Fragile X Syndrome: An Overview of Cause, Characteristics, Assessment and Management

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Conflict of Interest

The authors declare no conflict of interest

Abstract

Fragile X syndrome (FXS) is the most common identifiable cause of inherited intellectual disability and autism spectrum conditions, and is associated with a range of physical, cognitive and behavioural characteristics. Alongside intellectual disability, heightened rates of autism spectrum disorder, anxiety disorders, attention-deficit-hyperactivity disorder, self-injury and aggression are reported. Timely identification of FXS as well as assessments of common co-morbid psychological conditions and underlying health problems are essential to ensure individuals with FXS receive appropriate support. This article provides an overview for clinicians of current literature on the cause of FXS as well as the key physical, cognitive, and behavioural characteristics with a focus on children and adolescents.

Keywords: fragile X syndrome, intellectual disability, autism spectrum disorder, anxiety, attention-deficit-hyperactivity-disorder

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Genetic Cause

FXS is a single gene disorder resulting from an expansion of cytosine-guanine-guanine (CGG) trinucleotide repeats in the 5' untranslated region of the Fragile-X-Mental-Retardation 1 (*FMR1*) gene on the Xq27.3 site, at the tip of the long arm of the X chromosome. The normal CGG segment in the general population repeats 5-40 times. Individuals with more than 200 repeats have the fragile X full mutation and those with 55-200 repeats have the fragile X premutation with repeats of 41-54 known as the intermediate or 'grey zone'. The excessive repeats in the FXS full mutation causes methylation and silencing of the *FMR1* gene, halting production of Fragile-X-Mental-Retardation-Protein (FMRP), a protein crucial to the regulation of other proteins and neural synapse development.

Prevalence of Fragile X Syndrome

There is considerable variability in prevalence rates for FXS across studies. A meta-analysis estimated that 1 in 300 females and 1 in 850 males in the total population have the fragile X premutation; while 1 in 11,000 females and 1 in 7,000 males have the full fragile X mutation.

Fragile X Premutation

Females with fragile X premutation are at risk for Fragile X-associated Primary Ovarian Insufficiency (FXPOI) and males and females are at risk of developing the neurodegenerative condition, Fragile X-Associated Tremor/Ataxia Syndrome (FXTAS). Approximately 20% of female carriers experience FXPOI, defined as the cessation of menstrual periods before age 40. The risk of developing FXTAS increases with age and, overall, occurs in 40% of male

and 16% of female carriers. Core features include tremor and/or gait ataxia with Parkinsonism and cognitive decline also reported. Increased rates of other conditions have been reported in children with the fragile X premutation including anxiety, attention-deficit-hyperactivity-disorder (ADHD), social deficits and autism spectrum disorder (ASD). In adults, anxiety and depression are common, whilst obsessive-compulsive disorder, ADHD and substance abuse are also reported. These characteristics are important to consider when working with mothers of children who are accessing clinical services as mental health problems might be exacerbated by the stress of raising a child with FXS.

Heritability

Female premutation or full mutation carriers with one typically functioning X chromosome and one mutated X chromosome have a 50% chance of passing their mutated X chromosome onto offspring. The CGG repeats can increase during meiosis in females, meaning that a female carrying the premutation may have a child that is unaffected by FXS and has no mutation (if they inherit the typical chromosome), a child with the premutation, or a child with the full mutation. A female carrying the full mutation may have a child that is unaffected by FXS or a child with the full mutation. Male premutation carriers will pass their premutation to all daughters with the CGG repeat length not typically increasing during meiosis. As a genetically inherited condition, a diagnosis of FXS or of an ***FMR1*** premutation has implications for the wider family, typically explored through genetic counselling. Despite developmental delay appearing before 12 months of age in children with the full mutation, identification and diagnosis of FXS often do not occur until after 3 years of age and sometimes much later as symptoms may be attributed to ASD or developmental delay without exploration of the genetic cause. By this time, another affected sibling or extended family member may have been born. Given the high prevalence of the premutation, as well as

the associated conditions and wider familial implications, genetic testing for FXS is recommended for all people with an intellectual disability (ID) or global developmental delay.

Fragile X Full Mutation: Overview and Sex Differences

The full mutation in males is usually associated with moderate to severe ID with the average IQ score under 55. Due to random X-inactivation (i.e., the typical "turning off" of one X chromosome in each cell), females tend to be less clearly affected than males, with a more variable profile and often 'hidden' presentations. IQ is more heterogeneous in females ranging from no presence of ID to moderate ID. Specific challenges with maths, reading and visuospatial tasks are reported, alongside cognitive and social emotional features typically associated with FXS. These include anxiety, autistic characteristics, shyness and poor eye contact, and attention-deficit-hyperactivity characteristics including short attention span, overactivity and impulsivity. Alongside ID, FXS is associated with a range of physical and behavioural characteristics (detailed below and in Table 1). Less research has been conducted on females with FXS, most likely due to lower prevalence and less clear symptomatology. Given the available literature, the focus of the current review is on males with the full mutation of FXS.

[Insert Table 1 here]

Physical Features

FXS is associated with some facial characteristics but these, in isolation, are not highly diagnostic. Physical features associated with FXS include prominent ears, a long narrow face, macroorchidism in males, flat feet, a high-arched palate, hyper-flexible joints and hypotonia.

There is a heightened risk of some physical health problems including recurrent otitis media (55%), sleep difficulties (26-32%), epilepsy (10-20%), sleep apnoea (7%), mitral valve prolapse (0.5% in children increasing to 50% in adults), gastroesophagal reflux (11%) and ocular disorders including refractory errors and strabismus (18%)[1].

Physiological Hyperarousal, Stress and Anxiety

Physiological hyperarousal and stress is well-documented in FXS through elevated heart rate, reduced vagal activity, and elevated cortisol. Hyperarousal is believed to exacerbate many of the behavioural features of FXS such as impulsivity, self-injurious and aggressive behaviour, as individuals may be less able to control their behaviour whilst hyperaroused. The majority of people with FXS experience clinical levels of anxiety. Approximately 80% of males with FXS meet clinical cut off for an anxiety disorder with social phobia and specific phobias being the most common[2]. Antecedents of anxiety, such as negative affect, emerge early in young children with FXS. Many people with FXS do not receive a diagnosis of anxiety, which is a barrier to appropriate treatment, monitoring and management. A key challenge is the lack of suitable tools to measure and assess anxiety when self-report may not be possible and is often unreliable. Anecdotally, many individuals with FXS may present differently from typically developing individuals experiencing anxiety by displaying different behaviours while anxious, or by being affected by different triggers that interact with other phenotypic characteristics such as change in routine. However, evidence is limited by the use of measures designed for typically developing individuals which do not capture atypical presentation. There are behavioural markers that may indicate anxiety, particularly during social situations. These include eye gaze aversion, fidgeting/physical discomfort, face-hiding/eye-rubbing, hand-biting, refusals/fleeing situation/avoidance, reduced vocal

length/poorer vocal quality, and behavioural distress/negative affect. We strongly recommend that anxiety assessment and intervention (see below) should always be considered.

Social Avoidance

The social phenotype of FXS is characterised by avoidant behaviours such as eye gaze aversion, which is almost universal and is unlikely to be accounted for by heightened ASD characteristics alone. Over 80% of males with FXS show social avoidance but this decreases throughout the course of an interaction (a "warm up effect"). Social avoidance generally emerges in infancy, from 4 months of age, and increases in severity through childhood and adolescence, stabilising in early adulthood. Although the majority of males with FXS display social anxiety and socially avoidant behaviours, paradoxically they also show willingness to interact and similar levels of social motivation as people with Down syndrome.

A meta-analysis indicated that 30% of males with FXS meet criteria for ASD but prevalence figures vary widely. Sensory sensitivities are very common in FXS. Although there is symptom overlap between FXS and ASD, there are differences in the profiles of behaviours. Males with FXS, even those co-diagnosed with ASD, are more socially responsive, less likely to engage in pronoun reversal (a communicative behaviour characteristic of ASD), less likely to display some higher-order repetitive behaviours, and more likely to display language and cognitive impairments than males with idiopathic ASD. A co-diagnosis of ASD is associated with a higher risk for some physical health problems, more severe ID, heightened self-injury, and prolonged impulsive behaviour over time. Given the heightened prevalence and conferred risk for health and behavioural challenges, an autism assessment should be completed with all individuals with FXS. However, assessment and diagnosis of ASD in FXS is a challenge given the lack of available tools that are sensitive to the subtle differences in

presentation. Although there is debate surrounding additional diagnoses of behaviourally defined conditions (e.g. ASD, ADHD) in the context of a well-defined genetic condition, diagnoses may improve access to support services.

Cognitive Difference

Cognitive assessments and parental reports highlight particular difficulties with sustained attention, inhibition, impulsivity, executive function, and language over and above that expected given ID, and with profiles of weaknesses that manifest differently compared to other groups with ID of genetically identified aetiology[3]. These difficulties emerge early and are pronounced around age 4. Early intervention strategies are helpful. Many features of cognitive difference seen in FXS are associated with ADHD symptomatology. This is mirrored behaviourally, with hyperactivity and impulsivity well documented and a large proportion of males with FXS meeting criteria for an ADHD diagnosis (~60%;). ADHD symptomatology increases over time with impulsivity being the main driver. Language impairments are often more severe than non-linguistic cognitive impairments in males and some females.

Self-injury and Aggression

Although prevalence figures vary, the majority of studies indicate that self-injurious behaviour is observed in approximately 50% of males with FXS, with hand-biting being the most common form. Escaping from interactions, transitions and demands or tasks are common functions of self-injurious behaviour, as identified by functional analyses[4]. Persistence is high, with 77% continuing to show self-injurious behaviour over an eight-year time period. Aggressive behaviour also occurs in approximately 50% of males with FXS and

persists in 69% of individuals over an eight-year period. The most common forms of aggressive behaviour are hitting and kicking others.

Early markers of repetitive behaviour and impulsivity predict persistent self-injurious behaviour and aggressive behaviour, respectively. Therefore, young children displaying repetitive behaviour and impulsivity should be monitored for the emergence of self-injurious and aggressive behaviour. Research in other rare genetic syndromes has shown an association between pain and discomfort caused by underlying health conditions and self-injurious behaviour. Investigation of potentially painful health concerns, particularly otitis media given its frequent reoccurrence, should be undertaken in anyone displaying self-injurious behaviour.

Interventions

Environmental and behavioural interventions often applied in ID and autism populations for the FXS behavioural and cognitive characteristics can be applied to improve quality of life. These include:

- Psychological evaluations and interventions including positive behavioural support, functional behavioural analyses, relaxation training and desensitisation for specific phobias
- Speech and language therapy; including communication supports
- Occupational therapy; including sensory assessment and treatments and daily structures
- Social and welfare input
- Special educational input
- Vocational guidance

In combination with these environmental and behavioural strategies, judicious use of medications for specific emotional and behavioural symptoms may be considered but the efficacy of medical treatment in this population is not well understood. Selective serotonin reuptake inhibitors (SSRIs) may be prescribed to manage the symptoms of anxiety in adolescence and adulthood. However, there is currently limited research on their effectiveness. Methylphenidate is often prescribed to alleviate the symptoms of ADHD, especially in young males with FXS. Small studies show an improvement on attention measures with medication but research is limited.

Conclusion

Alongside ID, many people with FXS display behavioural characteristics and symptoms associated with ASD, ADHD and anxiety. The key challenges are diagnosing and treating co-morbid disorders given that the profiles, presentation, and developmental course of conditions often differ relative to the general population. In addition, subclinical levels of symptomatology may be more problematic for individuals with FXS than in the general population due to an interaction with the associated phenotype. However, there is wide variability in this syndrome. Co-occurring mental health problems predict less independence in adulthood and so appropriate monitoring and intervention is critical. Awareness of the heightened prevalence rates of ASD, ADHD, anxiety and behaviours that challenge is paramount to avoid diagnostic overshadowing and ensure individuals receive appropriate care. Emerging research on early markers of later ASD diagnoses (social avoidance), ADHD diagnoses (impulsivity), and behaviours such as repetitive behaviour and impulsivity, indicates the importance of monitoring emerging behaviours to adopt a preventative approach.

Finally, there are a number of positive outcomes for many people with FXS into adulthood. One study reported that the majority of males (60%) and females (73%) are in either supported placements, part-time or full-time employment, have multiple friendships (81% males; 91% females), and participate in three or more leisure activities (87% males; 96% females. In addition, a variety of behavioural interventions targeting language, cognitive, and social skills have documented efficacy for affected individuals.

Practice Points

- Identification of FXS and genetic counselling is crucial given the known phenotype and implications for families
- Anxiety, autism and ADHD assessments should be conducted in FXS allowing for atypicalities in presentation
- Underlying health conditions can exacerbate or cause anxiety, self-injurious behaviour, aggression, and attention problems, and should be identified and treated
- Early behavioural markers of social avoidance, repetitive behaviour and impulsivity should be monitored and intervention considered to prevent a negative impact of autism characteristics, ADHD characteristics, self-injurious behaviour and aggressive behaviour.

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Table 1. A summary of key information on fragile X syndrome (FXS)

Key information on fragile X syndrome (FXS)
FXS is the most common identifiable inherited cause of intellectual disability
People with FXS are at heightened risk of some physical health problems, notably connective tissue problems, otitis media and mitral valve prolapse
Heightened rates of anxiety, ASD and ADHD occur in FXS but the presentation may differ from that in the general population
Persistent self-injurious and aggressive behaviour may be associated with underlying health problems
Early behavioural markers predict later diagnoses of ASD, ADHD, as well as the presence of self-injury and aggression.