

# ARCHIVES OF DISEASE IN CHILDHOOD

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## Annotations

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### Angelman's syndrome

Angelman's syndrome is one of the causes of severe mental handicap that is associated with a characteristic facial and behavioural phenotype. It was first described by Harry Angelman in 1965<sup>1</sup> and was reported only infrequently in the literature up until 1987 when a proportion of patients with the syndrome were noted to have a small deletion of the long arm of chromosome 15 at 15q11–13.<sup>2,3</sup> Since then interest in Angelman's syndrome has grown, leading to an increased frequency of diagnosis and greater awareness of the clinical features of this condition.<sup>4</sup>

#### Clinical history

The infant with Angelman's syndrome is usually born after a normal pregnancy and the birth weight is approximately 200 g less than normal siblings. In the neonatal period feeding problems are common, with difficulty in establishing breast feeding, gastro-oesophageal reflux, and poor weight gain even though the infant appears to suckle for long periods. The babies are often tremulous on handling and frequent jerky movements become apparent during the first months of life. Smiling begins at the normal time but there is a delay in motor milestones with inability to sit unsupported until around 12 months. There is appreciable truncal hypotonia but in contrast the limbs are usually stiff. Crawling is commonly in the 'commando' style and independent walking is generally achieved at around 3 to 4 years, although some children walk as early as 2 years. A minority do not become ambulant, and these children tend to have the greatest degree of limb spasticity or additional problems such as scoliosis or cerebral palsy. The gait in Angelman's syndrome is characteristically ataxic with a wide base and stiff legs. The arms are upheld and flexed at the elbow, a posture which led to the condition being known as 'happy puppet syndrome'.<sup>5</sup> This name was not popular with parents and other carers and is no longer in common use.

Altogether 80% of patients with Angelman's syndrome suffer from a seizure disorder. The onset of seizures is generally between 18 and 24 months and the first is typically precipitated by a fever. Thereafter seizures may occur at any time and all seizure types are observed with myoclonic jerks and drop attacks being particularly frequent. Infantile spasms have also been reported,<sup>5</sup> but without the finding of hypsarrhythmia on the electroencephalogram (EEG). The seizure pattern is often episodic with severe bouts of seizures interspersed with fit free periods of several weeks or months. They may be very difficult to control but sodium valproate and clonazepam appear to be the most effective

anticonvulsants. The EEG appearances are striking and have been described by Boyd *et al*,<sup>6</sup> who noted several characteristic features, the most consistent of which was posterior slow wave activity with discharges, facilitated by or seen only on passive eye closure. The authors emphasised that more than one EEG may be needed to demonstrate the typical appearances. The changes are also age dependent, being less florid in the older children and reflecting the clinical findings, as seizures become less frequent in later childhood and may cease altogether. Computed tomograms are usually normal or show only mild ventricular dilatation and cerebral atrophy.

Children with Angelman's syndrome are unable to acquire more than two or three words of speech and must communicate by sign language or primitive gestures. The ability to acquire sign language varies but only a minority will have no means of communication. Comprehension skills appear to be significantly better than those of expressive speech. It is difficult to test accurately the level of cognitive functioning in this group of children who have specific problems with both speech and coordination but they fall within the educationally subnormal group.

#### Facial phenotype

The dysmorphic facial features in Angelman's syndrome are subtle and evolve with age, becoming more apparent from the second year of life. The head circumference falls within the lower half of the normal range, although only 25% are truly microcephalic. The skull is usually brachycephalic and there may be a horizontal groove in the skull just above the occiput. The mouth is typically wide and smiling and the upper lip is thin. The chin is pointed and prominent and the tongue protrudes between the wide spaced teeth. Approximately half of the children have fair hair and skin and most have blue eyes; 40% have an alternating strabismus. Fundoscopy in the more hypopigmented children reveals deficient choroidal pigmentation,<sup>7</sup> but this rarely affects the visual acuity.

#### Behavioural phenotype

Behavioural features provide the clue to diagnosis in younger children where dysmorphic facial features are not apparent, especially if the familial features are prominent. These children have a happy, sociable affect and laugh frequently, and sometimes inappropriately, for example on venepuncture. The laughter is not uncontrollable, however, and is always provoked, even though the stimulus may be

minimal. It is not related to electrical activity within the brain as in gelastic epilepsy. In association with the laughter there is a tendency to flap the hands when excited. Other characteristic behaviours include a love of water, reflections, and noises.

### Natural history

General health in Angelman's syndrome is good and there are no major life threatening physical problems. Scoliosis occurs in 10% of patients and is usually recognisable early in life and amenable to treatment by bracing, although some patients require surgery particularly if the scoliosis worsens at adolescence. Most patients remain mobile if they have regular exercise to prevent the development of contractures in their hypertonic limbs. After the hyperactivity of childhood the behaviour of older children is quieter and seizures absent or easier to control. The majority of patients will develop some self help skills and be able to feed themselves, toilet themselves by day, dress with help, and perform simple household tasks.<sup>8</sup> No patient with Angelman's syndrome has been able to live independently.

### Genetics of Angelman's syndrome

Angelman's syndrome arises as the end result of several different genetic mechanisms. Most cases are sporadic within a family but several families have been reported where there has been more than one affected child.<sup>9-11</sup> Around 60% of patients have a *de novo* deletion of chromosome 15q11-13 which is visible cytogenetically.<sup>12</sup> This deletion is in exactly the same place as that known to be associated with Prader-Willi syndrome.<sup>13</sup> The two conditions have distinct clinical phenotypes and although some minor features are common to both, such as fair hair colouring and blue eyes, the major clinical features do not overlap.<sup>14</sup> The parents' chromosomes are normal but in Angelman's syndrome the deletion always arises on the chromosome 15 which has been inherited from the mother and in Prader-Willi syndrome this same deletion is paternally derived.<sup>15</sup> Angelman's syndrome and Prader-Willi syndrome therefore provide a perfect human model for genomic imprinting, the phenomenon whereby genetic information is expressed differently depending on the parent of origin.<sup>16</sup> In a further 15% of families with Angelman's syndrome, though there is no apparent cytogenetic deletion, a deletion of 15q11-13 can be detected on DNA analysis.<sup>17</sup>

Two to three per cent of patients have inherited both of their chromosome 15s from a single parent, and are therefore said to have uniparental disomy for chromosome 15.<sup>18</sup> There are no deletions and both the 15s come from the father. It is likely that the conceptus was originally trisomic for chromosome 15 and that the maternal 15 was lost during the early cell divisions in order for the embryo to remain viable. In both uniparental disomy cases and those with a *de novo* chromosome 15 deletion parental chromosomes are normal and recurrence risks are judged to be low.

In around 5% of families there is a chromosomal rearrangement in the mother—for example an inversion or translocation which can give rise to Angelman's syndrome when passed to a child because of the predisposition to deletion of 15q11-13.<sup>19</sup> There is a risk to subsequent children and possibly other family members and so it is wise to check parental chromosomes in all cases of Angelman's syndrome in order to rule out this situation.

In the remaining families, around 15%, there is no evidence of a typical 15q11-13 deletion or of uniparental disomy using either cytogenetic or molecular genetic techniques. This is the group with the highest risk of recurrence because, to date, all families with more than one affected

child fall into this category. Current research suggests that the affected siblings may be inheriting a small mutation that came from one of the mother's chromosome 15s. Familial Angelman's syndrome is therefore likely to have an autosomal dominant mode of inheritance with a 50% recurrence risk. Angelman's syndrome will only result, however, if the mutation is maternally transmitted because of the phenomenon of genomic imprinting. This theory is supported by recent work from Japan.<sup>20</sup>

It is clear that the 15q11-13 region contains not one but several different genes and further molecular studies are now in progress to identify and sequence these genes. The gene for the GABA receptor  $\beta$  3 subunit was recently localised to 15q11-13 for example.<sup>21</sup> Lack of normal functioning of this gene could be relevant to the occurrence of seizures and hyperactivity and to the effectiveness of sodium valproate treatment. Investigations of gene expression may in due course provide an explanation for the symptomatology in Angelman's and Prader-Willi syndromes, a guide to treatment for these symptoms, and a clue to the mechanisms responsible for genomic imprinting in man.

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