# CASE PRESENTATION

## Fragile X Syndrome in a Bahraini Family

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**ABSTRACT**

**Fragile X syndrome (Martin Bell Syndrome) has been the subject of wide medical interest in the past decade. We are reporting the first cases in a Bahraini family documented to have fragile X syndrome. Four sibs and a maternal brother have mental retardation with the typical clinical and cytogenetic picture of the syndrome.**

The clinical picture, prenatal diagnosis and genetic counselling pertaining to this syndrome is discussed.

Fragile X syndrome is most commonly associated with moderate or profound mental retardation in affected males and some affected females. The frequency of fragile X syndrome is estimated to be 1 in 2,300 males and 1 in 2,400 females. Its estimated prevalence among mentally retarded individuals varies according to the type of population studied. [1,2] A recent report estimates it to be 3.4% in males and 2.3% in females attending special schools for the mentally retarded;[3] while in a Swedish study the prevalence was found to be 16% in a group of males with infantile autism.[4]

In 1969 Lubs demonstrated a fragile site which is seen as a gap or break at the end of the long arm of the X chromosome (Marker X) in four males with mental retardation. The fragile sight was present in few cells only in the affected males and in normal females who are obligatory carriers of the same X chromosome.[5] Subsequently, it was found that the media with less fetal calf serum, minimal thymidine and no folic acid permitted better detection of many fragile sites.[5]

### THE CASES

A Bahraini family with ten children and unrelated parents is reported. There are eight male members, four of whom are mentally retarded. While the two daughters are normal, the maternal brother is also mentally retarded, which indicates X-linked mental retardation. Although the mother is an obligatory carrier she is physically, mentally and cytogenetically normal. There is no history of mental retardation on the paternal side of the family (Fig 1).

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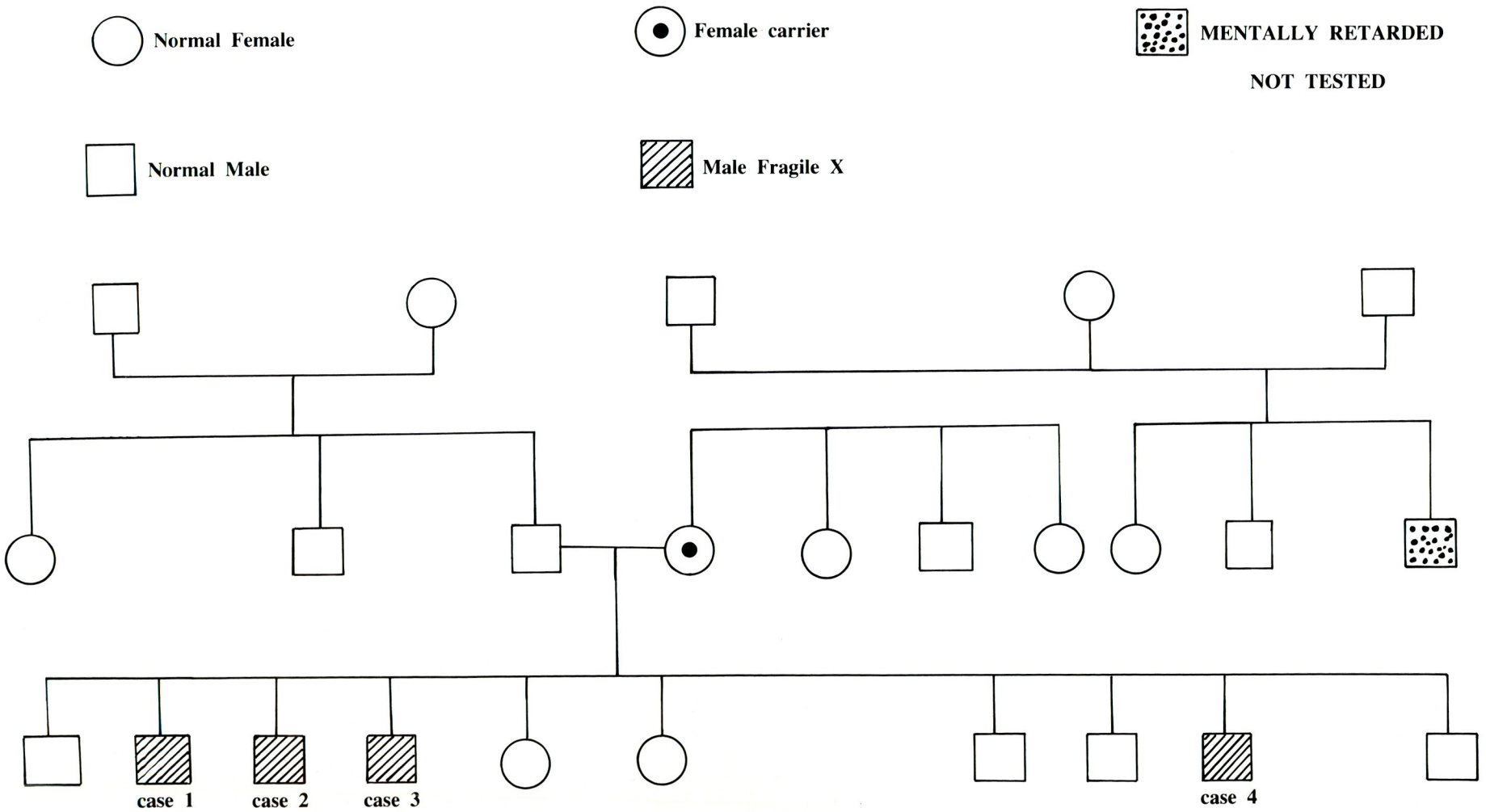
Figure 1

# FRAGILE X SYNDROME

## FAMILY PEDEGREE



**CASE 1**

He was a product of a full term normal delivery at Salmaniya Medical Centre born on 12-1-86. Pregnancy was uneventful apart from slight vaginal bleeding. Apgar score at birth was 7 & 9 at 1 & 5 minutes respectively. Birth-weight was 2900 gm, head circumference 33.5cm, chest circumference 33cm and length 48cm. No physical abnormality apart from tongue tie was detected.

On the third post-natal day he was admitted to Special Baby Care Unit for neonatal jaundice, with bilirubin of 14.7 mg/dl and he received phototherapy. He sat and crawled at one year, walked alone at 18 months and had delayed language development.

At the age of three years, he was hyperactive, irritable and uncontrollable. His head circumference, length and weight were 47cm, 92cm and 13.5 kg respectively. Abnormal features including strabismus, open mouth, big soft hands and feet, a palpable spleen, macro-orchidism and an ejection systolic murmur were present (Fig 2). Chromosomal studies revealed fragile (X) chromosome in about 70% of cells scored from low folate cultures.

**CASE 2**

He was a product of full term normal delivery after an uneventful pregnancy. At birth he weighed 3.1 kg, head circumference was 35 cm, chest circumference 34 cm and length was 51 cm. He was described as having odd features with big mouth, big ears, brachycephaly and strabismus. He had jaundice which was treated with phototherapy. At the age of one month he was hospitalized for chronic gastroenteritis and bronchopneumonia. During childhood he was described as hyperactive and irritable. At the age of eight years his weight was 25 kg, height 118cm with long face, macrocephaly, large ears, big feet and hands, macro-orchidism were also present (Fig 3). He was reported to have short attention span and mild mental retardation needing

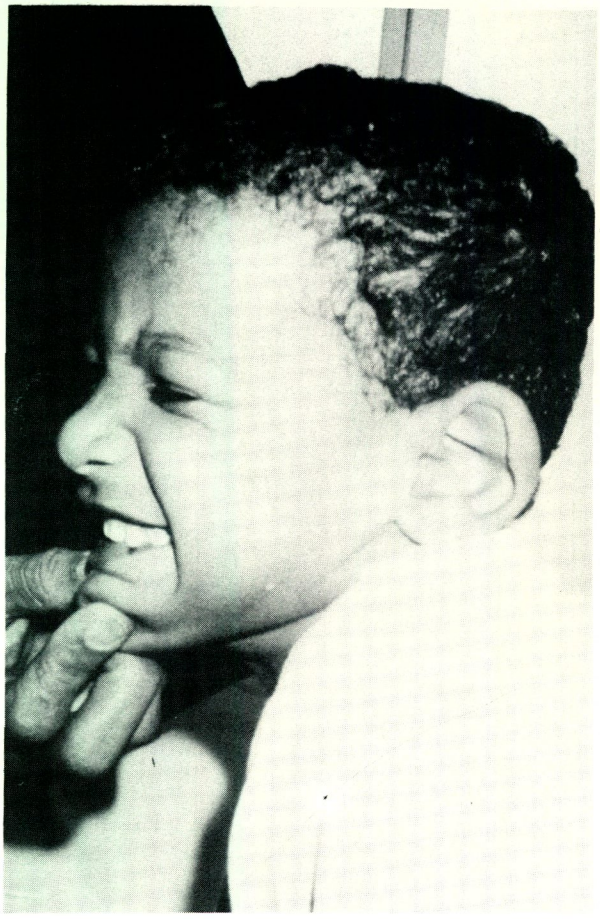


**Figure 2**

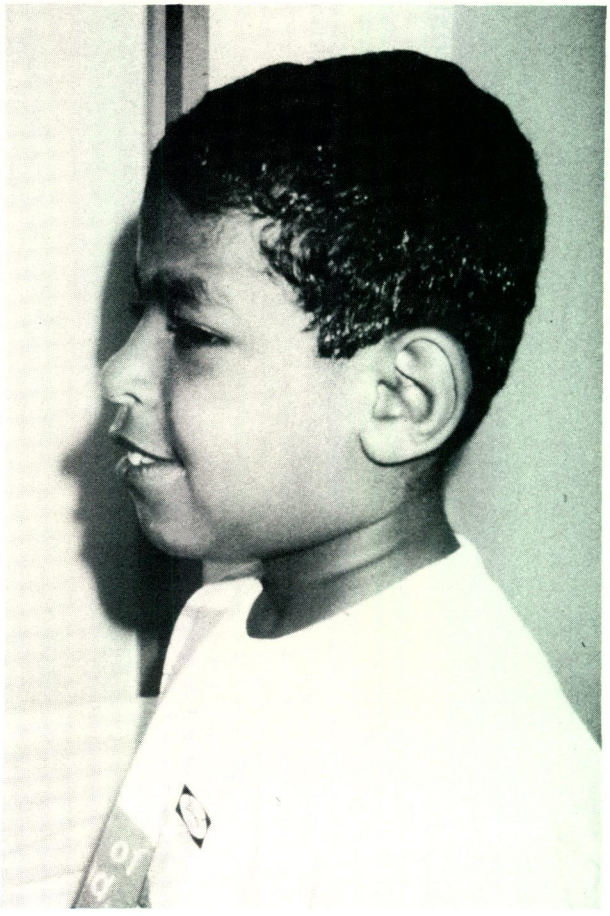


**Figure 3**

institution care. Chromosomal studies revealed fragile (X) in 50% of cells scored from low folate culture.

**CASE 3**

Figure 4 shows a thirteen year old boy, who is 50 kg in weight and 132 cm in height. His features were coarse, with long face, macrocephaly, large ears, big nose, big hands and feet and macro-orchidism. Although mildly mentally retarded, he is still attending regular school where his performance is reported to be poor. Chromosomal studies revealed fragile (X) in 20% of cells scored from low folate cultures.

**CASE 4**

Figure 5 shows a twenty year old man who is 65 kg in weight and 157cm in height. He has prominent jaws, hypotelerism, strabismus, large ears, big nose, big hands and feet with brachydactly, and macro-orchidism.

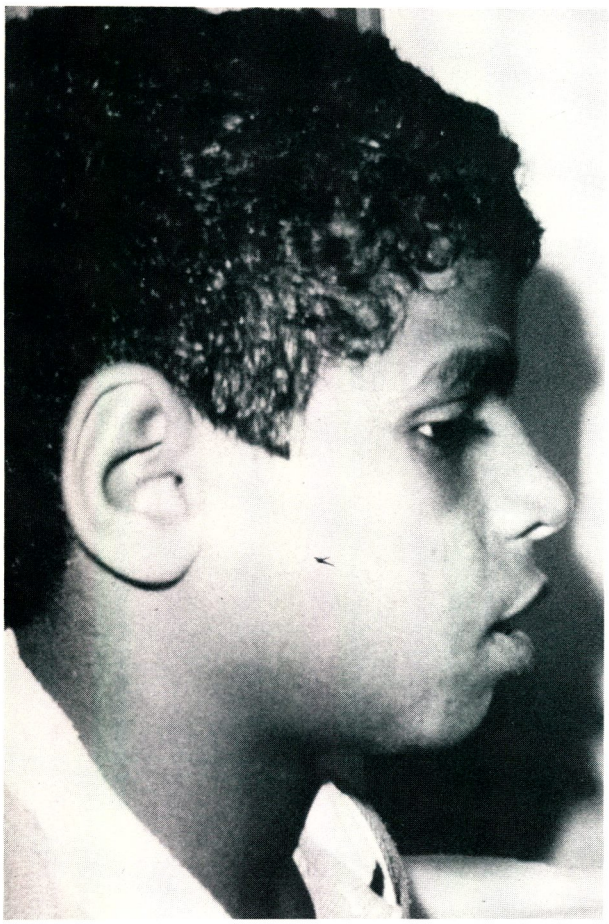


**Figure 4**

**Figure 5**

He also was a hyperactive child with attentional deficit and is now enrolled in the Hope Institute for the handicapped children. Chromosomal studies revealed the presence of fragile (X) in 10% of cells scored in low folate cultures.

Cytogenetic studies were performed for the other sibs, and all of them showed normal karyotypes except the elder daughter who is a carrier of the marker X, as fragile X was shown in 25% of the cells studied.

## DISCUSSION

The fragile X syndrome is a common genetic condition characterized by normal life expectancy and mental retardation that affects some 80% of males and 30% of females needing special education and support from social agencies.[6, 7] Approximately 25% to 50% of all cases of X-linked mental retardation are caused by this syndrome.[8, 9]

The usual presenting syndrome is developmental delay and a family history of mental retardation. The majority of affected males have a characteristic appearance which includes large ears, prominent forehead and jaw and large testes. In adult life there is decrease of stature involving upper limb length and upper face height with increase in jaw length, chest circumference and waist width in affected men and women. There is increase in palpebral fissure length and decrease in the inter-canthal distance.[10, 11] There are special dermatoglyphic changes.[12] Macro-orchidism is present in most post-pubertal males.[11]

Most of these patients have learning disability, attentional defects and hyperactive behaviour with autistic features.[13, 14] A characteristic form of speech has been described by many authors.[15] IQ in such patients ranges from 20-80, but in most instances it is in the 50-60 range. Verbal IQ is more depressed than performance IQ, but there are considerable variations as some affected males may be completely normal physically and mentally.[13]

Table 1 and 2 show the comparison between our cases and those reported from Australia.[10] It was noticed by many authors that sudden unexpected infant death is frequently observed in the progeny of obligate females.[16, 17]

**TABLE 1**

**Clinical Findings in Case 4**

**Based on Perth Series:**
**Traits from Possum Check List**

| *Physical Traits from Possum Checklist* | *Case 4* |
|---|---|
| (Occurring in over 50%) | |
| Long face | ± |
| Big ears | + |
| Big hands and feet | + |
| Photosensitivity | ± |
| Blond hair, light skin | − |
| Multiple pigmented Nevi | − |
| Narrow bifrontal diameter | − |
| Strabismus | + |
| Macrocephaly | + |
| Soft skin | ± |
| Hypotonia | − |
| (Occurring in fewer than 50%) | |
| Epicanthic folds | − |
| Patchy skin rash | − |
| Eunuchoidal build | + |
| Myopia | + |
| Gynecomastia | − |
| Hypotelorism | + |
| Narrow shoulder | + |
| Big (broad) nose | + |
| Ptosis | + |
| Skull asymmetry | − |
| Genua valga | − |

**TABLE 2**

**Physical Traits Found in Young Pre-pubertal Children**

**Findings in Cases 1, 2 & 3**

| *Findings* | *Case 1* | *Case 2* | *Case 3* |
|---|---|---|---|
| Puffy face | + | + | + |
| Narrow palpebral fissures | | | |
| – Big head relative to body | + | + | + |
| – High arched eyebrows | – | – | – |
| – Abnormal eyes | + | – | – |
| – Winged neck | – | – | – |
| – Puffy fingers | + | + | + |

It was also observed that individuals with FRA X Syndrome may be at increased risk of developing cancers, especially the unusual types such as Ewing's sarcoma, seminoma, sperm granuloma, malignant ganglioma.[18] Many cases of prenatal fragile (X) diagnosis have been confirmed and reported. Amniotic fluid, fetal blood and chorionic villus samples (CVS) have exhibited FRA (X g 27.3) in culture. Where fragile (X) is not present or is in very low frequencies in CVS and/or amniotic fluid cultures molecular methods by means of recombinent DNA technology can be resorted to using specific probes.[19, 20] Gestational age dating by ultrasonography is recommended as early as possible.

## CONCLUSION

**This is a report of the first family in Bahrain with fragile X syndrome. The diagnosis is important because many members of the family will be at risk, and the possibility of prevention aiming at reduction of mental retardation through genetic counselling, prenatal diagnosis is there. Therefore we recommend genetic counselling and cytogenic studies for all mentally handicapped, especially when there is positive family history of mental retardation and/or autism.**

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