

Angelman syndrome

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Abstract

Angelman syndrome (AS) is a neurogenetic disorder (prevalence 1/12000) that affects the brain and causes a pattern of clinical features including delayed motor activities such as walking or ataxic gait, mental retardation with minimal or absent speech, seizures, sleep disturbances, characteristic facial features and happy demeanor. Seizures typically occur before three years of age and can be associated with the following EEG changes: 1) runs of high amplitude delta activity with usually a frontal emphasis and high amplitude (often more than 300 mv); 2) runs of rhythmic theta activity in excess of 100 mv over a wide area. 3) runs of rhythmic sharp theta activity at 5-6/s over the posterior third of the head, forming complexes with small spikes. AS is caused by loss of function of a gene(s) in the region 15q11-q13, which is subject to genetic imprinting. The AS gene(s) is exclusively expressed from the maternal chromosome. Loss of the maternally contributed AS region can occur by five genetic mechanisms: deletion, paternal uniparental disomy, imprinting defects, mutation of the ubiquitin-protein ligase (UBE3A) gene and unidentified mechanisms. Although all these mechanisms have similar consequences in terms of neurological development, there are very important differences among the genetic classes of AS as to the risk of disease recurrence. The management of AS includes physic and psychomotor therapy, speech therapy, psychological and educational approaches and drugs for treating epilepsy, behavior and sleep disorders.

Key-words

Angelman Syndrome, happy puppet syndrome, genetic imprinting, behaviour phenotype, mental retardation, epilepsy, chromosome disorder, sleep disorder, socio-occupational integration.

Disease name and synonyms

Angelman syndrome (AS) was first described by Harry Angelman in 1965 (1), although some earlier non-medical depictions may constitute good illustrations of the syndrome, like Dopey dwarf of Walt Disney's Snow White and the

seven dwarfs (2). The condition was first known as "Happy puppet syndrome".

Diagnostic criteria/definition

The Scientific and Research Advisory Committee of the AS Foundation established a Consensus for Diagnostic Criteria in 1995 (3),

applicable for the three major types of AS: molecular deletions involving the critical region (deletion positive), uniparental disomy and non-deletion/nonparental disomy.

The diagnosis of AS is currently a clinical diagnosis that can be confirmed by laboratory testing in about 80% of cases (see Genetic testing). Developmental history and laboratory findings, clinical characteristics and behavior phenotype (3) are intended to assist in the clinical evaluation of AS.

Developmental history and laboratory findings in AS

- Normal prenatal and birth history with normal head circumference
- Absence of birth defects
- Developmental delay, functionally severe
- Delayed but forward progression of development (no loss of skills)
- Normal metabolic, hematological and chemical laboratory profiles
- Structurally normal brain using MRI or CT (may have mild cortical atrophy or dysmyelination)

Clinical characteristics of AS

Constant (100%)

- Developmental delay, mental retardation functionally severe
- Speech impairment, none or minimal use of words; receptive and non-verbal communication skills higher than verbal ones.
- Movement or balance disorder, usually ataxia of gait and/or tremulous movement of limbs.
- Behavioral uniqueness: any combination of frequent laughter/smiling; apparent happy demeanor; hyperactivity and attention deficit, easily excitable personality, often with hand flapping.

Frequent (more than 80%)

- Delayed, disproportionate growth in head circumference, usually resulting in microcephaly (absolute or relative) by age 2.
- Seizures, onset usually < 3 years of age.
- Abnormal EEG, characteristic pattern with large amplitude slow-spike waves (usually 2-3 Hz), facilitated by eyes closure.

Associated (20-80%)

- Flat occiput
- Occipital groove
- Protruding tongue
- Tongue thrusting; suck/swallowing disorders
- Feeding problems during infancy
- Prognathia
- Wide mouth, wide-spaced teeth
- Frequent drooling
- Excessive chewing/mouthing behaviors
- Strabismus

- Hypopigmented skin, light hair and eye colour (compared to family), seen only in deletion cases
- Hyperactive lower limb deep tendon reflexes
- Uplifted, flexed arm position especially during ambulating
- Increased sensitivity to heat
- Sleep disturbances
- Attraction to/fascination with water

Behavior phenotype

- Mental retardation in the severe range: 100% of cases
- Unprovoked laughter, smiling, apparent happy demeanor (95%)
- Hyperactivity and attention deficit (95%)
- Excitability

Differential diagnosis

AS patients are often misdiagnosed as having perinatal damage.

Particular diagnostic confusion may arise with some single gene disorders as Rett syndrome (common clinical features), X-linked alpha thalassemia-mental retardation syndrome, with chromosomal rearrangement, particularly 22qter deletion or del2q22-q23, associated with the Mowat-Wilson but also with the Lennox-Gastaut syndrome (common electroclinical data) (4) and mental retardation with autistic traits must also be excluded from differential diagnosis.

Prevalence

The incidence of AS is unknown, but some authors estimated it to 1/20000 newborn, with a prevalence of 1/12000 (5).

Clinical description

Age at clinical diagnosis is between 3 and 7 years (6). AS is not usually recognized at birth or in infancy because development problems at this age are non-specific, and the typical outbursts of unprovoked laughter, considered as one of the most striking features of the syndrome, usually appears between 16 months and three years, and seizures later in childhood. The early features are the jerky and uncoordinated movements. The syndrome is suspected in the first year of life on the basis of the EEG pattern and confirmed by genetic studies (7).

During adolescence, puberty may be delayed by 1 to 3 years, but sexual maturation occurs with normal sexual characteristics. Young adults are not known to have significant mental deterioration (8).

Normal life expectancy is possible, although scoliosis with cardiorespiratory complications have been reported in the disease's evolution.

Main signs and symptoms

Craniofacial changes

Microcephaly reflecting a small brain and prognathia resulting from excessive chewing and mouthing. Skull RX reveals impressive occipital flattening. Some AS cases have macrostomia and small wide-spaced teeth.

Laughter and happiness

It is not known why laughter is so frequent in AS. This kind of laughter is not related to epilepsy (gelastic seizures) and seems to be an expressive motor event, usually accompanied by grimacing. Persistent social smile is frequent and, later, several types of facial and behavioral expressions with burst of laughter are present in 70% of the patients, giving an apparent happy demeanor as predominant behavior.

Gait and movement disorders

Hyperkinetic movement of the trunk and limbs has been noted in early infancy, jitteriness and tremulousness are frequent in the first six months of life. Voluntary movements are often irregular, choreiform-like. Motor milestones are delayed (sitting at 12 months, walking 3-4 years of age). Mild cases can have almost normal ambulation, whereas more severely affected children can be stiff, with robot-like walking. Some children are so ataxic and jerky that walking is not possible until they are older. Ten percent of AS children may fail in achieving ambulation.

Mental retardation

Present in 100% of the patients, non-progressive and frequently severe. In milder cases it is manifested by hyperactivity and attention deficit, lack of speech and motor control. Therefore provision of a sheltered living situation will be needed in adult life.

Speech and language

Even in the highest functioning children, conversational speech does not develop. In the best cases, use of 10-20 words may occur, but with severe pronunciation difficulties.

Seizures and EEG abnormalities

More than 90% of AS are reported to have seizures, most with onset before 3 years, but occurrence in later ages (teenagers) is not exceptional. Seizures can be severe, myoclonic, tonico-clonic generalized, atonic and absences. Febrile convulsions are more frequent in male patients (5). Epilepsy in AS can be self-limited, patients becoming seizure-free, particularly after puberty.

EEG may reveal epileptogenic discharges before clinical evidence of seizures. In 98% of patients, it is usually characterized by three features (9, 10):

- Runs of rhythmic delta activity of high amplitude (more than 300 mv), usually with a frontal emphasis.
 - Runs of rhythmic theta activity in excess of 100 mv, seen over a wide area.
 - Runs of rhythmic sharp theta activity of 5-6 Hz over the posterior third of the head, forming complexes with small spikes. These are usually facilitated by eye closure.
- A rhythmic muscle bursting activity has been recently observed in AS patients while maintaining a certain posture. This activity did not correlate with electroencephalographic activity (11).

Sleep disorders

A decreased need for sleep and abnormal sleep/wake cycles are characteristics of AS (12).

Feeding problems and oral-motor behaviors

Feeding problems are frequent but generally not severe, and are expressed by difficulty in sucking and swallowing. In early infancy, hand sucking is frequent, and is later replaced by chewing and oral manipulation. Protruding tongue and drooling are also usually present.

Hypopigmentation and ocular albinism

Deletion of the pigment gene (the *P* gene), located close to the AS gene causes tyrosinase-positive oculocutaneous albinism. Not all AS children with deletions of the *P* gene have obvious hypopigmentation, but those affected are sun sensitive.

Central nervous system abnormalities

Brain is structurally normal in AS children. Occasional abnormalities are reported such as cerebellar hypoplasia, unilateral temporal lobe hypoplasia and vermian cyst. Neuroimaging abnormalities are mild, such as cortical atrophy or thinning of corpus callosum and decreased myelination seen in MRI studies.

Histological studies can show decreased dendrites arborization, decreased GABA in the cerebellum and increased glutamate in frontal and occipital lobes.

Genetics

AS is caused by a number of different genetic mechanisms occurring along the long arm of chromosome 15. All these mechanisms have similar consequences in terms of neurological development and behavior but there are very important differences among the genetic classes of AS as to the risk of disease recurrence in a family with an affected child (see "Genetic counseling").

Genetic mechanisms involved in AS include (13, 14):

- de novo* deletion of maternal chromosome 15q11-q13 (65%-70% of AS patients)
- Deletion resulting from parental chromosomal rearrangement (<1 %)
- Chromosomal 15 uniparental disomy (2-5 % of AS patients)
- Imprinting defects (2-5 % of AS patients) including two group of AS patients: patients with deletion of the imprinting center (20% of this group) and patients with unidentified imprinting defect mechanisms (80%)
- Mutations in the *UBE3A* gene encoding ubiquitin-protein ligase E3A (20% of sporadic AS patients with normal methylation pattern and around 75% of familial cases)
- Unidentified mechanism(s) (15-20% of AS patients)

The molecular study of the AS region has not yet provided insight into the cause of the neurological deficits. The submicroscopic AS deletion encompassing *GABAA receptor beta 3-subunit* gene (15) has been related to seizure disorder (6). On the basis of electroencephalographic studies in AS patients, it has been proposed that reduced expression of *UBE3A* (in all cases) and *GABRB3* (in deletion cases) cause dysregulation of synaptic GABAergic neurotransmission, which in turn will result in cortical and thalamo-cortical dysfunction (16).

Genetic testing

According to the Consensus for diagnostic criteria (3), the number of tests necessary in the search for genetic AS abnormalities and the order of testing may vary. Chromosome study, including high resolution G-bands confirmed by FISH, DNA polymorphism or methylation analysis, are necessary in all suspected cases to rule out chromosome rearrangements or other chromosome disorders. In AS patients fulfilling the clinical diagnostic criteria and exhibiting a normal methylation pattern, *UBE3A* sequence analysis is indicated.

Molecular genetic testing detects approximately 80% of AS cases.

Genetic counseling

The risk to sibs of an affected child of having AS depends upon the genetic mechanism of the loss of the maternally contributed AS region.

In *de novo* deletion, the risk of disease recurrence is estimated to be around 1%. The risk is higher in cases of unbalanced translocation.

In imprinting inheritance, offspring of carrier mothers are theoretically at 50% risk of having AS. In uniparental disomy, risk of recurrence is < 1%.

Prenatal diagnosis

Prenatal diagnosis is possible when the underlying genetic mechanism is known for the index case. Each anomaly, deletion, uniparental disomy, imprinting defect and *UBE3A* mutation could be detected by the appropriate method.

If mosaic trisomy 15 is detected on chorionic villus sampling, the possibility of trisomic rescue leading to AS (paternal UPD) or Prader-Willi syndrome (PWS) (maternal UPD) through the loss of a parental chromosome 15 must be considered.

Prenatal ultrasonography is not helpful in the detection of AS.

Management

No specific treatment is available for AS.

Symptomatic management is based on physiotherapy, education including early stimulation and enrichment programs, speech and communication therapy with emphasis on non-verbal methods, occupational therapy; individualization and flexibility are important factors in the education of AS children.

Sleep disorders have been treated with sedatives (diphenhydramine) or neuroleptics (thioridazine); melatonin (2-3 mg/day) has been reported as useful (8). Nevertheless most infants do not receive medications and, if they do, they usually do not require long-term use.

In epilepsy, benzodiazepines (clonazepam, clobazam) are the antiepileptic drugs of choice, either in monotherapy or in association with valproic acid. Vigabatrine and carbamazepine may worsen seizures and should be avoided (17, 18). Topiramate, a new antiepileptic drug with multiple mechanisms of action, including enhancement of GABAergic neurotransmission, was reported to be effective (19). Dietary treatments "methyl-donor enriched" (folates, betaine and other biochemicals) do not provide benefit in our knowledge.

Scoliosis can be treated with braces and surgical correction.

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