X linked mental retardation: a family with a separate syndrome?

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SUMMARY Four males with X linked mental retardation are described. Manifestations similar to those seen in the FG syndrome include severe constipation, tall, broad foreheads, hypotonia, and cowlicks of the hair line, but no individual patient had all the features of the syndrome and none had macrocephaly. The facial appearance was distinctive but different from that seen in the FG syndrome. The cases are presented in order to discuss the phenotypic limits of the FG syndrome and to consider the need to separate other distinct but similar entities.

Our understanding of X linked mental retardation was given dramatic impetus by the identification in many families of a fragile site on the X chromosome at Xq27. Most clinicians, however, excited by this advance, found to their disappointment that almost a half of their 'candidate' families were fragile X negative. Indeed it is possible that about half of X linked mental retardation might fall into other categories.¹

Phenotypically this is a difficult diagnostic group because, by virtue of being considered to have

fragile X mental retardation, most males are not strikingly dysmorphic, have normal to large heads at birth, and have little else besides varying degrees of mental retardation. We report a family in this category with mild dysmorphic features but who resemble one another so strikingly that they might have a recognisable syndrome. Whether they are further examples of the FG syndrome is discussed.

Case reports

CASE 1 (IV.6, FIG 1)

This boy was born at term by forceps delivery after

FIG 1 Pedigree of family.

an uncomplicated pregnancy. At birth, the weight was 3011 g (10th centile), the length was 46 cm (below the 3rd centile), and the head circumference was 34.5 cm (just above the 10th centile). There was no neonatal hypotonia but the mother found it difficult to feed him because of his very small mouth. Follow up was undertaken because of the family history of mentally retarded males and, indeed, development was delayed. He began to sit unaided at nine months. At 16 months, development was assessed using the Griffiths Mental Development Scales. Locomotor and personal/social development were at the 10 month level, eye and hand coordination were at the six month level, and performance was at the four to five month level. Hearing response was poor, possibly partly because of bilateral serous otitis media which was evident on tympanography. He had only one word of speech ("dada"). At 21 months he learned to walk around furniture but could not walk unaided.

General health was reasonably good although his mother reported that he tended to be 'chesty'. There was no history of constipation or seizures. A chromosome analysis showed no fragile sites on the X chromosome.

On examination at 20 months, the weight was 11.25 kg (25th centile), the height was 79.5 cm (10th centile), and the head circumference was 47.0 cm (25th centile). The face was round, with a small mouth, a short nose with anteverted nostrils, and a long, smooth philtrum (fig 2). The impression was of a relatively large face into which the eyes, nose, and mouth appeared to be crowded centrally. There were bilateral upsweeps ('cowlicks') of the frontal hair line, mild plagiocephaly, and protruding ears. The genitalia were normal and there were no joint contractures. The tone and deep tendon reflexes were normal.

The mother had one previous pregnancy which resulted in a spontaneous miscarriage at two months' gestation. Her maternal half sister had two sons (cases 2 and 3, IV.3 and IV.1) and she had a maternal half brother (case 4, III.15) who were similarly affected to case 1. In addition, the maternal great uncle of case 1 (II.5) had died at the age of five months and was said to have been developmentally delayed, and a great great uncle through the female line (I.3) was said to have been congenitally blind, mentally retarded, and 'died young', but further details about these two subjects were unavailable. The maternal aunt of case 1 (III.17) died with spina bifida and a female cousin (IV.2) had an atrophic scar of the skin overlying the lower lumbar spine together with a sacral dimple, but with no obvious radiological defects of the spine. She is otherwise normal.

FIG 2 Case 1. Note the round face, small mouth, and nose with anteverted nostrils; the facial features appear to be crowded centrally in the face. Note the cowlick of the hair line.

The three obligate carrier mothers of cases 1 to 4 were seen by the authors. They had no dysmorphic features and were of normal intelligence.

CASE 2 (IV.3, FIG 1)

This boy, the cousin of case 1, was born at term after a normal pregnancy and delivery. The birth weight was 3130 g (10th to 25th centile). At 36 hours he had a cyanotic episode and possibly a brief convulsion for which no cause was found. Cranial ultrasonography showed no evidence of intracranial haemorrhage. There was a small cavum septum pellucidum which is probably not abnormal. A screen for intrauterine viral infection was negative. Bile stained vomiting occurred soon after birth and an abdominal x ray showed dilated loops of bowel. The vomiting settled with conservative management. A barium swallow and meal showed neither a tracheo-oesophageal fistula nor an obstruction. He continued to regurgitate after feeds during infancy. Hypotonia was present initially, during the time of the acute illness. Development was delayed; at 13 months, the developmental quotient was 50. When seen at three years 11 months, he vocalised but had no words of speech, and he was unable to walk. He had suffered from recurrent chest infections and

had occasional stridor, more prominent when in a supine position. There was no history of constipation. Serum amino acids, thyroid function, and sweat electrolytes were normal. There was a pericentric inversion of chromosome 9 (46,XY,inv(9)(p11q13)), which was considered to be a normal variant. There were no fragile sites on the X chromosome. Hearing was reduced with a threshold of 50 decibels at the age of 32 months, but this may have been secondary to serous otitis media associated with enlarged adenoids and tonsils which were due to be removed.

On examination at three years 11 months, the weight was 16 kg (50th centile), the length was 97.4 cm (25th centile), and the head circumference was 49.5 cm (25th centile). The facial appearance was similar to that of his cousin (case 1) with a round face, small nose and mouth, and a long, smooth philtrum (fig 3). Again the facial features appeared to be crowded into the centre of the face. The skull was somewhat brachycephalic in shape. Both testes were undescended. Tone and deep tendon reflexes were normal. There was inability to extend the knees fully but the other joints were normal.

CASE 3 (IV.1, FIG 1)

This boy was the maternal half brother of case 2. He was born at term after a normal pregnancy, presenting by the breech. There is reference in the hospital

files to a difficult perinatal period, but specific details were not given. The birth weight was 3247 g (25th centile). His mother reported that he was 'always chesty' like his brother (case 2). At seven months, he was noted to have limited abduction and flexion of the left hip owing to 'pelvic obliquity'. Marked plagiocephaly, scoliosis, and a left undescended testis were also present. The hips were radiologically normal. After a closed left adductor tenotomy at 10 months, the range of movement at the left hip was almost normal. Subsequently, at 34 months, an x ray showed that the left capital femoral epiphysis was small and fragmented and presumably had undergone necrosis. The radiological appearance improved over the next six months. At three years the weight was on the 10th centile and head circumference was on the 3rd. This child also showed slow development and he never learned to walk or talk. He was not hypotonic. He suffered from severe constipation and was admitted to hospital for faecal impaction on several occasions. He usually required an enema in order to pass a stool. He had no convulsions. The mother had noted a 'cowlick' of the frontal hair line. He died at the age of three years from pneumonia.

CASE 4 (III.15, FIG 1)

This boy was the maternal uncle of cases 1, 2, and 3. He was not examined personally because he had

FIG 3 Case 2. Note similar facial appearance to case 1.

FIG 4 Case 4. Note the tall, broad forehead and that the features are crowded centrally in the face.

TABLE 1 Comparison of X linked mental retardation syndromes with normal or large head circumferences.

Reference	Special feature or syndrome name	MR	Head size	Stature	Obesity	Testicular size	Ears	Hypertelorism	Seizures	Other features
2 9	Fragile X MR. Martin Bell syndrome	Mild to severe	Increased	Normal or short	Absent	Large	Large	Absent	Occasional	—
10	Bilateral	Mild	Normal	Normal	Mild (one case)	Normal	?Normal	?Absent	Not mentioned	—
1 11	clasp thumbs Marfanoid habitus	Mild to severe	Normal or increased with large forehead	Tall	Absent	Normal to large	Low set	Absent	2 of 9 patients	Long, narrow face, hypernasal voice, small mandible, agenesis of corpus callosum
12	—	Moderate to severe	Increased with large, square forehead and prominent SOR	Short	Present (6 of 11 males, 3 of 7 females)	Large	Large	Present	3 of 11 males	Gap between upper central incisors, thick lower lip, broad nasal tip with anteverted nostrils
13	—	Moderate to severe	Normal or increased with large, square forehead and prominent SOR	Normal	Present	Large	Large	Absent	Absent	Gap between upper central incisors, thick lower lip, broad nasal tip
14	FG syndrome	Usually severe	Increased with tall, broad forehead	Short	Absent	Normal	Dysplastic	Present	Occasional	Severe constipation and hypotonia, ±anal abnormality, cowlicks of hair line

MR = mental retardation. SOR = supraorbital ridges.

died, at the age of three and a half years, of an intercurrent infection. He was described in the hospital records as hypotonic and mentally retarded. His mother reported that he was born at term after a normal pregnancy and delivery, weighing 3977 g (90th centile). He learned to sit unsupported at 18 months but never crawled. He had no seizures. Severe constipation was a constant problem and he usually required an enema in order to pass a bowel motion. A family photograph showed that he had a similar facial appearance to cases 1 and 2 (fig 4).

Discussion

It can be seen from the description of the phenotype that although the affected males are photographically very similar, the clinical handles are poor. Facially they all have broad foreheads, close set eyes, small mouths, and prominent ears. It appears from the photographs as if the main facial features are crowded together in the centre of the face.

Opitz and Sutherland,² sensing that the non-fragile X group of retarded males needed attention, listed those conditions with X linked mental retardation from the McKusick catalogue³ and selected out for further discussion those that might pose major diagnostic problems. Of these, a number have microcephaly and can be excluded from the present discussion. These include Renpenning's syndrome,⁴ the patients of Golabi *et al*,⁵ MHGS syndrome (mental retardation, hypotonia, gonadal and skeletal defects), described by Vasquez *et al*,⁶ Seemanová's syndrome,⁷ with spastic diplegia and seizures, and the JMS (Juberg-Marsidi syndrome) reported by these authors in 1980.⁸

Those X linked conditions with a head circumference in the normal range or with actual or relative macrocephaly are listed in table 1. Some are easy to exclude, for example, those with a Marfanoid habitus described by Lujan *et al*¹¹ and subsequently

by Fryns and Buttiens¹ and those with a clasped thumb abnormality discussed by Gareis and Mason.¹⁰ In both conditions the males have at least one good 'handle' which allows the diagnosis to be considered.

Most important in the differential diagnosis are the FG syndrome, the syndrome described by Atkin *et al*,¹² and that by Clark and Baraitser.¹³ The comparison can be seen in table 2.

The patients of Atkin *et al*¹² had a prominent forehead and supraorbital ridge, hypertelorism, broad nasal tip, thick lips, and diastema of the teeth. All postpubertal males had large testes. The family described by Clark and Baraitser¹³ was similar. Those affected had macrocephaly, a large, square forehead, a gap between the incisors, short stature, moderate obesity, and macro-orchidism. They did not have ocular hypertelorism. Atkin *et al*¹² suggested that they had a different condition because they lacked this feature. (See editor's note after the letter by Clark and Baraitser.¹³)

Especially problematical is the differentiation from the FG syndrome and a comparison is made in table 2. The five most constant features of that syndrome, besides mental retardation and the sex of the patient, are a tall, broad forehead, cowlick, congenital hypotonia, relative macrocephaly, and severe constipation. In a single patient nearly all of these features need to be present in order to make a confident diagnosis, although some intrafamilial variation has been commented on.¹⁴ The problem with the family in this report is that no single patient had all of the features of the FG syndrome, although case 4, who died early and whom we know only by history and from the photographs, might have had many of the cardinal features. His three affected relatives look the same, but do not fulfil the major criteria of the FG syndrome although each has some of the features.

We report this family in the hope that other clinicians might add further cases, thereby helping to decide the true phenotypic limits of the FG syndrome or alternatively to provide evidence for the separation of similar but distinct X linked conditions associated with facial features resembling those of these patients.

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TABLE 2 Comparison of manifestations of patients in the present report with those of the FG syndrome.

Manifestation	Published reports of FG syndrome (%)	Present report			
		Case 1	Case 2	Case 3	Case 4
Mental retardation	100	+	+	+	+
Tall, broad forehead	97	+	+	?	+
Cowlick	90	+	-	+	?
Congenital hypotonia	89	-	-	-	+
Relative macrocephaly	71	-	-	-	?
Constipation	69	-	-	+	+
Anal anomaly	38	-	-	-	-
Failure to thrive	67	-	-	-	?
Death in infancy	33	-	-	+	+
Hyperactive behaviour	51	?	+	?	?

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