X linked mental retardation with non-deletional \(\alpha\) thalassaemia (ATR-X): further delineation of the phenotype

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Abstract
Two sibs with non-deletional \(\alpha\) thalassaemia and mental retardation (ATR-X) have been ascertained showing variable neurological features. The proband had a complex neurological picture with recurrent apnoea, complex partial seizures, and prolonged periods of semiconsciousness between 12 and 17 months of age. Episodes of spontaneous laughter were also a feature. An EEG was initially normal. \(\beta\) H inclusions were present but rare in this family. The sole genital anomaly was deficiency of the foreskin, a feature not previously described in ATR-X.

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Facial dysmorphism, severe intellectual handicap associated with \(\beta\) H inclusions, and a normal \(\alpha\) globin complex was originally described in 1981\(^{1}\) and is now known as ATR-X syndrome. In the last three years attention has been drawn to this syndrome in terms of delineation of phenotype and confirmation of \(X\) linkage.\(^{2,3}\) A distinct syndrome of \(\alpha\) thalassaemia, \(\beta\) \(H\) inclusions, mental retardation, and variable clinical features associated with large deletions of the tip of chromosome 16p involving the \(\alpha\) globin locus has also been identified. This syndrome is known as ATR-16\(^{4}\) and is distinct from ATR-X. Confusion between ATR-X and other disorders has been noted previously, in particular Angelman syndrome, FG syndrome, Smith-Lemli-Opitz syndrome, and Coffin-Lowry syndrome.\(^{4,5}\) Coarsening of facial features over time has been described. We present two Australian brothers of northern European ancestry who initially posed a diagnostic dilemma, the older boy in the first 18 months of life exhibiting a complex neurological picture which at times suggested regression.

Case reports
The parents of the proband are non-consanguineous. Before the birth of the proband, there were three miscarriages and the birth of a healthy female who is intellectually normal.

The proband was born at 35 weeks’ gestation with a birth weight of 2670 g. He is now 3\(\frac{1}{2}\) years of age. Head circumference at birth was 31 cm (10th centile) and birth length was 47 cm (50th to 75th centile). The mother had an intravenous pyelogram and micturating cystourethrogram at 7 weeks of gestation. At 2 weeks of age he was noted to have poor feeding and cyanotic episodes, which apparently spontaneously improved. Marked head lag was noted from 1 month. He smiled at 6 weeks. At 3 months of age he was shown to have mild obstructive sleep apnoea. Gastro-oesophageal reflux was documented from 4 months of age and was initially managed conservatively.

At 12 months of age when seen by the genetics unit, all growth parameters were below the 3rd centile, with a head circumference of 40.5 cm, length of 71 cm, and weight of 7.44 kg. His dysmorphic features included upturned nares, a broad nasal bridge without measurable hypertelorism, and micrognathia. Teeth were widely spaced and small. The upper lip was tented and everted and he had low set ears with thick helices (figs 1 and 2). His irides were pale blue but not stellate. He had bilateral fifth finger clinodactyly and his penis exhibited deficiency of the foreskin with normal testes and scrotum. There was global developmental delay with overall function at 3 months. Historically it appeared that he was having recurrent episodes of fitting, though a cerebral ultrasound and EEG were normal. A diagnosis of Williams syndrome was considered at this time although his intellectual impairment and microcephaly were thought to be too marked for this diagnosis.

![Figure 1: Proband aged 12 months showing microcephaly and tented, everted upper lip.](http://jmg.bmj.com)
By 17 months of age he was having recurrent episodes of apnoea and well documented seizures. It was noted that he had now developed restless physical movement with episodes of spontaneous laughter. At this point there was a question as to whether he had regressed. Because of the onset of abnormal movement with inappropriate laughter the diagnosis of Angelman syndrome was considered. A synchronised G banded karyotype was normal 46,XY at 850 band resolution.

At 2 years of age he was having up to 15 episodes of apnoea per day, with recurrent vomiting. He made virtually no vocalisation and was unable to sit independently. In addition he had developed jerky choreiform movements, complex partial seizures, and prolonged periods of decreased level of consciousness. The episodes of semiconsciousness would often last up to 23 hours of the day and were evident during viral illnesses. They were associated with periods of hyperventilation and poor temperature regulation. A number of investigations were performed. These included a normal bicarbonate, urine metabolic screen, liver function tests, ammonia and plasma and CSF lactate and pyruvate. A CT scan of the head showed mild cerebellar hypoplasia and prominence of the sulci. An EEG showed immature rhythms with excess intermediate fast rhythms. Growth parameters showed that his head circumference had fallen well below the 3rd centile at 42 cm, his weight of 9.6 kg being just below the 3rd centile. His facial features had coarsened (fig 3). Following several episodes of right upper lobe consolidation, fundoplication and gastrostomy were performed at the age of 2 years 3 months in attempt to prevent further reflux and aspiration. At 3 years 6 months, his overall functional level was equivalent to 3 months.

A brother was born 2 1/2 years after the proband who at the time did not have an established diagnosis. His facial appearance (fig 4) was identical to his brother's as was his genital abnormality. His birth weight was 2250 g which is less than the 3rd centile as was his length of 46 cm and head circumference of 31.5 cm. He was noted to be only slightly hypotonic, but fed poorly and had recurrent vomiting. A barium study was normal at 2 months of age. Despite the absence of documented reflux, he had several episodes of right middle lobe consolidation. At 8 months a formal bronchoscopy showed no structural abnormality and a milk scan showed gross reflux when lying prone, but no evidence of aspiration. The reflux was managed conservatively. Developmental assessment at 8 months showed he was function-
ing at a 5 month level, though his motor skills and tone were significantly better than his brother’s at the same chronological age. A karotype was normal 46,XY.

With the birth of a second affected male, the phenotypic similarity to ATR-X, in particular the severity of the intellectual handicap, prompted more extensive haematological examination. The brother of the proband was initially investigated. His haemoglobin was 12·0 g/dl with an MCV of 76·7 fl. A haemoglobin electrophoretogram was normal. Red cell morphology showed hypochromasia, microcytes, and polychromasia. Hb H inclusions were seen on staining with brilliant cresyl blue, one in every two to five high power fields. The proband was subsequently investigated. His haemoglobin was 12·8 g/dl with an MCV of 89·9 fl. A haemoglobin electrophoretogram was normal and red cell morphology showed aniso-cytosis. Hb H inclusions were seen in one in every five to ten high power fields. The mother of the two boys had a haemoglobin of 12·7 g/dl with an MCV of 88·7 fl and a normal haemoglobin electrophoretogram. She had only two red cells with Hb H inclusions on review of four slides. We have recently looked for Hb H inclusions in the maternal grandmother of the two boys. None were found, though we are aware of a severely handicapped male who is the maternal uncle of the grandmother. No other information is available on that uncle. α globin genotyping was performed on both boys using probes α1 globin/HBA1, ψ(1) HBZ1, and α2 globin 3'HVR/D16S85. The α globin genotype in each boy was Xq12-q21.3.16 Confirming the diagnosis of ATR-X (R Gibbons, personal communication, 1993).

Discussion

Non-deletional α thalassaemia associated with mental retardation (ATR-X) has been shown in a number of pedigrees to be X linked and more recently there has been confirmation of localisation to Xq12-Xq21.3.16 The syndrome is characterised by a particular dysmorphic facial appearance, intellectual handicap, and genital anomalies. This family illustrates previous observations made in this disorder and exhibits additional features relevant clinically and diagnostically.

Both boys have a similar facial appearance to the published cases. Prenatal and postnatal onset of microcephaly has been described; however, fluctuation of level of consciousness together with choreiform movements and complex partial seizures has not been observed previously. Both boys have significant intellectual handicap but the proband is more severely affected with minimal skills. Differences in the severity of intellectual handicap within particular families has been previously described.16

The proportion of Hb H inclusions was higher in the symptomatically less affected brother, so that the percentage of inclusions in this family does not offer a correlation with the degree of disability. The mother’s obligate carrier status was confirmed by the presence of Hb H inclusions in small numbers on peri-}

pheral film. This would support the non-random X inactivation of the ATR-X locus shown in a significant proportion of obligate carrier women. A negative haematological result in an intellectually normal female with a single affected male would not exclude carrier status or germline mosaicism.

The family expands the phenotype of the ATR-X syndrome to include periods of semi-consciousness, complex partial seizures, and a unique genital anomaly of foreskin deficiency. The family also illustrated the diagnostic difficulties that may occur particularly when there is initially a single affected male whose clinical features may mimic other syndromes. The proportion of Hb H inclusions in the two boys was very low. The proband had 0·1% Hb H inclusions and the younger brother 0·2% Hb H inclusions. The lowest reported percentage of Hb H inclusions in affected males is 0·8%.4 The search of several high power fields may be required before considering exclusion of the diagnosis of ATR-X in an intellectually handicapped male. In addition it has been suggested that if the phenotype of the patient is strongly suggestive of ATR-X, then a globin synthesis ratio estimation may be a necessary adjunct to searching for Hb H inclusions, as this ratio is reduced in affected males and, as illustrated in this family, the percentage of Hb H inclusions could be low (D Higgs, personal communication, 1993).

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