Alpha thalassaemia mental retardation (ATR-X): an atypical family

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Abstract

A novel form of severe, X linked mental retardation associated with α thalassaemia (ATR-X syndrome) has recently been described. Two affected cousins are described, one of whom has an unusually mild haematological phenotype. HbH inclusions, which are the hallmark of this disease, were only detected in the peripheral red blood cells after repeated observations.

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In 1991 Gibbons *et al* defined a new, X linked form of mental retardation in 16 individuals with characteristic dysmorphic features and α thalassaemia (ATR-X).¹ At present a total of 44 affected patients have been identified (unpublished observation). Linkage analysis has localised the ATR-X disease locus to Xq12–q21.31.²

All affected individuals have a normal (46XY) male karyotype and are severely mentally retarded. The dysmorphic facial features are remarkably consistent including telecanthus, epicanthic folds, a flat nasal bridge with anteverted nares, and a 'carp shaped' mouth. Microcephaly is common and genital abnormalities are nearly always present. Affected boys often present with hypotonia and feeding difficulties in the neonatal period; subsequently they show developmental delay. Other less common features are constipation, gastro-

oesophageal reflux, and kyphoscoliosis. The diagnosis of ATR-X is made by demonstrating the associated haematological features of α thalassaemia, a condition that results from a reduced production of the α chains of adult haemoglobin (Hb $\alpha_2\beta_2$). The red blood cells are usually hypochromic and microcytic and contain excess β chains which form tetramers (β_4) referred to as HbH. In the presence of 1% brilliant cresyl blue HbH forms characteristic inclusions within the red cells. In all previous ATR-X cases HbH inclusions were readily detected (in 0.8–40% of red cells). In this report we describe an affected boy with unusually mild haematological features.

Case reports

CASE 1

The proband (fig 1) was born at 38 weeks' gestation by emergency caesarean section. He weighed 2340 g (3rd–10th centile) and Apgar scores were 2 at 1 minute and 7 at 5 minutes. He was transferred to the neonatal unit because of slow feeding and floppiness. On day 13 he developed necrotising enterocolitis and subsequently required a right hemicolectomy. By 12 months of age his head circumference was growing below but parallel to the 3rd centile. He showed telecanthus, anteverted nares, and a carp shaped mouth. A bifid left thumb, small soft testes, and deficient prepuce were also observed. Developmentally he was fixing and following, smiling responsively, and vocalising. He could only sit with support and was hypotonic with head lag on pulling to sit.

Investigations showed a normal 46XY karyotype, with no evidence of fragile X. TORCH screen, amino acids, organic acids, lysosomal enzymes, and thyroid function tests were normal.

A family history drew attention to a mentally retarded male cousin with similar facial features to case 1 (case 2).

CASE 2

This 14 year old, severely handicapped boy was born at term weighing 3320 g (10–50th centile) after a normal pregnancy and labour. In infancy he was noted to be dysmorphic and a provisional diagnosis of Smith-Lemli-Opitz syndrome was made.

At age 14.9 years (fig 2) his height was 118 cm and occipitofrontal circumference was 50 cm (–6 SD, –3 SD respectively). He was severely mentally handicapped with little comprehension and no recognisable speech. He was unable to walk and could only tripod sit

Figure 1 Case 1 aged 12 months.

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Figure 2 Case 2 aged 14.9 years.

for short periods. Severe gastro-oesophageal reflux and constipation were major medical problems.

On examination he also had telecanthus, anteverted nares, a carp shaped mouth with a large tongue, and in addition bilateral fifth finger clinodactyly, bilateral corrected talipes equinovarus, and a thoracic kyphoscoliosis.

Figure 3 Family history.

Haematological data

	Age (years)	Haemoglobin (g/l)	Mean corpuscular volume (fL)	Mean corpuscular haemoglobin (pg)	HbH positive cells (%)
Case 1	1.3	121	80.8	26.0	0.01
Case 2	14.9	123	84.8	26.7	0.25

He had a hypoplastic scrotum with bilateral cryptorchidism. Chromosomal analysis showed a 46XY karyotype.

FAMILY HISTORY (FIG 3)

The mother of case 1 had a poor obstetric history with one female stillborn infant and deaths of two preterm infants. Case 1 has a 6 year old sister who is developing normally. Elsewhere on the maternal side of the family six males had died prematurely. Four were said to be 'handicapped', one being in residential care up to his death at 14 years.

Results

In view of the dysmorphic features of case 1 a diagnosis of ATR-X was raised but the haematological indices were normal for a boy of this age and no HbH inclusions could be detected. Examination of case 2 confirmed that the boys were of similar appearance but in contrast to case 1, case 2 had 0.25% HbH inclusions. Case 1 was therefore re-examined but it was not until the third analysis on fresh blood that rare (0.01%) HbH inclusions were identified. Molecular studies revealed a normal α globin genotype ($\alpha\alpha/\alpha\alpha$) for each boy. The table shows the haematological data.

Discussion

The similar phenotype of these boys and the X linked pattern of inheritance was characteristic of the ATR-X syndrome. However, in one case it was particularly difficult to detect HbH inclusions and confirm the diagnosis. The demonstration of HbH inclusions in case 2 ensured a further attempt was made to detect them in case 1; without this second case in the family the diagnosis may have been overlooked. It may be relevant that the positive result was obtained with freshly drawn blood. The previous range for HbH inclusions was 0.8–40%; both boys had values below this and now the range extends to 0.01%. Therefore when there is a high index of suspicion from the family history and phenotype, a careful search for HbH inclusions should be made and repeated if necessary.

1 Gibbons RJ, Wilkie AOM, Weatherall DJ, Higgs DR. A newly defined X-linked mental retardation syndrome associated with alpha thalassaemia. *J Med Genet* 1991; 28: 729–33.

2 Gibbons RJ, Suthers GK, Wilkie AOM, Buckle VJ, Higgs DR. X-linked alpha thalassaemia/mental retardation (ATR-X) syndrome: localisation to Xq12–q21.31 by X inactivation and linkage analysis. *Am J Hum Genet* 1992; 51: 1136–49.