

NEUROGENETIC ENIGMA OF ANGELMAN SYNDROME: FROM IMPRINTING TO INNOVATION: A COMPREHENSIVE REVIEW

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ABSTRACT

Angelman Syndrome (AS) is a rare neurogenetic disorder characterized by severe developmental delay, intellectual disability, absent or minimal speech, movement abnormalities, and a unique behavioral phenotype marked by frequent laughter and an excitable personality. The disorder results primarily from genetic abnormalities involving the UBE3A gene on chromosome 15q11–q13. This review provides an overview of the etiology, clinical features, diagnostic approaches, management strategies, and recent therapeutic advances in Angelman Syndrome. Despite the absence of a definitive cure, early diagnosis and supportive interventions significantly improve quality of life. Therefore, this review highlights the epigenetic aspects involved in the AS in order to provide a better understanding and clarification of the mechanisms, hopefully paving the way for future research to improve the treatment of affected individuals.

Keywords: Angelman Syndrome, chromosome, Deletions, Uniparental Disomy

INTRODUCTION

Angelman Syndrome (AS), first described by Dr. Harry Angelman in 1965, is a rare genetic disorder with an estimated prevalence of 1 in 12,000 to 20,000 live births. AS is a neurodevelopmental disorder whose main features are intellectual disability, lack of speech, seizures, and a characteristic behavioral profile. The behavioral features of AS include a happy demeanor, easily provoked laughter, short attention span, hypermotoric behavior, mouthing of objects, sleep disturbance, and an affinity for water. It is caused by disruption of the maternally inherited UBE3A gene, which encodes an E3 ubiquitin ligase critical for neuronal development and function. Clinically, AS is characterized by intellectual disability, impaired communication, movement disorders, epilepsy, and a distinct behavioral profile. Advances in molecular genetics have facilitated accurate diagnosis and opened avenues for novel therapeutic approaches.

Children with Angelman syndrome typically have a happy, excitable demeanor with frequent smiling, laughter, and hand-flapping movements. Hyperactivity and a short attention span are common. Most affected children also have difficulty sleeping and need less sleep than usual.

ETIOLOGY AND GENETICS

Chromosomal Deletions: Approximately 70% of AS cases result from deletions in the maternal 15q11–q13 region.

UBE3A Mutations: Around 10% of cases arise from mutations within the maternal UBE3A gene.

Paternal Uniparental Disomy (UPD): Occurs in 2–5% of cases when both copies of chromosome 15 are inherited from the father.

Imprinting Defects: Found in 3–5% of cases due to errors in DNA methylation and gene expression.

UBE3A is normally expressed from the maternal allele in neurons, while the paternal allele is silenced. Loss of maternal UBE3A expression leads to the clinical manifestations of AS.

CLINICAL FEATURES

1. Developmental and Neurological: Severe developmental delay, intellectual disability, and absent or minimal speech.
2. Motor Dysfunction: Ataxia, tremulous movements, jerky gait, and poor coordination.
3. Seizures: Present in 80–90% of cases, often resistant to treatment.
4. Behavioral Phenotype: Happy disposition, frequent smiling, inappropriate laughter, excitability, and hyperactivity.
5. Other Features: Microcephaly, sleep disturbances, hand flapping, fascination with water, and light hair/skin pigmentation in some patients.
6. Developmental delays are first noted at around age six months; however, the unique clinical features of AS do not become manifest until after age one year.

DIAGNOSIS

Diagnosis is based on clinical criteria combined with genetic testing, including:

DNA methylation analysis of chromosome 15q11–q13 (detects 80% of cases).

UBE3A sequencing to identify mutations.

Chromosomal microarray or fluorescence in situ hybridization (FISH).

Electroencephalogram (EEG) often shows characteristic patterns, supporting diagnosis.

MANAGEMENT

Currently, there is no curative treatment for AS. Management focuses on supportive interventions:

Pharmacological: Antiepileptic drugs (valproic acid, levetiracetam, clonazepam) for seizure control; melatonin for sleep regulation.

Therapeutic Approaches: Physical and occupational therapy for motor skills; speech therapy with augmentative communication devices.

Behavioral Support: Structured routines, behavioral therapy, and educational interventions tailored to cognitive abilities.

Multidisciplinary Care: Pediatricians, neurologists, geneticists, psychologists, and therapists play key roles.

GENETIC COUNSELING

Individuals with AS typically represent simplex cases (i.e., a single affected family member) and have the disorder as the result of a *de novo* genetic alteration associated with a very low recurrence risk. Less commonly, an individual with AS has the disorder as the result of a genetic alteration associated with an imprinting pattern of autosomal dominant inheritance or variable recurrence risk. Reliable recurrence risk assessment therefore requires identification of the underlying genetic mechanism in the proband and confirmation of the genetic status of the parents. Prenatal detection of all the known molecular genetic alterations in the 15q11.2-q13 region that give rise to AS is possible and is an option for families once the underlying genetic mechanism in the proband has been identified.

RECENT ADVANCES

Recent research explores targeted therapies, including:

Gene Therapy: Reactivation of the paternal UBE3A allele using antisense oligonucleotides (ASOs).

Pharmacological Approaches: Trials of topoisomerase inhibitors to unsilence paternal UBE3A.

Neurotechnology: Use of brain-computer interfaces to aid communication in nonverbal patients.

Although still experimental, these strategies hold promise for disease-modifying treatment.

CONCLUSION

Angelman Syndrome is a complex neurogenetic disorder with distinct clinical and behavioral characteristics. Advances in molecular diagnostics have improved early detection, while supportive therapies enhance functional outcomes. Although no curative treatment exists, emerging gene-based approaches provide hope for future therapeutic breakthroughs. Multidisciplinary care and continued research are essential to improving quality of life for individuals with Angelman Syndrome.

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