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Original articles

Is it possible to make a clinical diagnosis of the fragile X syndrome in a boy?

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SUMMARY Clinical observations were made on a series of 156 boys with severe mental retardation, before cytogenetic results were known. The clinical features that helped to distinguish the 14 boys with the fragile X chromosome from those without were: head circumference over the 50th centile, postpubertal testicular volume over the 50th centile, and an IQ between 35 and 70. If the above clinical features were all present, then the chance of finding the fragile X chromosome was 1 in 3·6, whereas the chance of finding this abnormality in any boy with severe idiopathic mental retardation, regardless of his clinical features, was 1 in 9.

Two boys with fragile X syndrome did not, however, possess any of the above clinical features. Moreover, some of the other retarded boys had clinical features of the syndrome, or an X linked pedigree, but lacked the chromosome abnormality.

X linked genes were first shown to be an important cause of moderate mental retardation by Turner and Turner in 1974,[1] but the association between a cytogenetic marker (a fragility in the X chromosome) and mental retardation had been previously described by Lubs.[2] He found that all four retarded males in a family in which X linked mental retardation was segregating, carried a secondary constriction in the distal portion of the long arm of the X chromosome. Further cytogenetic studies on families with X linked mental retardation showed this constriction to be a fragile site at Xq27.[3 4]

Studies of patients who have been ascertained because of mental retardation and an affected male relative have shown that certain clinical features are often, though not exclusively, associated with the fragile X chromosome. These features are heavy birthweight compared with siblings, large heads, large protuberant ears, large nose, heavy lower jaw, high forehead, delayed development of speech, IQ in the moderately retarded range, amiable personality, and large testes, especially after puberty.[5–9]

Through a study of boys with severe idiopathic mental retardation[10] we have been able to assess prospectively the extent to which any of the above clinical features are helpful in selecting from the group, those boys who possess the fragile X chromosome. We also wished to know whether the clinical features said to be characteristic of the fragile X chromosome could occur in the absence of the chromosome abnormality. In this account we have taken the term 'fragile X syndrome' to denote a mentally retarded subject who possesses the fragile X chromosome, and we have attempted to assess the limits of the clinical features of this syndrome in a boy.

Methods

A population study was undertaken of severely educationally subnormal boys living within the boundaries of six education authorities in the West Midlands—Coventry; Central, North, East, and South Warwickshire; and Walsall. The racial distribution and the types and sizes of the population in these areas have been discussed by Bundey *et al.*[10] Permission for the study was obtained from the local ethical committees and education authorities. The boys included all those in school during 1982 and 1983 with a date of birth before August 31, 1978.

Initially the school or the local health authority medical records, or both, were examined, to exclude boys with a definite cause for their severe mental retardation.[10] The parents of the remaining boys were contacted and their permission sought for examination and venepuncture. Permission was

obtained for 156 boys who form the basis of this study. They were examined with particular reference to head circumference and current height and weight, and these features were compared with the charts of Westrupp and Barber,[11] Nellhaus,[12] and Tanner.[13] A note was made of the appearance of the ears, nose, and other facial features. The hand circumference was measured at the level of the carpo-metacarpal joints of the four digits. Foot lengths were measured and a centile score derived using the charts of Blais *et al.*[14] Testicular volume was determined using a Prader orchidometer, and a centile score obtained for those boys who were aged over 10 years, using the charts of Taranger *et al.*[15] A neurological examination was also performed. Information recorded from the notes included the birthweight for which a centile score, adjusted for length of gestation, was calculated using the standard charts of Gairdner and Pearson,[16] and compared with those of normal siblings. In addition a note was made of any recorded observation of delay in speech development made in a psychological assessment of the boy.

Each boy's IQ was assessed using the Vineland social maturity scales. The IQ range awarded to each boy was then assessed by the head teacher and if he or she considered that this social rating did not accord with the child's innate intelligence, then the child was moved to a more appropriate IQ group. After the clinical examination and before the cytogenetic results were available, the family of each boy was visited in order to draw up a pedigree. The family was not available in seven instances where the index patient was in the care of the social services' children's department.

The χ^2 test was used to compare the population of boys with the fragile X syndrome with that without the marker, to see whether they differed significantly.

Results

There were 360 boys requiring education in schools for the severely subnormal in the area defined. One hundred and eighty five boys were excluded from the study as they were considered, from their notes, to have specific causes for their mental retardation. Parental consent for examination was refused for 19 boys. One hundred and fifty six boys were therefore included in the study, and 14 (9%) of these were found to have the fragile X chromosome.

After examining the boys and obtaining further medical history from the parents, 39 boys of the original 156 were considered to have a specific cause for their severe mental retardation.[10] One boy with the fragile X chromosome was among these 39, for he was asphyxiated at birth and had a spastic quadriplegia. If these 39 boys are omitted, the prevalence of the fragile X chromosome in the remainder becomes 13 of 117, or 11·1%.

Clinical features. We were able to compare the clinical features of the 14 boys with the fragile X chromosome with those 142 with idiopathic severe mental retardation who did not have the cytogenetic abnormality. The clinical features, as mentioned earlier, were assessed before the cytogenetic findings were known.

Birthweight

For this comparison only, we omitted the 39 boys who were considered to have a specific condition after blood samples had been taken for cytogenetics, because some of the 39 specific diagnoses were likely to be associated with low birthweights. Also birthweights were not documented for all boys in the study. The distribution of birthweight centiles adjusted for gestation (Fig. 1) resembles a normal Gaussian distribution for the 12 boys with the fragile X chromosome, whereas the distribution for the 76 boys without the fragile X shows a definite skew to lower birthweights. Thus the boys with fragile X syndrome are heavier at birth than other boys with non-specific mental retardation, but are not heavier than the general population. Two unrelated boys with the fragile X chromosome in the centile range 10 to 49 are dizygotic twins. When 15 normal siblings were compared with the boys who had the fragile X syndrome there were seven who had lower

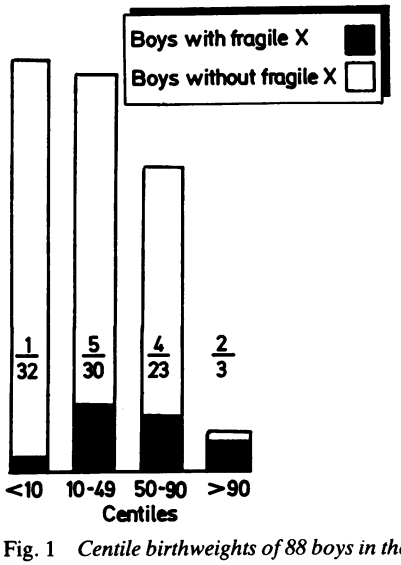

Fig. 1 *Centile birthweights of 88 boys in the study.*

birthweights compared with their affected brothers, three who were the same, and five who were heavier. The twins and the boy with cerebral palsy were excluded from the comparisons.

Heights and weights

The centile heights and weights of boys with the fragile X chromosome show a similar distribution to the rest of the boys in the study.

Hand and foot sizes

There are no centile tables for the hand measurement that we took, but comparing the hand circumference of the boys carrying the fragile X chromosome with the other boys in the study, 10 of the 14 boys with the fragile X chromosome had hand circumferences greater than the mean for their age.

The foot length centiles are shown in Fig. 2. Eight of the 14 boys with the fragile X chromosome have foot lengths over the 50th centile, compared with only 19 of the 136 remaining boys. This is statistically significant at 99% level.

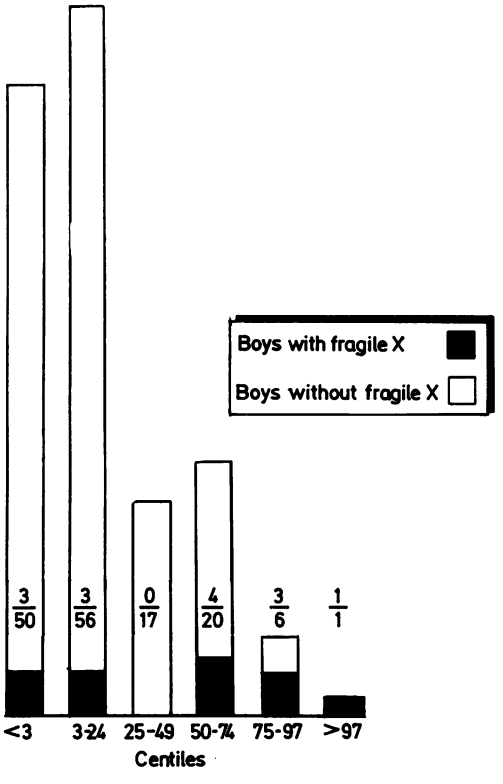

Fig. 2 *Centile foot lengths of 150 boys in the study.*

Head circumference

The head circumference centiles of the boys with the fragile X chromosome are significantly larger than those of the other boys studied (Fig. 3). Twelve of the 14 boys (86%) with the fragile X chromosome have head circumferences greater than the 50th centile compared with 56% of the other boys (statistically significant at 95% level). Ten of the 14 boys (71%) with the fragile X chromosome have a head circumference over the 75th centile compared with 45% of the remaining boys (statistically significant at 95% level). If megalencephaly is taken to mean 0·5 cm over the 98th centile, then three of the 14 boys so defined possess the fragile X chromosome. The one boy with a head circumference less than the 3rd centile was of low birthweight and was preterm.

Testicular volume

The centiles of testicular volumes for the 94 boys over 10 years of age with normally descended testes are shown in Fig. 4. Ten of the 94 boys have the fragile X chromosome, and nine of these have testicular volumes over the 50th centile compared with 42 of the remaining boys (statistically significant at 99% level). Six boys with the fragile X chromosome have testicular volumes over the 90th centile; this is 60%, compared with 18% of the other boys (statistically significant at 99% level).

Fifty one boys in the study were under 10 years of age. Prader[17] takes a testicular volume of between

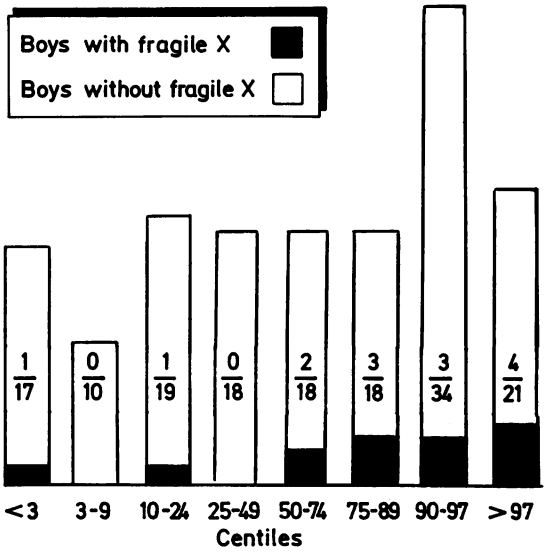

Fig. 3 *Head circumference centiles of 155 boys in the study.*

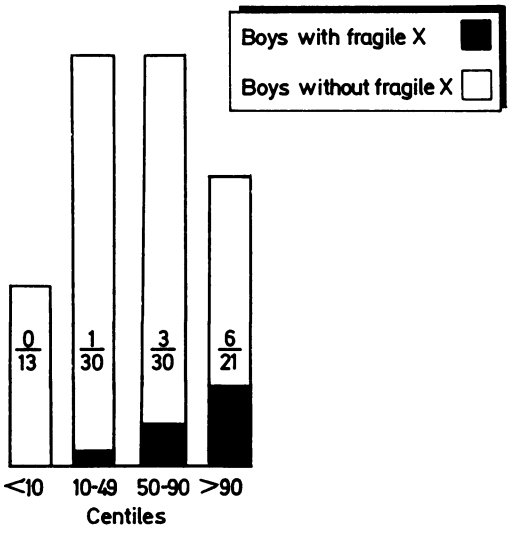

Fig. 4 *Centiles of testicular volumes of 94 boys who were aged 10 or over.*

0·5 ml and 2 ml as normal for boys of this age. Nine of these boys had no testicular volume measured, either because the testes were undescended or the boys were uncooperative. Twenty boys had testicular volumes 0·5 ml to 2 ml and 22 greater than 2 ml. The three boys with the fragile X chromosome had testicular volumes 4 ml, 6 ml, and 15 ml respectively (see Fig. 5) and this is statistically significant at 99% level.

IQ ranges

These are shown in Table 1. Eleven of the 14 boys with the fragile X chromosome have IQs in the range 35 to 70; this is 79%, compared with 57% of the remaining 142 boys. The one boy with the fragile X chromosome and an IQ of less than 20 is the boy with the spastic quadriplegia caused by birth asphyxia.

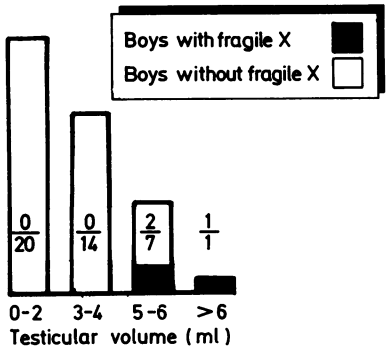

Fig. 5 *Testicular volumes of 42 boys who were aged under 10 years.*

Table 1 *IQ ranges for the 156 boys studied using an adjusted Vineland social maturity scale*

IQ range	*All boys in study*	*Boys with fragile X*
More than 70	3	0
50–69	30	5
35–49	59	6
20–34	43	2
Less than 20	21	1
Total	156	14

Other features

Neurological examination was abnormal for only one of the boys with fragile X chromosome, namely the boy with a history of birth asphyxia who had a spastic quadriplegia. Forty nine boys in the study had a history of epilepsy, which included two who had the fragile X chromosome. Four of the epileptic boys were preterm with birthweights under 2·3 kg, including one of the boys with the fragile X chromosome. The other boy with the fragile X chromosome and epilepsy was the first of twins born at 36 weeks' gestation with a birthweight of 2·23 kg, and both his parents are epileptic.

There were other physical features examined and recorded which occurred more frequently in the boys with the fragile X chromosome than in the other 142 boys studied. Large flat ears occurred in three (21%) of the boys with fragile X chromosome and in five (3·5%) of the others, and although these numbers are too small to be statistically significant, protruding ears occurred in six (43%) of the fragile X boys and in only 14 (10%) of the other boys (significantly different at the 95% level). A large nose was observed in two (14%) of the boys with the fragile X chromosome compared with four (3%) of the rest, but again numbers were too small for significance tests to be accurate. Although delay in speech has been observed on several occasions in the fragile X syndrome, it was noted in five (36%) of the fragile X subjects in this study but also in 22 (15%) of the other boys; the difference is not significant at the 95% level. Eye colour was recorded for 147 boys, of whom 63 had blue eyes, 69 brown, and 15 green. Five boys with the fragile X chromosome had blue eyes and the other nine brown.

X linked pedigree

This was defined[10] as one in which a maternal male relative (other than a brother) had severe idiopathic mental retardation that seemed similar to that in the index patient. The presence of a retarded female relative did not prevent the pedigree from being labelled 'X linked'. Five boys with the fragile X chromosome had an X linked pedigree, while only eight of the other 136 boys from whom a pedigree was available showed an X linked pattern.

Discussion

We wished to assess how far certain simple clinical features could lead one to suspect the presence of the fragile X chromosome, and therefore increase the chance of detecting it. Many of these clinical features have been described in Figs. 1 to 5. The boys with fragile X syndrome were heavier at birth than the other boys in the study. Turner *et al*[7] found that the mean birthweight of boys with the fragile X chromosome was on the 70th centile, and also that they had a higher birthweight than their normal siblings when this was corrected for gestational age, sex, and being the first born. In this study, the mean birthweight of the affected boys (excluding the twins and the boy with cerebral palsy) was on the 60th centile and we did not find them to be greatly heavier than their normal siblings.

The boys with the fragile X chromosome had normal heights and weights in agreement with the findings of Jacobs *et al*[5] and Mattei *et al*.[9] The feet of the affected boys are large (Fig. 2), and their hands have a larger circumference than the mean for this study group. Jacobs *et al*[18] noted that in six of nine affected men, the head circumference was greater than the 90th centile. Turner *et al*[7] observed that although the head circumferences were increased in infancy and childhood, this did not persist into adult life. Figure 6 shows that in our group of 14 boys with the fragile X chromosome, head circumferences were large at all ages. The unaffected boys in this study, however, also tend to have large heads. It is possible that some of these children had arrested hydrocephalus, but it is also possible that some boys have a similar clinical picture to the fragile X syndrome, but lack the chromosomal abnormality.

Similarly, in considering the distribution of testicular volume (Figs. 4 and 5), although nine of 13 affected boys had large testes, so did 15 of the other 142 boys. Conversely, four of the 13 affected boys with the fragile X chromosome have normal sized testes. Other observers have found large testes in varying numbers of mentally retarded boys, both with and without the fragile X chromosome. Fishburn *et al*[19] found large testes in all 12 of their

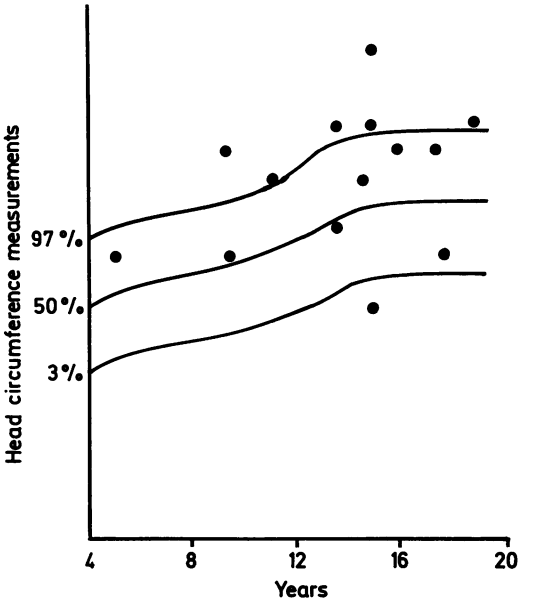

Fig. 6 *Head circumferences of 14 boys with the fragile X syndrome, plotted against age and showing centiles.*[11 12]

affected subjects, but also in six of the other 33 subjects with X linked mental retardation. Mattei *et al*[9] reported large testes in five of 19 affected subjects and Levitas *et al*[20] in six of 10. When a population of mentally retarded males with macro-orchidism was screened for the fragile X chromosome, seven of 26 white males were found to be positive.[21]

Other features were recorded which also gave clinical pointers to the diagnosis. Delay in the development of speech was noted by Martin and Bell[22] in their original family with X linked mental retardation, some members of which were subsequently shown to have the fragile X chromosome.[23] We found delay in the development of speech in only five of the 14 affected boys. Other workers[6 7 9] found delay in all aspects of mental development but most notably in speech development.

Nine of our 14 affected boys (64%) had either large or protuberant ears compared with only 19 of the other 142 boys in the study (17%). Jacobs *et al*[5] comment that ears tend to be large. Mattei[9] found very large, poorly formed ears to be the most characteristic facial feature, while Jennings *et al*[6] found that eight of nine had ear lengths greater than the 75th centile.

The boys with the fragile X chromosome in our survey were pleasant, amenable, non-disruptive boys who were living at home. In only one case did

the family comment that an affected boy was liable to have uncontrollable bouts of rage. This is similar to other observations,[7] but is in contrast to those of Fryns,[24] who noted that the most characteristic finding in the boys with the fragile X chromosome was the psychological profile with severe hyperkinetism, hypersensitivity, hand biting, and autistic features in some of them. Levitas *et al*[20] have also suggested that there may be an association between autism and the fragile X chromosome, as they found autistic features in six of 10 affected subjects.

In the main, the boys with fragile X syndrome had IQs in the 35 to 70 range, as noted by other observers.[7–9] Indeed, only three of the 14 boys had IQs below 35 (Table 1). Three features—the IQ, size of head, and size of testes—seem to be the most useful in suggesting the diagnosis of the fragile X syndrome in a severely retarded boy. In Table 2 we have attempted to assess their usefulness by indicating to what extent a particular range of IQ, head size, or testicular volume will identify boys with the fragile X chromosome out of a group of boys with similar clinical features, and to what extent the diagnosis will be missed.

Table 2 *Clinical features as indicators of the fragile X chromosome*

Clinical feature	*Prevalence of fragile X chromosome among all ESN(S) boys in study who possessed this clinical feature*	*Numbers of boys with fragile X who did not possess this clinical feature*
Head circumference (HC)		
Megalencephaly*	3/14 (1 in 5)	11/14
97th centile and over	5/30 (1 in 5)	9/14
90th centile and over	7/55 (1 in 8)	7/14
75th centile and over	9/73 (1 in 8)	5/14
50th centile and over	12/91 (1 in 7·5)	2/14
Under 50th centile	2/64 (1 in 32)	12/14
Testicular volume†		
Over 90th centile	6/21 (1 in 3·5)	4/10
Over 50th centile	9/51 (1 in 5·7)	1/10
Over 10th centile	10/81 (1 in 8·1)	none
Under 10th centile	0/13	
IQ range		
IQ over 50	5/33 (1 in 6·6)	9/14
IQ over 35	11/92 (1 in 8·4)	3/14
IQ over 20	13/135 (1 in 10·3)	1/14
IQ under 20	1/21 (1 in 21)	13/14
Family history		
An X-linked pedigree‡	5/13 (1 in 2·6)	9/14
An ESN(S) brother	5/14 (1 in 2·8)	9/14
An ESN(M) sister	1/7 (1 in 7)	13/14
Combination of apparently most useful features		
IQ 35–70, HC over 50th centile, testicular volume† over 50th centile	8/29 (1 in 3·6)	2/10

ESN=educationally subnormal; (S)=severe; (M)=moderate.
*Megalencephaly=0·5 cm above 98th centile.
†In boys aged 10 years and over.
‡See text for definition.

The presence or absence of an X linked pedigree is not particularly helpful in the diagnosis of the fragile X syndrome. This is because, firstly, only a minority of boys with an X linked disease will have an X linked pedigree. For example, the figures are 20% for Duchenne muscular dystrophy, 40% for haemophilia, and 30% for Lesch-Nyhan syndrome. Secondly, the patterns of familial mental retardation that occur with the fragile X syndrome are unusual: females may be affected[25 26] and healthy males may transmit the condition.[22 26] In this study five boys with fragile X syndrome had an X linked pedigree (as defined earlier) and nine did not.

A genetic analysis of the whole sample[10] showed that only two thirds of the boys with recognisable X linked mental retardation expressed the fragile X chromosome. Eight of the nine who did not had large heads and/or large testes and/or IQs over 35, and therefore bore some resemblance to those boys identified as having the fragile X syndrome. In addition, the unusual distribution of head size and testicular volume in the whole series suggests that there may be other boys in the sample with the clinical features of the fragile X chromosome, no cytogenetic abnormality, but who probably have a similar X linked disorder. Further studies on the gene itself are required to determine whether or not the clinical features in these boys are due to the fragile X syndrome present at a cytogenetically undetectable level, an allelic form of the same gene but not showing the cytogenetic abnormality, or dysfunction of another gene situated elsewhere.

The test for the fragile X chromosome is not one that is performed routinely when a chromosome analysis is requested from the cytogenetic laboratory on a mentally retarded patient. As a result of our study, we think it should be requested in any mentally retarded male who has three or more of these six features; testicular volume greater than 50th centile, if over 10 years of age, and greater than 2 ml if under 10; head circumference greater than the 60th centile, foot length greater than 50th centile, large or prominent ears, large nose, and X linked pedigree. Twelve of our 14 boys with the fragile X chromosome had three or more of these features. The only two who did not were the boy with spastic quadreplegia and the boy with a small head who was preterm and light for dates.

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