X linked α thalassaemia/mental retardation: spectrum of clinical features in three related males

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Abstract

We describe three males (two brothers and a cousin) who have the X linked α thalassaemia/mental retardation (ATR-X) syndrome. The diagnosis, originally suspected in the brothers because of similarity in dysmorphic features to previous cases, was confirmed haematologically in the surviving brother. The cousin has less typical dysmorphism and a virtually normal routine blood count, but haemoglobin H inclusions were found in his red blood cells showing that he has the same condition. This report expands the clinical phenotype of the ATR-X syndrome and emphasises that a normal blood count does not exclude the diagnosis.

X linked α thalassaemia/mental retardation (ATR-X) was first described in 1990.¹ Originally named the 'non-deletion' type of α thalassaemia/mental retardation syndrome, the designation 'ATR-X' was recently proposed² after the recognition of familial cases showing an X linked pattern of inheritance.²⁻⁴ Although the original cases were ascertained haematologically,¹⁻³ further patients have been recognised from the characteristic pattern of dysmorphism.^{2,4} Here we describe the clinical features of a further three related males.

Case reports

FAMILY HISTORY

The pedigree (fig 1) is remarkable for the high frequency of miscarriages and deaths of known

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males in utero or during childhood, and the paucity of normal males surviving to adulthood. Little information is available on the specific causes of death, although subject III-2 was said to have been brain damaged and died aged 6 years. The mothers of the three cases described below are sisters (subjects IV-5 and IV-2 in the pedigree).

CASE 1

The proband was born after a normal 41 week pregnancy with a birth weight of 3070 g (-0.8 SD). He required intermittent tube feeding on the Special Care Unit for the first 10 days; global developmental delay ensued. Findings at the age of 9 months were hypotonia, facial dysmorphism, a small perimembranous ventricular septal defect (confirmed on echocardiogram), undescended left testis, right hydrocele, and a mild microcytic anaemia (Hb 10.7 g/dl, mean cell volume 63 fl). Cytogenetic analysis was normal (46,XY) and no diagnosis was reached.

He made slow developmental progress, sitting with support at 18 months, standing with support at 2 years, and walking at 10 years. At the age of 3 years he was re-evaluated, when hypertelorism, a low nasal bridge, epicanthic folds, and a triangular mouth were noted (fig 2A). Height (94.3 cm, $+0.3$ SD) and OFC (49 cm, -1.0 SD) were normal. CT brain scan showed cerebral atrophy and an EEG indicated a generalised excess of slow waves. Ophthalmological examination, visual evoked responses, and electroretinogram were normal. Skeletal survey showed a retarded bone age of 18 months, bilateral coxa valga, and small terminal phalanges (the latter were also observed in his mother). Taking into account the findings in the other cases described below, a diagnosis of the Coffin-Lowry syndrome was suggested; although some doubts remained about this conclusion, his picture became featured in a standard textbook of dysmorphology.⁵

The similarity in appearance to a subject with the ATR-X syndrome^{2,4} eventually prompted reinvestigation at 14 years of age. Haematological analysis (table) showed a mild hypochromic anaemia with haemoglobin H (Hb H) demonstrable both on electrophoresis and in a blood smear stained with 1% brilliant cresyl blue. His α globin genotype was normal ($\alpha\alpha/\alpha\alpha$); in combination with the clinical

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Figure 1 Family pedigree traced back through the maternal line. Case 1 is V-5, case 2 is V-6, and case 3 is V-4.

features these findings are diagnostic of the ATR-X syndrome. Now aged 15 years (fig 2A), case 1 is severely retarded, having no expressive speech, extremely limited comprehension, and only partial bowel and bladder control. However, tone is normal, he has never had seizures, he can finger feed, drink from a cup, and walk short distances unaided. His OFC is normal (53.0 cm, -1.2 SD), but he has marked telecanthus (inner canthal distance 3.7 cm, $+2.2$ SD). In addition to the dysmorphic features already noted, the digits of his hands are tapering and the fifth fingers show clinodactyly, but the feet are unremarkable. He has widely spaced nipples and a mild kyphosis. Dentition is satisfactory, despite frequent rumination and tooth grinding. His right testis is small and high lying and the left is atrophic; no pubertal growth spurt has occurred (height 148 cm, -4.0 SD). He has scanty pubic hair but no other secondary sexual characteristics.

CASE 2

The proband's younger brother was born weighing 3420 g (-0.2 SD) after a normal term pregnancy. He was markedly hypotonic, required tube feeding for one week, and at 6 months had an operation for a right sided inguinal hernia with an ectopic right testis. OFC was 44 cm at 11 months (-1.7 SD). At 14 months developmental delay was apparent and he was noted to have similar facial features to his brother, with telecanthus, epicanthic folds, strabismus, a depressed nasal bridge, and carp mouth (fig 2B). A skeletal survey showed mildly delayed bone age (12 months), bilateral coxa valga, absent skull

sinuses, ovoid vertebral bodies, and 'drumstick' terminal phalanges. Cytogenetic analysis was normal (46,XY).

Developmental milestones included sitting with support at 9 months and standing up at 22 months, but subsequently he made little further progress and was never able to walk unsupported or acquire intelligible speech, although he had no seizures. He developed persistent rumination, for which no organic cause was found, and severe attrition of his premolar teeth, requiring extraction at 3 years of age. His height was 100 cm aged 4 years 6 months (-0.4 SD). He died of acute pneumonia aged 4 years 11 months; no haematological data are available.

CASE 3

The cousin of cases 1 and 2 was born after a normal term pregnancy, weighing 2730 g (-1.4 SD). Although well at birth, his condition deteriorated and at 30 hours he required a lumbar puncture. This episode settled quickly but feeding difficulty persisted and by the age of 9 months hypotonia and global delay were apparent. He sat with support at 3 years and stood with support at 5 years. Absence attacks developed at the age of 1 year and grand mal seizures have occurred occasionally. At the age of 10 years the EEG showed stereotyped sharp waves of uncertain significance; skeletal survey at 11 years 9 months indicated delayed bone age (7 years), absent frontal sinuses, thoracolumbar kyphosis, and prominent distal phalangeal tufts. His karyotype was normal (46,XY).

Figure 2 Facial features of the affected boys. (A) case 1 aged 3 years (left) and 15 years (right); (B) case 2 aged 15 months; (C) case 3 aged 1 month (left), 4 years (centre), and 23 years (right).

Haematological analysis of cases 1 and 3 and their female relatives.

Subject	Age (y)	Hb (g/dl)	RBC ($\times 10^{12}/l$)	MCV (fl)	MCH (pg)	Hb H el (%)	Hb H inc (%)
Case 1	14	10.7	4.85	69.3	22.1	2.3	14
Mother (IV-5)	38	13.1	4.07	94.0	32.3	ND	<0.01
Sister (V-7)	3	12.0	4.54	82.2	26.4	0.9	3.4
Case 3	23	13.3	4.72	85.2	28.2	0.9	3.5
Mother (IV-2)	55	12.2	4.05	93.7	30.2	ND	<0.01
Sister (V-3)	25	13.0	4.31	90.2	30.3	ND	0

Hb, haemoglobin; RBC, red cell count; MCV, mean cell volume; MCH, mean cell haemoglobin; Hb H el, % Hb H observed on Hb electrophoresis; Hb H inc, % red cells positive for Hb H after 1% brilliant cresyl blue incubation at room temperature; ND, not determined.

Currently aged 23 years (fig 2C), he is very severely handicapped and, unlike case 1, is unable to walk unaided or feed himself; he has no intelligible speech or comprehension of language and no bowel or bladder control. He is very short (height 145 cm, -4.5 SD) and microcephalic (OFC 51.5 cm, -3.1 SD), but does not have telecanthus (inner canthal distance 3.1 cm, $+0.2$ SD), and the nasal bridge is well developed. He has marked midfacial hypoplasia, a prominent chin, and a large mouth that is frequently held open, accompanied by vocalisation and tongue thrusting. His dentition is worn and there are several supernumerary teeth. He is generally hypertonic and has a severe kyphosis, but he can bear weight and manage one or two steps with support. Both testes are small and situated at the external inguinal ring; penis growth and hair distribution show fairly normal post-pubertal changes. Examination of the peripheral blood (table) showed a very mild anaemia with otherwise normal red cell indices. However, the presence of a faint Hb H band on electrophoresis and Hb H inclusions in the blood smear, together with a normal α globin genotype ($\alpha\alpha/\alpha\alpha$), confirmed the diagnosis of ATR-X.

PHENOTYPE OF THE FEMALE RELATIVES

Both mothers (IV.2 and IV.5) of the affected boys are obligate carriers of the ATR-X gene but have normal haematological indices (table); however, very occasional Hb H inclusions can be found in their blood. The sister (V.7) of cases 1 and 2, currently aged 3 years, has normal developmental milestones but a facial appearance somewhat reminiscent of her brothers. Her blood contains unexpectedly frequent Hb H inclusions (3.4% of cells) and a faint band of Hb H is visible on electrophoresis; she is presumed to carry the disease gene. The sister (V.3) of case 3 is clinically and haematologically normal.

Discussion

The three patients described here contribute further to the clinical delineation of the ATR-X syndrome. The accompanying article in this issue of the journal⁶ reviews the current situation in detail, but a few points specific to this family are worth highlighting. Case 3 has been particularly instructive, for it is doubtful whether the diagnosis would have been suspected in him without the family history. This is primarily because the lack of telecanthus or epicanthic folds and the well formed nasal bridge give a

different gestalt to his facial appearance. He is otherwise typical in many respects, having a similar lower face (with a flat midface, triangular open mouth, and dental anomalies), microcephaly, short stature, undescended testes, and severe mental retardation. The minor skeletal anomalies in these patients were considered similar to those in the Coffin-Lowry syndrome, and it is important to beware of this diagnostic pitfall.

The family shows two notable haematological phenomena. First, the virtually normal routine blood count and barely detectable Hb H band on electrophoresis in case 3 serve to emphasise that the diagnosis of ATR-X in affected males can only be excluded by a negative examination for Hb H inclusions, when conducted in an experienced laboratory. Second, the presumed carrier sister of cases 1 and 2 manifests α thalassaemia in a much more severe fashion (overt Hb H disease) than previously encountered in a carrier female, yet is of normal intelligence: the possibility that this is explained by differential X inactivation is being investigated.

Finally, the history of three male stillbirths in generation III is intriguing. Together with the death of the three other male children in this generation, this suggests that subject II.1 carried the disease gene, and that the ATR-X syndrome may sometimes be lethal in utero. If so, it would be interesting to document the phenotype of such fetuses, as this may provide further insight into the pathophysiology of the syndrome.

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