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Angelman Syndrome: Clinical Aspects

Campos JG[1]*, Moya C[1], Guevara-González J[2] and Rendón ID[2]

[1]Department of Pediatrics, Felipe Guevara Rojas Hospital, Venezuela

[2]Department of Pediatrics, Miguel Pérez Carreño Hospital, Venezuela

***Corresponding author:** José Guevara-Campos, Department of Pediatrics, Felipe Guevara Rojas Hospital, El Tigre, Anzoátegui 6050, Venezuela

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Abstract

Angelman syndrome is a neurodevelopmental disorder that is characterized by lack of speech, cognitive impairments, unusually happy demeanor, easily provoked laughter, short attention span, motor deficits and seizure, ataxia, and an affinity for water, among other symptoms.

Microcephaly and subtle dysmorphic features are additional features seen most affected individuals.

Angelman syndrome is due to deficient expression of ubiquitin protein ligase E3A (*UBE3A*) gene, which displays paternal imprinting.

There are four molecular classes of Angelman syndrome, and some genotype-phenotype correlations have emerged. The most common mechanisms that render the maternally inherited *UBE3A* nonfunctional are deletion of the maternal chromosomal region 15q11-q13. Other mechanisms paternal uniparental disomy, imprinting defects, and UBE3A gene mutations.

Further analysis of *UBE3A* gene would further confirm 90% of cases. There was still 10% of clinically diagnosed Angelman syndrome that would be rendered "test negative". With the advancement of medical genomic technology like array comparative genomic hybridization (array CGH), patients of these "test negative" Angelman-like syndrome actually had alternative genetics diagnoses.

We review the Angelman Syndrome making greater emphasis in clinical aspects that allow early genetics orientation to achieve genetics counseling and rehabilitation therapies.

Introduction

Harry Angelman, an English pediatrician, first described this condition in 1965 when he reported three children that he referred to as "Puppet Children" because of their unusual arm position and jerky movements [1]. At this time, his paper was not immediately recognized as important. It wasn't until 1982, when Charles Williams and Jaime Frías of the department of Pediatrics, University of Florida College of Medicine, and Gainesville submitted a paper to the American Journal of Medical Genetics reporting studies of six patients and comparing their data to those from previous reports. They proposed the name of this disorder be changed to Angelman Syndrome [2].

In the nearly fifty years since that original report, have greatly increased the number of cases reported in various medical journal in different countries.

Incidence

Angelman syndrome affects about 1 in 12,000 to 20,000 peoples [3].

Clinical Review

Angelman syndrome is a neurodevelopmental disorder resulting from deficient expression or function of the maternally inherited allele of UBE3A gene on chromosome 15, which plays an important role in the cellular ubiquitin-proteasome pathway and synaptic development [4]. See Table 1 for consistent, frequent, and occasional/ associated features of Angelman syndrome.

Most infants with Angelman syndrome do not show any signs of the disorder at birth.

Development delays in Angelman syndrome are usually evident within the first year of life, with delayed attainment of gross motor, fine motor, receptive language, expressive language, and social skill [5]. Motor skill delays can be severe, and many children with Angelman syndrome are not able to walk.

The behavioral characteristics of Angelman syndrome are present in all patients irrespective of the type of genetic abnormality and often prompt clinicians to consider the diagnosis [6].

Apparent happiness is the hallmark of the syndrome, associated with profuse smiling, poorly specific laughing and general exuberance, with hyperactive, stero types, and proactive social contact [4-7].

The behavioral features of Angelman syndrome include a happy demeanor, easily provoked laughter, short attention span, hypermotoric behavior, mouthing of objects, sleep disturbance with reduced need for sleep, and affinity and fascination for water [5,7].

Children with Angelman syndrome are described an easily excited. Thought paroxysms of laughter are said to occur in Angelman syndrome, the laughter is not truly "unprovoked", since an inciting event can usually be identified; however, the responding laughter is frequently excessive or inappropriate to the triggering stimulus [5].

Disruptive behaviors are displayed by the majority of patients, including biting, pinching, hair-pulling and grabbing. Rarely are these behaviors intended to cause harm; they usually result from

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Table 1: Features Os Angelman Syndrome.

Consistent (100%)	Frequent (80%)	Associated (20-80%)
Developmental delay	Seizure	Hypotonia
Ataxia and/or tremors	Microcephaly	Strabismus
Absent speech		Fascination with water
Happy demeanor		Sleep disturbances
		Mouthing behaviors

easy excitability, desire for attention, poor control over movements, reduced repertoire of need expression, and occasionally frustration over an inability to communicate effectively [5].

Cognitive ability is severely impaired, however, cognition is difficult to ascertain due to the profound lack of speech, hyperactivity, and inability to pay attention in individuals with Angelman syndrome [7].

Language development in children with Angelman syndrome is severely impaired. Most individuals with Angelman syndrome are entirely non-verbal, some will speak a few words, and a rare few have some phrase speech [5-7]; some can communicate using sign language and others can use gesture or augmentative communication device [4].

Movement disturbances, abnormalities of tone, and impaired balance contribute to the delayed acquisition of motor skills (sitting after 12 months, walking between 2 and 6 years). Movement disorders include jerkiness, ataxic gait, and tremors [4,5,7]. Hand flapping is common when walking or excited [7].

Epilepsy occurs in 80 to 95% of children with Angelman syndrome, typically with onset before 3 years of age. Seizure types include myoclonic, atypical absence, generalized tonic-clonic, and atonic seizures [5-8]. Status epilepticus, frequently myoclonic or electric no convulsive, has been reported to occur in up 90%. EEG often shows a characteristic pattern, most classically with posterior predominant spike and sharp waves mixed with high amplitude sharply contoured 3-4 Hz activity [7]. Epilepsy tends to be more severe in those with a maternal deletion, as does disease severity in general.

Most children with Angelman syndrome have an apparently reduced need for sleep (sometimes as little as 5-6 hours per night) and abnormalities of sleep-wake cycle, with long or frequent periods of wakefulness during the night .Despite sleep disruption, most individuals with Angelman syndrome do not exhibit daytime somnolence [5].

Although microcephaly is frequent finding in patients with Angelman syndrome and delayed myelinization was repeatedly observed in infants' patients gross structural abnormalities of their brains have not been reported [9].

Individuals with Angelman syndrome are generally non-dysmorphic as infants, but a subtle craniofacial phenotype develops with time, consisting of midface recession, prognathism, and broad mouth (the latter two are possibly consequences of tongue thrusting, mouthing behaviors and increased smiling) [5].

Ocular problems in Angelman syndrome include refractive errors (usually hypermetropia and astigmatism), iris and choroidal hypopigmentation, and esotropia and exotropia .The presence of refractive errors in all the children with Angelman syndrome underlines the importance of an early neuro visual evaluation to detect the type of refractive errors and to prescribe optical devices [4,5].

Genetics: Angelman syndrome is caused by lack of function of maternal *UBE3A*. This arises due to one of four mechanisms: 1) deletion of maternal 15q11.2-q13 is found in approximately 74% of individuals with Angelman syndrome, 2) loss of function mutation of maternal *UBE3A* is found in approximately 11% of individuals with Angelman syndrome, 3) paternal uniparental disomy (UPD) is found in approximately 8% of individuals with Angelman syndrome, 4) Imprinting defect is found in approximately 7% of individuals with Angelman syndrome [7].

The mechanism by which loss of *UBE3A* causes Angelman syndrome is still not completely understood.

Conclusion

Angelman syndrome is characterized by severe intellectual disability, absent speech, epilepsy, and characteristic happy affect. It is caused by the loss of brain function from the maternal *UBE3A* gene.

An early and careful assessment of motor, behavioral, neuro visual, cognitive, linguistic and attention abilities should be essential for a correct identification of children with Angelman syndrome.

Molecular testing can diagnose most, if not all, cases. Molecular diagnostic test should be performed in all children suspected of Angelman syndrome.

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