

The Fragile X Society

The Health & Social Aspects of Fragile X Syndrome

by Dr Jeremy Turk, Professor of Developmental Psychiatry & Consultant Child & Adolescent Psychiatrist, St George's, University of London & South West London & St George's Mental Health NHS Trust, March 1996 (revised August 2008)

The fragile X syndrome is the most common inherited cause of intellectual disability. Despite its sex-linked mode of inheritance about one third of female “carriers” are affected clinically (some severely so) while a fifth of males with a fragile X chromosome are clinically unaffected. The syndrome derives its name from the appearance of a ragged, hypochromic site just above the tip of the X chromosome when peripheral lymphocytes (white blood cells) are cultured in folate deficient medium. Even so, the characteristic feature is only seen in a small proportion of cells - usually 5-40%. This special test will only be undertaken by specific request. Standard chromosomal analysis will not reveal the fragile site. Unlike other chromosomal conditions such as Down's syndrome mosaicism, the number of cultured cells demonstrating the fragile site bears no relationship to the degree of learning disability. Modern laboratory tests based on DNA analysis give much more accurate results.

Understanding of the molecular basis of the condition has been revolutionised by discovery of the abnormal DNA sequence at the site of the Fragile X Mental Retardation gene (FMR1). This consists of recurrent CGG repeats. Up to 3% of the population may have an abnormally increased CGG repeat length (the so-called premutation) which following amplification during oogenesis (development of ova) may manifest as the full blown syndrome clinically. DNA analysis provides the quickest, cheapest and most accurate diagnosis.

Physical Aspects

All physical features occur in other syndromes as well as in normal individuals and none are necessary for diagnosis. Nonetheless their presence should alert one to the possible presence of fragile X syndrome. Facial features become more marked with age and are also present in female carriers where their vividness correlates with the degree of intellectual impairment.

Associated Physical Features

- Connective tissue anomalies: joint laxity, flat feet, scoliosis (curved spine), soft velvety skin, post-pubertal testicular enlargement, aortic dilation, mitral valve prolapse.
- Abnormal dermatoglyphics (hand and foot creases)
- Largish head with long face
- Large jaw
- Large protruding ears
- Nasal bridge long and flattened
- High arched palate

Psychological Aspects

Interest is now focussed on the characteristic profile of developmental and behavioural features attributable to the underlying genetic anomaly – the so-called behavioural phenotype.

Intellectual functioning is usually in the mild to moderate learning disability range, but up to one third of affected individuals can have severe learning disabilities while others may have very subtle cognitive impairments. A verbal/performance discrepancy manifests as relative strengths in vocabulary, and speech and language. Special needs are often present for numeracy and tasks requiring good visuo-spatial skills. Simultaneous processing of information is stronger than sequential processing (taking data one bit at a time) and has implications for remedial education programmes. Relative strengths are also seen with verbally based factual material with weaknesses in abstract reasoning and symbolic language. The trajectory of intellectual development seems to slow towards puberty thereby increasing the discrepancy between cognitive functioning of people with fragile X and their unaffected peers. This is probably due to the greater emphasis of cognitive tests on abstract concepts and reasoning and sequential information processing skills - areas of difficulty for fragile X individuals.

Speech and language development is usually delayed and often shows distortions reminiscent of autistic disturbances. It has been described as jocular, litanic-like (to describe up and down swings of pitch) and cluttered (a combination of rapid and dysrhythmic speech). Cluttering is probably a combination of central information processing difficulties, palatal anomalies and temporo-mandibular ligamentous laxity. Echolalia is often heard in the context of highly repetitive, perseverative chatter. Speech therapy assessment and intervention is therefore highly desirable.

Attentional deficits in the form of overactivity, poor concentration, restlessness, impulsiveness and ready distractibility are frequent difficulties for fragile X children and often occur irrespective of location, time and company. While most parents are aware of their child's limited cognitive capacity, many feel strongly that the above disabilities are further handicapping their learning potential and are occurring more frequently and severely than in other children with similar cognitive impairments. Appropriate structured educational settings with a high staff-to-pupil ratio, a minimum of distractions, and focused individualised programmes aim at slowly developing attentional skills. Stimulants such as methylphenidate (Ritalin, Equasym) and dexamphetamine (Dexedrine) may also be of benefit.

A substantial minority of children with fragile X syndrome qualify for a label of **autism** due to multiple qualitative impairments in the domains of social functioning, language and communication, ritualistic/stereotypic tendencies and imagination deficits. A few individuals with autism turn out to have fragile X syndrome. Thus, any person with autistic features should be tested for fragile X syndrome. Far more children with fragile X demonstrate a characteristic profile of autistic-like disabilities while failing to fulfil diagnostic criteria for typical autism. These features contrast with those of children with typical autism. In fragile X, social anxiety is far more frequent than social indifference. Crowded environments like parties, supermarkets and public transport may cause excessive distress while one-to-one settings with ample space are preferred. A generalised sensory defensiveness manifests as an aversion (not indifference) to eye contact. Auditory defensiveness can present as hyperacusis. Tactile, olfactory and gustatory sensitivities have also been reported. Self-injury is common in the form of biting the base of the thumb, usually in response to anxiety or frustration. Imitative and symbolic play is usually delayed but does develop. Individuals often demonstrate stereotyped repetitive behaviours such as hand flapping and an insistence on routine with a dislike of variety.

Females and Fragile X

One third of female carriers have substantial learning disabilities which may or may not be accompanied by emotional difficulties and challenging behaviours. Clinically unaffected carriers often report specific cognitive difficulties as well as emotional disturbances such as anxiety and low frustration tolerance. Intellectual functioning shows the same uneven profile as in males.

Female premutation carriers are prone to early menopause due to premature ovarian insufficiency. Male and female premutation carriers are at risk of middle-age onset of the fragile X-associated tremor/ataxia syndrome (FXTAS).

The Importance of Diagnosis

There are many imperative medical and psychological reasons why underlying pathology should be investigated vigorously. Of particular note is the importance of skilled genetic counselling for the entire extended family given the condition's complicated hereditary nature. Also, certain interventions are particularly important. As well as speech and language therapy, and including training in augmentative communication skills, occupational therapy will facilitate visuomotor integration. In particular, the technique of sensory integration can assist in desensitising the individual to the effects of multiple strong incoming stimuli and help him or her make more sense of them. Educational provision should focus on the numeracy and visuo-spatial difficulties with an emphasis on concrete tasks of a discrete nature, for example computer-assisted learning which allows for immediate feedback and reward.

The important reasons for pursuing an underlying aetiology for a child's learning disabilities include:

- The right of the individual and family to know
- Relief from uncertainty
- Facilitation of grief resolution
- Orientation towards the future
- Genetic counselling
- Awareness of likely strengths and needs
- Early instigation of multidisciplinary interventions relating to profile of strengths and needs
- Identification with other members of support group or society

Medically, vision and hearing assessment are necessary given the occurrence of squints and refractory errors, and chronic secretory otitis media ("glue ear"). Specialist cardiac or orthopaedic opinions may be required. Epilepsy affects 20-30% of males and usually responds well to carbamazepine. Psychostimulants (methylphenidate, dexamphetamine) and folic acid should be considered where serious attention deficit-hyperactivity disorders have failed to respond to psychological and educational interventions. Behavioural modification programmes, including environmental evaluation and a functional analysis of the presenting behaviour with its associated antecedents and consequences, are the psychological treatment of choice for such disturbances. This is ideally provided in a family context enlisting the help of parents and siblings as cotherapists. Individual psychotherapy can be invaluable to older affected individuals and carriers for emotional and adjustment problems.

Conclusion

Awareness of fragile X syndrome has gone a long way in explaining the phenomena of families with apparently inexplicable learning disabilities which seem to follow a sex-linked inheritance pattern, and the presence of greater numbers of men than women in units for people with learning disabilities. The condition reminds us that biologically determined disorders can cause mild as well as severe intellectual impairment, and can also produce behavioural disturbances which may mistakenly be attributed to psychosocial adversity. Given the syndrome's high frequency, and the continuing clarification of the complex behavioural phenotype, there should be a low threshold for referring children with unexplained developmental delays for screening. The following practical points should always be born in mind:

1. Suspect fragile X syndrome in any person with unexplained development delay, irrespective of degree of severity.
2. Do not be deterred from referring for fragile X evaluation simply because the family pedigree does not fit snugly into a sex-linked pattern, or because there is an absence of commonly associated physical features.
3. The apparently paradoxical juxtaposition of a likeable, happy/friendly personality with a limited number of autistic-like social impairments should raise suspicions of fragile X.
4. Speech and language anomalies, and hyperactivity with inattentiveness and poor impulse control, are often the most striking behavioural features and should prompt testing.
5. Management must be a collaborative team effort involving medical, psychological, educational and social aspects on the basis of each individual's strengths and needs.

Further reading

Cornish, K., Turk, J. & Hagerman, R.J. (2008) The fragile X continuum: new advances and perspectives. *Journal of Intellectual Disability Research*, **52**, 469-482.

Dew-Hughes, D. (2003) *Educating Children with Fragile X Syndrome*. London: Routledge Falmer.

Hagerman, R.J., & Hagerman, P.J.. (2002) *Fragile X Syndrome: Diagnosis, Treatment & Research*. Baltimore: Johns Hopkins University Press.

Turk, J., Graham, P.J. & Verhulst, F. (2007) *Child & Adolescent Psychiatry: A Developmental Approach (4th edition)*. Oxford: Oxford University Press.

Turk, J. (2004) Children with developmental disabilities and their parents. In: *Cognitive Behaviour Therapy for Children and Families, 2nd edition* (ed.: Graham, P.). Cambridge: Cambridge University Press. Pp. 244-262.

Turk, J. (2005) The Mental Health Needs of Children with Learning Disabilities. In: *Mental Health Learning Disabilities, A Training Resource*, (eds.: Holt, G., Hardy, S. & Bouras, N.). Brighton: Pavilion Publications.

The Fragile X Society

Rood End House

6 Stortford Road

Great Dunmow

Essex

CM6 1DA

Tel: 01371 875100

Email: info@fragilex.org.uk

Website: www.fragilex.org.uk

The Fragile X Society is a registered charity no 1003981