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Angelman syndrome

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1. Introduction

Angelman syndrome (AS) is a neurodevelopmental disorder which was first described by Dr. Harry Angelman in 1965 [1]. It has a frequency of 1 in 20,000–40,000. The main clinical features are severe learning disability, ataxia, absent speech, seizures, acquired microcephaly, and a sociable disposition with easily provoked and often inappropriate laughter [2]. AS is often associated with subtle dysmorphic facial features including deep-set eyes, a wide mouth, which is held open, and a prominent chin (Fig. 1). These features become more marked with age. The back of the head is often, but not always flat [1].

The features of AS are not apparent at the time of birth but infants with this condition feed poorly and are often tremulous. Developmental milestones are delayed, with a mean age of sitting at 13 months. It is common for children with AS to commando crawl and then to begin to walk around 3 years of age. Around 15% will never walk independently. Jerky, ataxic movements and decelerating head growth become apparent from a few months of age. Eighty percent of AS children will have seizures, commonly beginning around 12–18 months. The electroencephalogram shows characteristic features in 95% patients. These are not usually present in infants under 6 months. The three main features are high voltage 2–3/sec activity over the frontal regions with notched delta waves, 4–6/sec activity in the centro-temporal regions and 3–6/sec high amplitude activity, often with spikes, posteriorly. The abnormalities are not associated with seizure activity and may be present throughout the recording. Runs of occipital sharp components triggered by passive eye closure are a characteristic feature. Seizures are most common during early childhood, remitting during late childhood but often returning as adulthood approaches [2]. Adults particularly exhibit cortical myoclonus that resembles coarse tremor. Children with AS frequently demonstrate truncal hypotonia but have increased tone in the limbs, giving rise to a characteristic broad based, stiff legged gait. As time goes on contractures may develop at the hips and knees and mobility can be impaired in adulthood. Further complications, which may develop, are scoliosis and reflux [3].

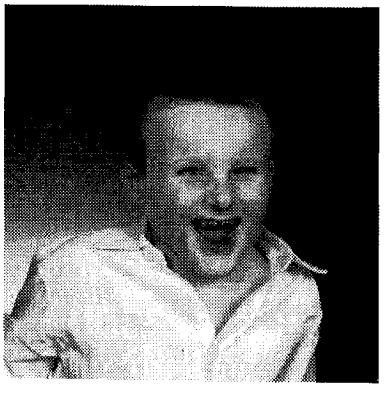

Fig. 1. Facial features of Angelman syndrome. Note deep-set eyes and prominent chin.

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Table 1
Genetic mechanisms giving rise to Angelman syndrome

Mechanism	%	Methylation	Inheritance
15q11-13 deletion	75	Abnormal	Usually de novo but rule out maternal chromosome rearrangement
Uniparental disomy chromosome 15	2–3	Abnormal	Sporadic rule out Robertsonian translocation
Imprinting defect	3–5	Abnormal	Majority sporadic, 10–20% familial many are mosaic with milder features
UBE3A mutation	10	Normal	75% sporadic, 25% familial. Risk that mother is gonadal mosaic
No 15q11-13 abnormality	10	Normal	Heterogeneous group. May be mosaic rule out other conditions e.g. SLC6A9. Significant recurrence risk

The behavioral features of AS are striking and often provide the most important clue to the diagnosis. Smiling occurs early, and children will laugh with minimal stimulation, though not without a reason. The gait is often lurching and associated with upheld arms, which are flexed at the elbows. Hand flapping is frequent, particularly when excited. Although individuals with AS are able to comprehend simple sentences, and have good visual memories, they do not usually develop speech beyond a couple of words and most communicate by gestures or picture communication systems. Other characteristic behavioral features are a love of water and sleep disorder, which is helped by melatonin in around 50%. They are often described as naturally inquisitive but stubborn [3].

AS is caused by a variety of genetic mechanisms, which all impair normal expression of the UBE3A gene on chromosome 15q11-13 [4]. The UBE3A gene is subject to genomic imprinting and expression within the brain is only from the maternal copy of chromosome 15. This, a maternally inherited deletion of chromosome 15, paternal uniparental disomy for chromosome 15, a mutation within the maternally inherited UBE3A gene or a problem with imprinting of the gene can all cause AS. These mechanisms are outlined in Table 1. The first line test for AS is methylation analysis of 15q11-13, a DNA-based test, which will identify patients with deletions, uniparental disomy and imprinting defects. A chromosome 15q11-13 fluorescence in situ hybridization test can be used to confirm a deletion if methylation is abnormal. If the methylation test gives a normal results but the clinical signs are typical, the UBE3A gene should be screened for point mutations and deletions. There are some minor differences in clinical features between the different groups of AS, one of them being that individuals with AS caused by a deletion of chromosome 15q11-13 are frequently hypopigmented due to the fact that the 15q11-13 region also contains the gene for Type II oculocutaneous albinism. Patients with UPD are normally pigmented and may have better language skills. Whilst in the majority of cases AS is a sporadic occurrence within a family, it can be familial and genetic counseling should be offered to all families to discuss their individual case, including recurrence risks and the risks for other members of their extended family [3].

Treatment of AS is symptomatic with physiotherapy, occupational therapy and medication for seizures. The UBE3A gene is expressed in several areas of the brain including the hippocampus and cerebellum. Its precise role in the pathogenesis of AS remains unknown but some progress is being made the identification of proteins which may be involved in the symptomatology of this condition and which may provide the possibility for future treatments [5].

There are many patients who present with clinical features of AS but in whom none of the genetic abnormalities above can be identified. Whilst it is possible that some of them may have a mosaic phenotype [6] or an as yet undiscovered abnormality of chromosome 15, it is possible that they do not have AS. Conditions to be considered in the differential diagnosis are Mowat-Wilson syndrome, Rett syndrome, Pitt Hopkins syndrome [7] and other chromosome disorders. Recently, boys with an X-linked condition resembling AS have been identified as having mutations within a gene called SLC9A6 and this should be considered in males [8].

2. Editorial comment

In addition to atypical febrile seizures and later epilepsies, those with AS syndrome may rarely lose consciousness because of cardiac asystole triggered by laughter [9]. Ambulatory electrocardiography should clarify this: at the time of the cardiac asystole the laughter will be signaled by rapid notched deflections that resemble the appearance of the expiratory grunts better known in early childhood reflex syncopes.

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