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SYNDROME OF THE MONTH

Angelman syndrome

J Clayton-Smith, M E Pembrey

In 1965, Harry Angelman, a general paediatrician from Warrington, Cheshire, England, reported three children with a similar pattern of mental retardation, seizures, ataxia, easily provoked laughter, absent speech, and dysmorphic facial features.[1] He called them 'puppet children'. In subsequent reports by other authors, this name was altered to 'happy puppet syndrome'[2] and this term continued in popular use for many years. It is, however, considered derogatory by the majority of parents and many professionals and the name 'Angelman syndrome' (AS) is now the preferred one. In the first 20 years after its description, Angelman syndrome was reported only rarely. Over the last five years, however, the phenotype has been more widely reported owing to both increasing interest in the cytogenetic[3] and molecular genetic[4] abnormalities on chromosome 15 and to the report by Boyd *et al*[5] of the characteristic EEG findings in this condition. This has led to an increase in the number of Angelman patients diagnosed and to diagnosis at a younger age. The incidence of Angelman syndrome is estimated to be around 1 in 20 000.

Clinical details (figs 1–6)

The clinical features of the syndrome are shown in the table. The data in the table have been gathered from the personal experience of one of the authors (JCS) of 80 cases in the UK and from some of the larger studies published.[6–8] All the patients have severe mental retardation and delayed motor milestones. The dysmorphic facial features are not apparent at birth but evolve during infancy and childhood. Typical features include brachycephaly and a head circumference below the 25th centile. The mouth is large and the teeth widely spaced. There may be bowing of the upper dentition possibly because of persistent tongue thrusting. The chin is pointed and prognathic and there is usually a thin upper lip and midfacial hypoplasia. The eyes are deep set and usually blue. Hypopigmentation of the skin, hair, and eyes compared to other family members is seen in the majority but not all AS

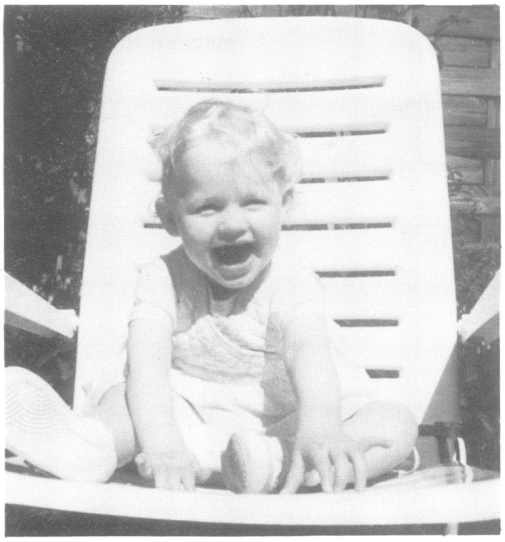

Figure 2 Same child as in fig 1 at 18 months of age. Note wide, smiling mouth and more prominent chin.

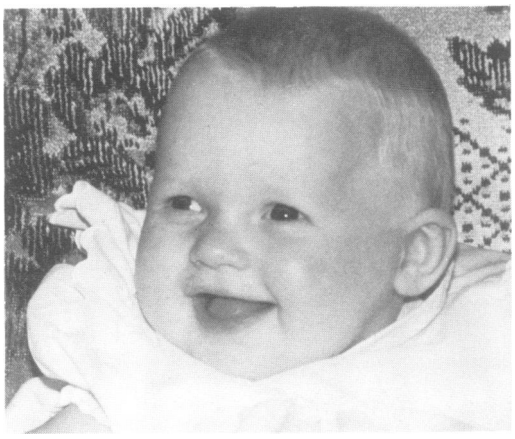

Figure 1 The facial features in infancy are unremarkable.

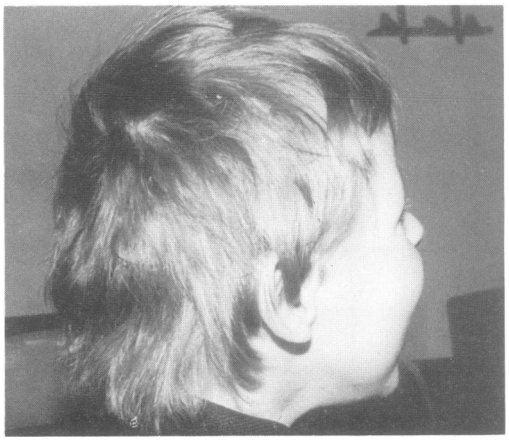

Figure 3 Brachycephaly is seen in around 90% of patients.

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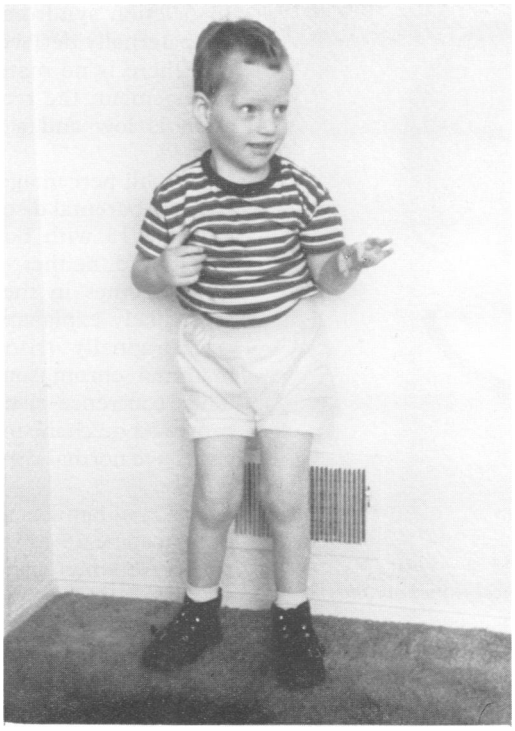

Figure 4 The arms are typically flexed at the elbows and upheld. There is a wide based, stiff legged stance.

patients. The diagnosis of AS is made not on the physical appearance alone, but includes the behavioural phenotype. The jerky movements, tongue thrusting, mouthing, and hand flapping behaviour which these patients exhibit are all characteristic.

Neurological findings

Children with AS have delayed motor milestones, sitting unsupported at around 12 months of age, crawling (usually in the commando style) or bottom shuffling at 18 to 24 months, and walking on average at 4 years; 10% of patients are never able to walk independently. The gait is ataxic and stiff legged. There is usually truncal hypotonia with hypertonia of the limbs so that the babies are stiff to handle, for example on bathing, rather than floppy. Reflexes are brisk. Seizures occur in 80% of patients and commonly begin between 18 and 24 months of age. All seizure types are seen and the pattern of fits is episodic with periods of severe fitting lasting up to several weeks interspersed with relatively fit free periods. No anticonvulsant seems completely effective during these severe periods, but sodium valproate and clonazepam are commonly used as maintenance drugs with good effect. The EEG findings are characteristic, consisting of large amplitude slow wave activity (4 to 6 c/s) persisting for most of the record and unrelated to drowsiness, very large amplitude slow activity at 2 to 3 c/s occurring in runs and more prominent anteriorly, and spikes or sharp waves mixed with large amplitude 3 to 4 c/s components, seen posteriorly and usually only on passive eye closure. It may require more than one EEG to elicit all the features and they become less florid with age. CT scans are usually normal or show features compatible with mild cerebral atrophy.

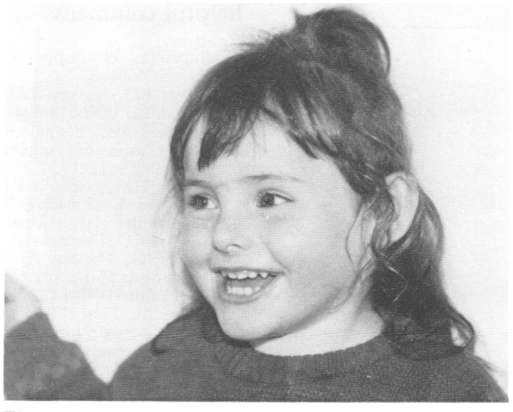

Figure 5 Two year old with Angelman syndrome; 35% of patients do not have hypopigmentation.

Natural history

Pregnancy and delivery are usually uneventful but the babies tend to weigh 200 to 300 g less than their sibs on average. They are often miserable babies and feeding problems are a common cause for concern. Jerky movements become apparent during the first few months and motor delay is obvious by 9 months of age. Seizures begin around 2 years and remain a problem until 7 or 8 years when they decrease in frequency and may cease altogether. Hyperactivity and sleep disturbance, which are common in childhood, improve with age. The facial features are not usually apparent in infancy but evolve over the first five years of life. Language does not develop, most patients having only one or two words, in spite of having reasonable comprehension of simple commands and sentences. Some patients can communicate using Makaton sign language or other gestures. Most patients remain ambulant into adulthood if kept mobile to prevent contractures developing in the hypertonic limbs. General health is good. Scoliosis occurs in 10% patients. This is an infantile type of scoliosis, apparent before the age of 5 years but progressive, particularly during the adolescent years. Cardiorespiratory difficulties may arise if it is left untreated.

Patients with AS can acquire some simple skills, such as eating with a knife or spoon and fork, dressing and washing with help, and performing simple household tasks; 80% become toilet trained by day. None acquires sufficient skills to be able to live independently.

Differential diagnosis

The diagnosis of Angelman syndrome is based on the history, clinical features, and EEG findings, plus or minus the presence of a deletion on chromosome 15. Some girls with Rett syndrome[9] have overlapping clinical features with the main distinguishing feature being a history of regression with loss of acquired skills in Rett syndrome, whereas Angelman

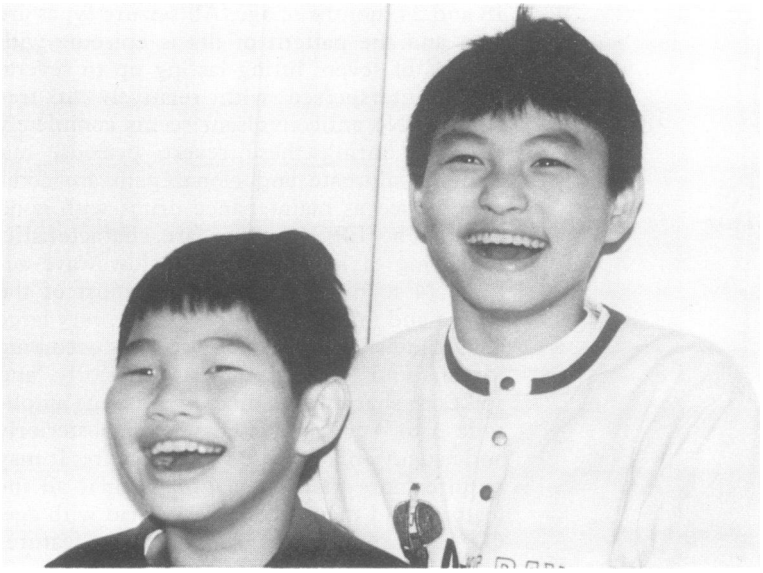

Figure 6 Sibs with Angelman syndrome have identical clinical features to the sporadic cases.

children never acquire the skills from the outset. The recently delineated syndrome of X linked α thalassaemia and mental retardation (ATR-X)[10] has many phenotypic features in common with Angelman syndrome and the diagnosis of ATR-X has now been confirmed in a boy known to the authors who was previously thought to have Angelman syndrome. Ataxic cerebral palsy also enters into the differential diagnosis but the degree of intellectual retardation is much less severe in this condition, there are no dysmorphic facial features, and speech is usually present.

Genetic mechanisms in Angelman syndrome

Several different genetic mechanisms have been shown to give rise to Angelman syndrome. At least 50% of patients have a maternally derived de novo deletion of chromosome 15q11–13, visible on cytogenetic analysis, and this figure can rise to 75 to 80% if molecular genetic techniques are included.[11 12] (In Prader-Willi syndrome, the alternative 15q11–13 deletion syndrome, the deletion arises on the paternally derived chromosome.) Provided that there is no maternal chromosome 15 rearrangement, the recurrence risk in this situation is low and a risk of 2% is presently quoted.

A small percentage of patients, around 3%, have uniparental disomy for the whole of chromosome 15 with both 15s coming from the father and neither from the mother.[13] The chromosomes in these cases are intact. The most likely explanation is that the conceptus was originally trisomic, and then lost the maternal chromosome 15 to remain viable. The recurrence risk is uncertain but if this proposed mechanism is correct, and both parents have normal chromosomes, then it should be low.

In 5% of families there is a rearrangement of chromosome 15 in the mother which can give rise to AS when passed to the child.[14] There is a risk to subsequent children, thus emphasising the need for chromosome analysis in all parents of AS children.

In the remaining 10 to 15% of families there is no cytogenetic deletion, no disomy, and molecular analysis with current probes shows no abnormality. This is the group where there is the highest risk of recurrence because to date familial cases have not shown a cytogenetic deletion. Research suggests that in these few families there may be an autosomal dominant mode of inheritance with affected sibs inheriting the same maternal chromosome 15. Recently, Hamabe *et al*[15] reported one family in which the unaffected mother, the maternal grandfather, and three affected children carried the same small deletion (smaller than the 'typical' molecular deletion in AS). This supports the theory of dominant inheritance modified by genomic imprinting because the mother inherited the mutation from her father, a transmission where the AS locus is silenced anyway, and not from her mother. The mutation is therefore inconsequential.

It is clear, then, that patients with Angelman syndrome are a genetically heterogeneous group and it is necessary to elucidate the genetic mechanism responsible in each family in order to offer accurate genetic advice.

Frequency of the clinical features seen in Angelman syndrome.

	%
OFC < 3rd centile	25
OFC < 50th centile	98
Brachycephaly	90
Occipital groove	35
Feeding problems	75
Delayed motor milestones	100
Seizures	80
Absent speech/< 3 words	98
Ataxia	100
Blue eyes	88
Blonde hair	65
Macrostomia	75
Pointed chin/prognathism	95
Widely spaced teeth	60
Bowed primary dentition	35
Tongue protrusion	70
Scoliosis	10
Truncal hypotonia	90
Limb hypertonia	85
Hyperreflexia	85
Cerebral atrophy on CT scan	30
Strabismus	40

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