, interaction through e-mail is less intimidating.

Occasionally, behaviour problems such as mood instability, temper outbursts, aggression, or severe anxiety can interfere with vocational and social endeavours. Significant behavioural problems which interfere with daily living occur in approximately 50% of adults with FXS, and around one-third have problems with aggression (Hagerman, 1996b), although a longitudinal study showed that aggression was less of a problem after 7 years in follow-up (Einfeld, Tonge & Turner, 1999). A variety of psychopharmacological interventions can be helpful for these behaviour problems (see below). In addition, environmental modifications can significantly decrease excessive stimuli in a vocational setting, thereby decreasing hyperarousal, anxiety and subsequent aggression. In employment many individuals do well in settings without excessive stimuli or noise, such as janitorial work in an office building after hours, or working in a library or garden.

## **Social and emotional adjustment**

Although the majority of adults with FXS do not have autism or severe social deficits, mild social interactional difficulties are common and are exacerbated by anxiety or hyperarousal. There is a tendency towards greater social with-

drawal in adulthood, simply because many adults feel more comfortable watching their favourite television programmes or listening to the stereo in the quiet of their room, instead of interacting socially (Einfeld et al., 1999). It is important for adults with this tendency to have regularly scheduled and predictable social interactional activities to avoid increasing social isolation.

Higher functioning males and females with FXS are able to engage in more intense social interactions and sexual activity. Counselling can be helpful to deal with problems such as tactile defensiveness, and other difficulties associated with intimacy. Executive function deficits are typically seen in individuals with the full mutation who are higher functioning, or even in those with a normal IQ. These lead to problems in the ADHD spectrum, including impulsivity, attentional difficulties and organizational problems. In addition, features such as tangential language, poor topic maintenance and schizotypal features are commonly seen and are associated with the degree of executive function deficits that an individual manifests (Sobesky, 1996). It is unusual for a male with FXS to reproduce, but this occasionally occurs; in such cases all male children would be unaffected by FXS, but females would be premutation carriers. On the other hand, females with the full mutation more frequently reproduce than males, because their cognitive abilities are generally higher. Significant social and emotional problems occur, however, when the children of women with FXS are also significantly affected. We have seen several cases of child abuse when the mother herself has significant impulse control problems related to FXS and the children also have FXS. Significantly affected mothers, particularly those with mild learning disabilities, need high levels of support in their efforts to raise children with FXS, as well as unaffected children. Psychological intervention can be helpful, and can provide guidance to the parents in behavioural management and in sorting out the difficulties that they may be experiencing in their own lives (Sobesky, 1996).

In terms of psychiatric disorders, delusional behaviour (Silva, Ferrari & Leong, 1998) or even overt psychotic thinking may occasionally occur in adults with FXS (Hagerman, 1996a,b). These problems require treatment with antipsychotic medication as described below. Women with the premutation often experience significant levels of anxiety or depression, particularly if they are raising children with FXS (Franke et al., 1996; Franke et al., 1998). Supportive therapeutic work can provide guidance, behaviour management and further understanding and problem solving advice regarding their own psychopathology (Sobesky, 1996).

## Physical problems

Connective tissue problems including loose joints and joint dislocations usually improve with age, perhaps related to changes in the tendons allowing for greater stability of the joint. Problems including hernia formation may persist into adulthood. On rare occasions, more significant orthopedic problems may occur in adulthood (Davids, Hagerman & Eilert, 1990), for example severe pes planus which requires orthopedic intervention, such as surgery, may occur in adulthood (Davids et al., 1990).

Approximately 50% of adults have mitral valve prolapse, presumably related to the elastin abnormalities associated with the connective tissue dysfunction in FXS (Waldstein et al., 1987). The mitral valve prolapse is usually benign, although on rare occasions it can lead to mitral regurgitation (Hagerman, 1996b). There have been a number of cases of sudden cardiac death in adults with FXS (Hagerman, 1996b; Sabaratnam, 2000; D.Z. Loesch, pers. comm.). It is possible that these deaths were caused by an arrhythmia associated with mitral valve prolapse, or a rare conduction problem which may be associated with the absence of FMRP. Further studies of cardiac pathology and sudden death are necessary. This problem may also explain the slightly increased rate of sudden infant death syndrome (SIDS) in infants with FXS (Fryns et al., 1988).

Hypertension is not uncommon in men with FXS, but it has not been studied. Perhaps the elevated blood pressure that is frequently seen relates to the anxiety that some individuals experience when they are seen in a clinic situation (Hagerman, 1996b). It is also possible that the connective tissue disorder and abnormal elastin fibres affect the resiliency of the blood vessel walls and predispose individuals to hypertension.

There are rare reports of patients who have also experienced dilated ureters and reflux associated with renal scarring and atrophy. There may be a predisposition for dilated ureters because of the connective tissue problems and elastin abnormalities seen in FXS (Hagerman, 1996b).

On occasion, seizures may persist into adulthood, although most disappear in adolescence or earlier (Musumeci et al., 1999).

Growth abnormalities can occur in individuals with FXS. These include an enhancement of growth in early childhood, and blunting of the adolescent growth spurt leading to a higher incidence of short stature in adulthood (Loesch, Huggins & Hoang, 1995). Hypothalamic dysfunction is probably related to these mild growth abnormalities, and it may also be the cause of macro-orchidism. The typical adult testicular size in men with FXS is approximately 50 ml, which is twice as large as normal, although sizes up to 100 ml

have been reported (Butler et al., 1992). Macro-orchidism itself is not associated with medical problems, although it is possible that the weight of a significantly large testicle may predispose an individual to an inguinal hernia.

## Interventions

Although no cure is yet available for FXS, there are various interventions that can be helpful. Usually a variety of interventions can work synergistically. For instance, the use of psychopharmacology, individual therapy in the language and motor area and psychological interventions can be quite helpful for the developmental and behavioural difficulties associated with FXS (Hagerman, 1996a; Scharfenaker et al., 1996; Sobesky, 1996).

## Childhood

Young children present with hypotonia, language delays and motor problems (Bailey et al., 1998a). Behaviour difficulties such as irritability, tantrum behaviour or hyperactivity are also common. Early childhood intervention programmes that include language therapy and motor therapy are essential in the first 3 to 4 years of life. Many families find that working with a behavioural specialist to help with problems at home, including behavioural management techniques such as 'time out' and appropriate positive reinforcement, can be very beneficial. The use of sensory integration therapy through an occupational therapist has also been found to be helpful, although no controlled studies have been conducted (Scharfenaker et al., 1996). The occupational therapist can work on the development of fine and gross motor skills, in addition to motor planning and sensory integration.

Approximately 10% of children with FXS do not speak in short phrases by 5 years of age. Children with lower verbal abilities or those who are non-verbal require even more intensive speech and language therapy than those with mild delays. The combination of language therapy and occupational therapy can be beneficial, because the use of movement, rhythm, and even music can help to facilitate verbalizations. Augmentative communication techniques can also be helpful, including low-tech programmes such as the Picture Exchange Communication System (PECS) or high-tech aids such as a computer system that can be programmed for verbalizations (Hagerman, 1999).

Ongoing support with special education in elementary school is beneficial for the majority of children affected by FXS. Whenever possible, education in the mainstream situation should be sought, as most children with FXS will

mimic the behaviours of other pupils in their class. If autism is present, then an intensive autism educational programme which includes behavioural strategies and the use of structured teaching programmes such as TEACCH, is helpful (Lovaas, 1987; Schopler, Mesibov & Hearsey, 1995; Rogers, 1998).

Medications can be beneficial for a variety of behavioural problems. Stimulants, including methylphenidate, dextroamphetamine, or Adderall, are generally used for the treatment of hyperactivity or ADHD symptoms (Hagerman, 1996a). If significant hyperarousal is present, then the use of clonidine or guanfacine can be helpful (Hagerman et al., 1995). Both of these agents have a calming effect and decrease the amount of noradrenaline at the synapse. This is clinically beneficial for many children with FXS, perhaps related to excessive sympathetic stimulation in FXS, although one of the side effects is significant sedation (Hagerman, Bregman & Tirosh, 1998). When clonidine is combined with stimulant medication then careful follow-up with electrocardiograms is needed to make sure that prolongation of cardiac conduction does not occur.

Treatment of excessive anxiety or obsessive–compulsive behaviour is frequently carried out with the use of a selective serotonin reuptake inhibitor (SSRI). Fluoxetine (Prozac) was one of the first SSRIs used clinically, and it is associated with significant social activation. Fluoxetine has been helpful in treating individuals with autism or pervasive developmental disorder (PDD-NOS) because of the beneficial effects on social activation and on enhancing language (DeLong et al., 1998). An SSRI such as fluoxetine may be considered in early childhood for those who have both FXS and autism. An SSRI such as fluoxetine, sertraline, paroxetine or fluvoxamine can also be given in middle childhood or adolescence if significant problems with anxiety or obsessive–compulsive behaviour develop. For mild degrees of moodiness, an SSRI may be helpful in smoothing out irritability or mild outbursts. More severe mood instability, however, requires the use of a mood stabilizer such as carbamazepine, valproic acid or lithium. The newer atypical antipsychotics such as risperidone, olanzapine or quetiapine (Seroquel) are also helpful in stabilizing mood and/or decreasing aggression when other agents are not effective. The atypical antipsychotics have a lower risk for tardive dyskinesias and are usually well tolerated (Kapur & Remington, 1996). An increase in appetite, which can lead to significant obesity, is a frequent problem with the use of risperidone and olanzapine. This problem is less likely with quetiapine but there has been very little paediatric experience with the use this drug. Risperidone has been used most commonly of all the atypical antipsychotics in childhood and it is usually well tolerated when the dose is kept low, i.e. 1–2 mg per day (Hagerman, 1999).

Medical intervention is important in the treatment of children with FXS.

Because recurrent otitis media infections are common and can interfere significantly with language development, it is important to treat recurrent infections aggressively with antibiotics and/or placement of PE tubes (grommets). In addition, children with FXS should be evaluated by an ophthalmologist or an optometrist to identify and treat problems such as strabismus and refraction errors, so that amblyopia does not develop. Normalization of both hearing and vision are essential for appropriate development and subsequent academic learning.

When there is a possible history of seizures, the person should receive an EEG, and if spike wave discharges are present, subsequent treatment with an anticonvulsant should be considered. Treatment with carbamazepine or valproic acid is usually sufficient to control the seizures (Wisniewski et al., 1991; Musumeci et al., 1999), although occasionally additional anticonvulsants such as gabapentin, lamotrigine or topiramate may be required. The newer anticonvulsants can be very beneficial as adjunctive agents in controlling seizures and may also be helpful in mood stabilization (Hagerman, 1999).

## Adulthood

The transition from adolescence to adulthood may be difficult because of developmental problems including cognitive deficits and emotional difficulties. Some families have found that a gradual transition into living more independently can be helpful. For example, one family built an apartment attached to the family home to give their son with FXS some degree of independence, thus allowing for limited supervision from the family. Participation in adult programmes associated with supervised apartment living or group homes are more common alternatives. Most adult males with FXS require some degree of supervision in their living situation, but the supervision may be limited, such as daily or weekly visits. Adult programmes should involve some plans for enhancing social interaction, such as a bowling night or regularly scheduled group activities.

Behavioural problems that occur in adulthood include periodic outbursts with either verbal or physical aggression. These behaviour problems are often associated with anxiety and mood instability. Sometimes treatment with an SSRI alone will significantly decrease anxiety and obsessive-compulsive behaviour and smooth out minor problems with moodiness or aggression (Hagerman, 1999). In some instances, however, additional medication such as clonidine, a mood stabilizer, or an atypical antipsychotic, such as risperidone or quetiapine, is needed. Often an SSRI is combined with an atypical antipsychotic to decrease aggression and decrease anxiety. On occasion, sensory integration

**Table 8.1. Clinical implications of fragile X syndrome (FXS)**

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- Counselling and cognitive-behavioural treatment with a psychologist or social worker can help individuals with FXS to recognize their emotional state and utilize self-calming techniques
  - Counselling can also be helpful to treat interpersonal difficulties, and sexuality issues
  - Anxiety and obsessive/compulsive behaviour is common in adult males and females with FXS and usually responds well to psychological interventions and medication
  - Occasional excessive activation or mania may develop with the use of an SSRI, but this frequently responds to lowering the dose
  - Social withdrawal is common in adulthood and requires efforts to plan and facilitate social interactions
- 

therapy with an occupational therapist can be helpful to teach the adult calming techniques that can be carried out by the patients themselves or family members. Referral to a psychologist or social worker may also be beneficial to help the individual recognize his or her emotional state and to teach self-calming techniques such as visualization, counting or simply walking away from a situation that could cause a behavioural outburst. Counselling can also be helpful to sort out interpersonal difficulties or sexuality issues (Brown, Braden & Sobesky, 1991).

After an individual is diagnosed with FXS, genetic counselling is an essential part of the treatment programme (Cronister, 1996). The whole family tree needs to be reviewed, and individuals at risk for being carriers or affected by FXS should be tested with DNA studies to document the extent of the CGG repeat expansion. Genetic counselling can also be helpful in prenatal diagnostic studies that involve either chorionic villus sampling or amniocentesis. Decisions regarding continuation of a pregnancy or termination of an affected fetus are personal decisions made by the family and should be supported by the genetics counsellor and by the treatment team.

Families should also be referred to a parent support group where available and to the national and international support groups which have been set up to help families, to promote research and provide information and advice about the syndrome for families and professionals.

In the future, it can be expected that gene therapy or protein replacement therapy will be available for individuals with FXS. Until then a co-ordinated treatment programme that involves the input of a variety of professions, in addition to medical interventions, can lead to very productive lives and significant well being in those affected by FXS.

For a summary of the clinical implications of FXS see Table 8.1.



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