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Fragile X syndrome

The past few years have witnessed dramatic advances in our understanding of the fragile X syndrome. Clarification of the underlying molecular abnormality at the gene level¹ has enabled the development of more sensitive and specific diagnostic tests based on Southern blot and polymerase chain reaction technology.² Increasing definition of the associated behavioural phenotype is of potential use diagnostically and therapeutically.^{3–5} Also, specific problems associated with female carrier status are being increasingly recognised.^{6–7}

Epidemiology

Many paradoxes persist, however, along with ethical dilemmas surrounding the issue of whether or not to undertake presymptomatic screening for an as yet incurable disorder, and if so on which populations this should be undertaken. The condition is certainly common,⁸ although exact prevalence statistics vary considerably.⁹ However, it is still generally acknowledged as the most common inherited cause of learning disabilities affecting between one in 1000 and one in 3000 individuals. Some authorities even speculate that once the proportion of affected individuals who are identified increases, the frequency may even match that of Down's syndrome.¹⁰

Recent audit of a regional genetic service's pick up of fragile X cases found a substantial shortfall compared with expected numbers based on reported prevalence rates.¹¹ The authors felt that regional variation in prevalence rates was unlikely to be the explanation. Sensitivity problems with the more traditional chromosomal diagnostic analysis may have played a part¹² but it was concluded that the most likely reason was under-referral of appropriate cases for testing. This view is supported by evidence that clinicians who refer individuals for fragile X testing with a suspicion based on behavioural features are usually wrong (J Turk, unpublished data). Thus where selection criteria are being used to determine which children to refer to genetic services, they are presumably often inappropriate. This implies that either more children should be tested or that criteria for genetic referral need to be improved.

Genetics

The fragile X mental retardation gene (FMR-1) is located at the Xq27.3 'fragile' locus and consists of multiple CGG trinucleotide repeats.¹ Transgenerational progression from premutation in normal transmitting males and their daughters to full mutation in grandchildren is explained by progressive expansion of the CGG repeat in the 5' untranslated region of the FMR-1 gene. This expansion

produces abnormal DNA hypermethylation and disturbed protein synthesis.

Normal X chromosomes have approximately six to 45 CGG repeats with most clustering around 30 (D Nelson, 8th International Congress of Human Genetics, Washington, 6–11 October 1993). In the general population, 1% may have a small CGG expansion which represents carrier status and is known as a 'premutation'. These heterozygous premutation carriers have an expansion of between 52 and 200 triplet repeats that is unstable on maternal transmission, with the chance of progression to a full mutation reaching 100% for women with a premutation of 90 repeats or above.^{13–14} In the full mutation, repeat sequences exceed 200 triplets in size. Normal transmitting males have length increases of about 500 base pairs. Affected males have an increase of between 500 and 5000 base pairs, with hypermethylation of the site.¹⁵ It should be noted that these figures represent *base pairs* and not *CGG repeats*. The reason for this was the use in the study of probes to detect very localised DNA rearrangements that constituted the fragile X mutations, and whose target was a 550 base pair GC-rich fragment. The insertion size in females may relate to clinical severity but this has yet to be confirmed.¹⁵ It has also been demonstrated that amplification of the CGG repeat blocks FMR-1 gene transcription, which results in absence of the FMR protein.¹⁶ Efforts are under way to identify the protein whose production is interfered with by the fragile X mutation. The protein's function is as yet unknown, although it has been postulated to be of importance in gene regulation.¹

Fragile X variants have been identified. These manifest with a similar hypochromic fragile site cytogenetically. However, the molecular abnormality is elsewhere. A common fragile site¹⁷ is located at Xq27.2 and has been assigned FraX-D to distinguish it from fragile X syndrome (FraX-A). This site is a potential source of misdiagnosis in female carriers, prenatal testing, and occasional males with very low levels of fragile site expression.¹⁸ Its prevalence in the general population is unknown, but it is not thought to be associated with mental retardation. High quality banded cytogenetic preparations have confirmed a fragile site distal to the FMR-1 gene, in the proximal portion of Xq28.¹⁸ This site (FraX-E) is folate sensitive. Cytogenetically it is virtually indistinguishable from FraX-A. The molecular abnormality in FraX-E does appear to expand through generations though perhaps not as consistently as in FraX-A.¹⁹ Mental retardation is usually mild. Individuals have amplifications of a GCC repeat.²⁰ A third fragile site, FraX-F, has been identified in Xq27-q28.²¹ Using fluorescent in situ hybridisation (FISH) the site has been shown to lie distal to FraX-A and

FraX-E. It is folate insensitive and therefore manifests on standard chromosomal culture. The family described showed a lack of association between mental impairment and fragile site expression. The degree of intellectual impairment in affected individuals (all girls) was felt to be unusually severe for fragile X heterozygotes. Furthermore, there were no major behavioural problems or dysmorphic features.

Neurology

Increasingly research is focusing on the identification of abnormalities that may be mediating between the genetic anomaly and the consequent developmental and behavioural disturbance. Neurophysiological studies suggest a common co-occurrence of fragile X syndrome and rolandic epilepsy.²² Clinically, seizures affect approximately 20% of males. Epilepsy usually presents in early childhood as staring spells, akinetic episodes, complex partial seizures or generalised tonic-clonic episodes. They are usually infrequent and respond well to standard anticonvulsant medications such as carbamazepine.²³ More recent research has reported fragile X individuals with epilepsy as having characteristic brain activity similar to that seen in benign childhood epilepsy with centro-temporal spikes.²⁴

Neuropsychological studies have yielded rather contradictory findings with some authors suggesting generalised non-dominant hemispheric dysfunction,²⁵ while others propose more localised damage in the dominant hemisphere.²⁶ The most exciting reports have been of findings from magnetic resonance imaging. These studies found significantly decreased cerebellar vermis areas, particularly posteriorly, and larger fourth ventricular volumes in fragile X men²⁷ and women²⁸ when compared with age and IQ matched controls. Interest has been increased by comparison of the above with earlier observations of small neocerebellar vermal lobules in non-fragile X autistic individuals.²⁹ However, there are several possible explanations for these findings, including small experimental group sizes, nature and degree of mental retardation in fragile X subjects and coexistence of fragile X and autism in experimental subjects. Such anatomical abnormalities have not been consistently found in samples of autistic individuals³⁰ suggesting that the neuroanatomical abnormality is more likely to be associated with the genetic anomaly (fragile X) rather than with a psychiatric syndrome (autism).

Behaviour

Accumulating evidence confirms that only 2–3% of autism can be shown to be associated with fragile X syndrome.³¹ Also there is evidence that the prevalence of autism in fragile X syndrome is no greater than in learning disabled children generally.³² Of greater academic and practical interest has been to ask what it is about children with fragile X that reminds us of autism. It seems that non-fragile X autistic children suffer more social and symbolic disturbance while fragile X children with autistic-like disturbance have more communicatory and ritualistic disorder, in particular in the forms of gaze aversion, delayed echolalia, repetitive speech, and hand flapping. This goes some way to explaining the apparent paradox whereby many fragile X children fulfil diagnostic criteria for autistic spectrum disorders yet show good ability in, and good awareness of, social interaction.

The possibility of an association between fragile X and hyperactivity remains contentious with some authors describing major co-occurrences³³ and others denying any link.³⁴ As with the autism debate, the answer may well lie

in there being only certain constituent features of hyperactivity (or more broadly speaking *attention deficit disorder*) that show a specific association.³⁵ Teachers, in particular, rate fragile X boys significantly higher than Down's syndrome boys and boys with idiopathic learning disabilities on the nervous overactivity dimension of the childhood behaviour checklist. In addition they rate them as having more attentional deficits, restlessness, and anxiety. Detailed parental interview confirmed fragile X boys as more inattentive, restless, and fidgety than both other groups. Activity levels were similar in all groups and declined with increasing developmental ability. However, subjects with fragile X and Down's syndrome did not show the significant correlations between developmental level and inattentiveness or restlessness noted in subjects with idiopathic learning disability – poor concentration and restlessness in fragile X boys did not improve with developmental age. This suggests underlying aetiology may have an important bearing on inattentiveness, restlessness, and fidgetiness (fragile X more, Down's syndrome less) but not overactivity. Aetiology may also influence the developmental progress of these behavioural features, although confirmatory longitudinal studies are required.

Female carriers

The term 'carrier' is confusing when used in relation to fragile X syndrome and requires clarification. Females carrying an abnormal expansion of CGG repeats at the site of the FMR-1 gene can be symptomatic or asymptomatic. Symptomatic females have a fragile X mutation with CGG repeats exceeding 200. The clinical severity in this instance probably depends on the relative ratio of inactivated 'healthy' X chromosomes to fragile X chromosomes within the central nervous system. Hence females can be asymptomatic yet have the fragile X mutation with more than 200 CGG repeats provided most of these fragile X chromosomes have been inactivated. These individuals could be called carriers with justification. Alternatively, females can be asymptomatic and have the premutation comprising 52–200 CGG repeats. These individuals could be called carriers as well.

Research reviewed in this section deals mainly with studies of mothers with affected boys where the above three categories could not be distinguished. Hence some variability in findings would be expected. Indeed females heterozygous for fragile X have been found to display substantial variability in cognitive functioning. However, non-retarded female carriers do often demonstrate the same verbal/performance discrepancy as affected males. They obtain diminished numeracy and visuospatial scores on intelligence testing in the presence of relatively good performance in vocabulary and comprehension. Neuropsychological studies of normal intelligence heterozygote females have also shown significant frontal lobe ('executive function') deficits in cytogenetically expressing individuals. Features include perservation, tangential speech, impulsivity, distractibility, and difficulty with transitions.³⁶

Depression has been reported in over 70% of low expressing fragile X positive women compared with 40% of control women who have developmentally delayed non-fragile X children.³⁷ Depression is also common in heterozygous women negative for fragile X who do not have significant cognitive deficits. The relative contributions of the fragile X gene and environmental stressors are as yet unknown. Thus the subtlest effect of the fragile X gene may involve personality changes including shyness and a predisposition to anxiety or depression. Now that more fragile X boys with severer learning disabilities are

being diagnosed, the onus is on clinicians to identify the more intellectually able, yet emotionally and socially disadvantaged, affected girls.

Further research and replication of the above studies is required utilising the exact number of CGG repeats as well as noting methylation status of the FMR-1 gene and the ratio of inactivated fragile to healthy X chromosomes.

Intervention

There is no cure for the fragile X syndrome but much can be done medically, psychologically, educationally, and socially to maximise potential and minimise handicap. In the classroom compliance and behaviour can be enhanced by awareness of the common gaze aversion,³⁸ numeracy and visuospatial difficulties, and sequential information processing problems.³⁹ Psychotherapeutic approaches, both behavioural and psychodynamic, have been described as being of potential benefit.⁴⁰ Additionally, there is evidence that the attentional deficits and overactivity often associated with the condition can frequently be helped both by traditional stimulant medications such as methylphenidate⁴¹ and by folic acid.^{42 43}

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'Fragile X syndrome: advances and innovations', a multidisciplinary conference, will take place on 15 and 16 June 1995 at St George's Hospital Medical School, University of London. Further information can be obtained from: The Conference Unit, Mental Health Sciences, St George's Hospital Medical School, Cranmer Terrace, London SW17 0RE.

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