

Angelman Syndrome: An Updated Review of Pathophysiology, Diagnosis and Management

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Abstract: The illness now referred to as Angelman syndrome (AS), originally termed the "Puppet Children," was first recorded in 1965 by a British physician named Harry Angelman. Angelman observed that three children with cognitive disability had certain traits: a positive disposition towards people, uncoordinated or spasmodic motions, and limited or absent verbal communication abilities. In 1987, Ellen Magenis discovered two children with notable deletions on chromosome 15. This genetic abnormality was linked to a phenotype characterized by severe ataxia, seizures, and episodes of prolonged and spontaneous laughter. Due to its exclusive imprinting in the brain, the expression of the UBE3A gene is limited to the neurological system, leading to most of the manifestations of Angelman syndrome (AS) being confined to this system. Patients who are suspected of having Angelman syndrome are initially assessed by clinical evaluation using DNA methylation assays, specifically targeting the differentially methylated SNRPN promoter/exon 1 region. The current approach to managing Angelman syndrome is mostly focused on addressing symptoms; however, there are promising gene-based medicines under development. The primary emphasis of medications used in the treatment of epilepsy in Angelman syndrome is on moderate motor or akinetic seizures. Valproate, clonazepam, topiramate, lamotrigine, and levetiracetam have demonstrated potential, whilst carbamazepine, phenobarbital, oxcarbazepine, and vigabatrin have shown limited potential.

Keywords: Angelman Syndrome, Chromosome 15, Puppet Children, Haploinsufficiency Syndrome, UBE3A Gene.

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I. INTRODUCTION

The condition now referred to as Angelman syndrome (AS), originally named the "Puppet Children," was initially documented in 1965 by a British physician named Harry Angelman. Angelman delineated the specific attributes of three children afflicted with cognitive impairment: an absence or limited ability to communicate verbally, uncoordinated or spasmodic movements and a favorable disposition towards others. Angelman syndrome (AS) is a rare genetic neurodevelopmental disorder that occurs in around 1 out of every 10,000-24,000 newborns. AS is clinically defined by intellectual disability, global developmental delay, seizures, and sleep disturbances.^[1] Angelman syndrome is a rare neurogenic disorder. This is an example of genomic imprinting, where the expression of a specific area of the genome changes depending on whether it came from the mother or the father's chromosome. Autism spectrum disorder (AS) is a neurodevelopmental condition that predominantly affects the neurological system. Intellectual and developmental issues, a puppet-like appearance, hyperactivity, sleep problems, and ataxic movement characterize it.^[2] The UBE3A gene inherited from

the mother is not active in the specific areas of chromosome 15 known as 15q11-13, resulting in Angelman Syndrome (AS). Genomic imprinting in typical individuals inhibits neurons from expressing the paternal version of UBE3A. UBE3A expression in Angelman Syndrome (AS) is influenced by many processes, including pathogenic mutations of the maternal copy of UBE3A (Mut), imprinting deficits (IPD), and paternal uniparental disomy (UPD) of chromosome 15. Deletions may also have an impact. Deletions are responsible for more than 70% of all diagnoses of AS, whereas UBE3A pathogenic variants, IPD, and UPD each account for around 10%. Here, we do not consider the potential that individuals exhibiting symptoms similar to those with Autism Spectrum Disorder may have genetic issues that are either absent or not well comprehended.^[3]

II. CLINICAL OVERVIEW

In 1965, an English doctor called Harry Angelman recorded an atypical disease. Three children with this condition exhibited seven distinct symptoms: a concave area in the back of the skull, optic nerve damage with incomplete development of the choroid, abnormal air encephalograms

indicating cerebral shrinkage, cognitive impairment, sudden bouts of laughter, lack of coordination, and the ability to extend their tongue outward. The first designation for the children was "Puppet Children," but it was subsequently modified to "AS."^[4] AS is associated with a variety of other neurodevelopmental diseases that exhibit similar symptoms. Some examples of these conditions are Rett syndrome, Mowat-Wilson syndrome, alpha-thalassemia, X-linked mental retardation (ATRX), Lennox-Gastaut syndrome, and infantile autism, among others. That is the reason why it has been erroneously categorized as one of these disorders. However, AS is distinguished by a range of symptoms in its clinical manifestation, such as seizures, abrupt movements, absence of speech, excessive activity, and inappropriate laughter, cognitive challenges, and conduct resembling autism. The diagnosis is often made between the ages of one and four.^[5] The diagnostic criteria for AS include a breakdown of clinical characteristics based on the frequency of the syndrome. Consistent features are present in 100% of cases, frequent features in 80% of cases, and related aspects in 20-80% of cases. All individuals with Angelman Syndrome (AS) exhibit common features such as ataxia, substantial developmental delay, hypermotor behavior (including excessive laughter and smiling), and speech impairment (characterized by limited or absent verbal communication but increased reliance on nonverbal signals). Microcephaly, which is defined by an abnormally small head circumference, is observed in more than 80% of individuals with AS before the age of 2. Additional symptoms encompass anomalies in electroencephalograms and recurrent and intense seizures throughout infancy, which may persist or resolve as the kid matures. Between twenty and eighty percent of people with AS exhibit additional symptoms such as irregular sleep-wake cycles, obesity, scoliosis, constipation, a protruding tongue, a wide mouth, strabismus, pale skin, light hair, abnormal eating behaviors, a strong attraction to water, and several others. To receive a diagnosis of AS, all criteria don't need to be present, but patients must continuously exhibit all four indications. It is recommended to verify the diagnosis by AS molecular testing. The prevalence of AS in children and young people varies from 1 in 12,000 to 1 in 24,000 individuals, and it has been observed in individuals of various ethnic backgrounds.^[6]

III. GENETIC ETIOLOGY

In 1987, Ellen Magenis discovered two children with notable deletions on chromosome 15. This genetic abnormality was linked to a phenotype characterized by severe ataxia, seizures, and episodes of prolonged and spontaneous laughter. The term "mega deletions" is used to describe these deletions due to their significant size, ranging from five to seven megabases. Despite the prior association of this chromosomal region with Prader-Willi syndrome (PWS), the patient's symptoms were indicative of Angelman syndrome (AS). AS is caused by the loss of the maternal half of a certain location, whereas PWS is caused by the loss of the same region from the paternal chromosome. In 1993, Robert Nicholls and colleagues showed that abnormalities in the chromosomal region 15q11-13 (chr15q11-13) are related to both AS and PWS. After one year, Mitsuyoshi Nakao

identified the UBE3A gene as a highly potential candidate for Angelman Syndrome (AS). Eventually, Kishino and Matsuura provided a detailed description of newly occurring mutations that cause the gene to be shortened.^[7]

The absence of the maternal UBE3A gene in the chromosomal region 15q11-13 is now recognized as the etiology of Angelman Syndrome (AS). Genomic imprinting surprisingly regulates gene expression. Genomic imprinting is an epigenetic mechanism that results in the expression of genes from just one allele, depending on whether it was inherited from the mother or the father. An imprinting center (IC) is a regulatory region where the two paternal alleles deposit a distinct epigenetic mark at the level of DNA methylation. This results in a monoallelic pattern of expression that is distinct from the parent of origin. This elucidates the reason why deletions that are similar on the paternal chromosome result in Prader-Willi syndrome (PWS), which is characterized by the loss of imprinted genes expressed paternally. Conversely, identical deletions on the maternal chromosome lead to Angelman syndrome (AS), characterized by the loss of the maternally expressed UBE3A gene.^[8] The 15q11-q13 region is known for containing two imprinting regulatory regions, namely the AS-IC and the PWS-IC. AS-IC is located 35 kb upstream of the SNURF-SNRPN promoter in the maternal germline. It plays a role in initiating transcription from the upstream exons of the SNURF-SNRPN bichromatic gene. The SNURF-SNRPN bichromatic gene leads to CpG methylation at the PWS-IC as a result of transcription.^[9] This area is located on the main promoter and associated exon. As a result, methylation takes place on the allele inherited from the mother, but not on the allele inherited from the father. The SNRPN and SNURF transcripts, as well as other RNA molecules such as the IPW transcript and a cluster of C/D snoRNAs, are all regulated by the unmethylated paternal allele. The UBE3A gene is expressed from both alleles in non-neuronal cells due to the absence of transcriptional activity from the SNURF-SNRPN promoter on the paternal allele. The presence of a boundary element prevents the elongation of the SNHG14 transcript. Conversely, the paternal UBE3A gene is suppressed in neurons by the SNHG14 noncoding RNA, which originates from the polycistronic transcription unit. Currently, the most likely reason for the silence of UBE3A is believed to be transcriptional interference between these two antisense transcripts.^[10] The loss of the maternal copy of the UBE3A gene can be attributed to four different molecular mechanisms. Approximately 3-5% of cases involve paternal uniparental disomy (UPD) in chromosome 15q11-q13. Another 3-5% of cases result from imprinting defects that lead to the silencing of the maternal UBE3A expression. This includes small deletions within the PWS-IC that affect DNA methylation in 10% of these cases. Additionally, 10-20% of cases are caused by intragenic mutations in the UBE3A gene inherited from the mother. The most common type, accounting for 70-80% of cases, is the occurrence of de novo maternal-inherited megadeletions in the 15q11-q13 chromosomal region, which includes the UBE3A gene. These deletions typically occur at previously identified breaking points. The illness severity is negatively correlated with the kind of genetic mechanism involved. Among the causes of

AS, large deletions of the 15q11-q13 region are the most severe. For instance, whether comparing people with UPD, an imprinting issue, or a UBE3A mutation, those with a maternal mega loss have more severe impairments in motor and language skills. The presence of just one functional copy of several neural genes in the 15q11-q13 region, which is lost in mega deletions, is likely to contribute to the increased severity observed in these patients. Individuals with more severe types of epilepsy, ataxia, and major cognitive deficits are linked to larger mega deletions, especially those found around the proximal and distal breakpoints on chromosome 15.^[9,11]

Utilizing molecular testing is essential in verifying the phenotypic diagnosis and identifying the disease's source, considering all molecular pathways linked to AS. At the preimplantation whole-genome single-cell level, we initially assess the DNA methylation state of chromosome 15q11–13. Fluorescent in-situ hybridization is performed to detect large deletions in the chromosome when abnormal methylation is detected. Genomic marker testing is conducted to detect paternal uniparental disomy (UPD) in situations when large deletions are absent. If the test shows no methylation, the diagnosis of AS caused by an imprinting issue is confirmed. If the levels of methylation fall within the normal range, the further course of action involves doing a mutation analysis of the UBE3A gene to detect any point mutations or deletions that might potentially be responsible for Angelman Syndrome (AS). If any of these tests yield negative results, probably, someone has probably erroneously diagnosed, since they may instead be suffering from another ailment that presents similar symptoms.^[12]

IV. PATHOPHYSIOLOGY

Due to its exclusive imprinting in the brain, the expression of the UBE3A gene is limited to the neurological system, leading to most of the manifestations of Angelman syndrome (AS) being confined to this system. Therefore, the brain is the initial organ affected by a pathological loss of function mutation of maternal UBE3A.^[13]

E6-associated protein (E6-AP) is an enzyme that attaches ubiquitin molecules to target proteins, and it is produced by the UBE3A gene. The ubiquitin-proteasome system plays a crucial role in the functioning of neurons and the ability of synapses to change, and E6-AP is essential for ensuring this process works correctly. Loss-of-function mutations in E6-AP hinder the degradation of several proteins through the ubiquitin-proteasome pathway. Some of the identified targets of E6-AP include ephexin5, Arc, p53, and p27. P53 and p27 are crucial regulators of cell survival in the neurological system. Elevated Arc levels impede the transmission of excitatory signals after synapses by enhancing the internalization of AMPA receptors on the cell surface. The increased synthesis of ephexin5, a protein that regulates synapse formation, led to a decrease in this process. The presence of higher amounts of ephexin5 and Arc leads to a reduction in experience-dependent synapse remodeling. As a result, there are disruptions in brain function.^[14]

Mouse models of Angelman Syndrome (AS) resulting from the maternal gene UBE3A being knocked out exhibit motor impairments, ataxia, seizures, and brain shrinkage. Moreover, these models have demonstrated that individuals with AS have compromised long-term potentiation (LTP) in the hippocampus, leading to difficulties in learning and memory. Furthermore, some studies have observed a decrease in spine density and abnormal dendritic morphology in these individuals. This might potentially provide insight into the underlying factors contributing to AS's motor and cognitive deficits.^[15]

When UBE3A ceases to function, it often occurs due to one of four factors. The four categories are deletion, mutation, imprinting, and uniparental disomy.

The deletion subtype is distinguished by its highly severe symptoms, with class 1 displaying the most severe clinical presentation. Several symptoms associated with this condition include oculocutaneous hypopigmentation, seizures, microcephaly, global developmental delay, and aphasia. Deletion mutations elevate the likelihood of seizures by eliminating segments of the GABA gene sequence. The potential factors contributing to oculocutaneous hypopigmentation encompass the deletion of the OCA1 gene and the regulatory influence of UBE3A on MC1R.^[13,15]

V. DIFFERENTIAL DIAGNOSIS

Angelman syndrome can potentially be diagnosed as one of many chromosomal microdeletion syndromes or a few specific single-gene disorders. Fortunately, chromosomal microarray testing can identify various abnormalities that bear similarities to Angelman syndrome. Currently, most clinicians employ this technology as a first step in the diagnostic process. Microdeletion syndromes such as Phelan-McDermid syndrome (22q13.3 deletion), MBD5 haploinsufficiency syndrome (2q23.1 deletion), and KANSL1 haploinsufficiency syndrome (17q21.31 deletion) are few examples. Although there have been occasional reports of additional microdeletions, none have been discovered in older children with symptoms like classic Angelman syndrome. Although the microarray test yields normal results, it is still worthwhile to investigate for single-gene anomalies. The potential possibilities comprise TCF4, SLC9A6, ZEB2, and MECP2. Pitt-Hopkins syndrome, induced by TCF4 haploinsufficiency, is the clinical presentation in older children that most closely resembles Angelman syndrome.^[16] Common symptoms observed in youngsters include an exaggerated gait, a constricted nasal bridge, a wide mouth, a pleasant demeanor, and significant difficulty in producing words. This diagnosis can be deduced from the presence of hyperventilation. Individuals afflicted with X-linked Christianson syndrome, which is caused by mutations in the SLC9A6 gene, have convulsions, a euphoric state, and an unsteady gait throughout childhood. However, as they enter puberty, they progressively develop motor dysfunction and muscle atrophy. Mowat-Wilson syndrome, caused by ZEB2 haploinsufficiency, is often associated with Hirschsprung disease or severe constipation issues. This illness is marked by distinct physical traits, such as thick,

block-like eyebrows, a large nasal columella and chin, and slanted ear lobes. Additionally, it can also be identified by central nervous system issues, such as agenesis of the corpus callosum. Mutations in the MECP2 gene can cause Rett syndrome in young females.^[14] It exhibits similar symptoms as Angelman syndrome, such as an unsteady stride, epilepsy, and absence of speech. Midline movements and psychomotor slowness are characteristic features of Rett syndrome. Affected individuals rapidly develop these symptoms. Male MECP2 duplication may have symptoms resembling those of Angelman syndrome, however, microarray analysis is often capable of identifying this genetic anomaly. Only a small number of additional disorders caused by a single gene are being considered as a possible diagnosis. Several genes, such as EHMT1 (associated with Kleefstra syndrome), FOXG1, ATRX, ADSL, and CDKL5, may be responsible for this disorder. Most of these genes are currently included in next-generation screening panels for generalized intellectual impairment. However, the physician still has the choice to request individual sequencing for any of these genes. If UBE3A mutation analyses and methylation profiles yield normal results, people who exhibit symptoms associated with Angelman syndrome may also be suitable candidates for whole-exome sequencing.^[17]

VI. GENETIC TESTING

Patients who are suspected of having Angelman syndrome are initially assessed by clinical evaluation using DNA methylation assays, specifically targeting the differentially methylated SNRPN promoter/exon 1 region. Angelman syndrome is the result of either a failure in imprinting or a loss of 15q11.2-q13 that occurs in the mother. In individuals who are not impacted, both the alleles inherited from the father and mother at the SNRPN gene undergo methylation. However, in patients who are affected, only the allele that is not methylated on the paternal side may be detected. Ramsden et al. argue that more investigation is necessary to distinguish between these potentialities and ascertain the probability of recurrence. Approximately 80% of Angelman syndrome patients may be detected using DNA methylation testing. Individuals with a UBE3A mutation frequently have a certain DNA methylation pattern. Therefore, it is imperative to sequence this gene in situations when methylation anomalies are absent but there is still suspicion of Angelman syndrome. When UBE3A data indicate normal methylation, it is crucial to investigate other genes and potential differential diagnosis.^[18]

VII. SYMPTOMATIC TREATMENT AND CARE

The current approach to managing Angelman syndrome is mostly focused on addressing symptoms, however, there are promising gene-based medicines under development. While the complete range of seizure symptoms has been recorded, the primary emphasis of medications used in the treatment of epilepsy in Angelman syndrome is on moderate motor or akinetic seizures. Valproate, clonazepam, topiramate, lamotrigine, and levetiracetam have demonstrated potential, whilst carbamazepine, phenobarbital, oxcarbazepine, and vigabatrin have shown limited potential.

Efforts to adopt low-glycemic and ketogenic diets have had varying outcomes.^[19] Seizures generally diminish in severity as individuals age, although there have been instances of seizures recurring. Consequently, the typical approach to treating adults with Angelman syndrome involves the administration of long-term anticonvulsant medication. Individuals with Angelman syndrome can improve their walking abilities by utilisation of ankle and foot braces. In exceptional circumstances, surgical interventions may be employed to reduce stiffness. The treatment of scoliosis may require the placement of surgical rods and/or vertebral fusion. The primary emphasis in educational activities is on nonverbal communication, sometimes utilizing computer-based technologies that facilitate visual and nonverbal communication. However, having unsteady hands can significantly hinder one's ability to use a computer effectively. Individuals with hypermetric habits and distractibility may find it difficult to achieve focused learning, particularly in situations where there is a strong social interest in others.^[16,20]

Treatment is often needed for behavioral difficulties. Individuals with Angelman syndrome frequently exhibit self-injurious or "aggressive" behaviors such as gripping or pinching others as a way to get attention and seek social interaction. Occasionally, medication is suggested to calm or sedate hypermotoric youngsters when their conduct impedes family activities and school integration. The presence of persistent behaviors in older persons with Angelman syndrome may suggest the presence of anxiety or a compulsive disorder. Potential therapies encompass the use of antidepressants and other neuroleptic medications. The majority of patients with Angelman syndrome often do not require significant psychoactive medication as severe behavioral problems are uncommon.^[21]

Angelman syndrome is marked by sleep disturbances, including insomnia, excessive daytime sleepiness, sleep parasomnias, and a prolonged time to fall asleep. Individuals afflicted with this ailment may discover that the administration of melatonin facilitates a more expeditious onset of sleep and a prolonged duration of uninterrupted sleep. Bedrooms that have been architecturally adapted allow for safe and efficient handling of awakenings during the night. Modifications in conduct can also contribute to achieving a more restful night's sleep. While there is currently no specific study on the use of sedatives such as clonidine and clonazepam for Angelman syndrome, it may be worthwhile to consider their potential effectiveness. Angelman syndrome exhibits specific symptoms that are also seen in other intellectual disability conditions, such as gastrointestinal problems including rumination, constipation, reflux, and ingestion of foreign objects. While extreme obesity is rare, being overweight is a disease that frequently starts throughout adolescence. Both pediatricians and adult doctors might employ identical strategies to treat similar issues.^[17,20]

VIII. RESEARCH AND DEVELOPMENT

Thus far, the results of several clinical trials have been underwhelming. We are now examining data from a randomized, placebo-controlled investigation that utilized levodopa/carbidopa as a treatment for AS. Prior efforts to alter UBE3A methylation by enhancing transcription from the paternal allele through the use of pro-methylation vitamin supplements did not result in any alteration of the AS phenotype. This experiment was conducted based on two reports of persons with AS and Parkinsonian symptoms who showed positive responses to levodopa. Additionally, the presence of dopaminergic neuronal degeneration in AS animal models further supported the rationale for this trial. In addition, a study using rats as a model for Parkinson's disease demonstrated that levodopa had an impact on the phosphorylation of threonine residues in calcium/calmodulin-dependent protein kinase II.^[21] Encouraging preclinical studies and the findings from a short open-label study on minocycline treatment suggest that there may be new therapeutic alternatives on the horizon. Numerous attempts have been made to activate the inactive paternal version of Ube3a. Large-scale small-molecule screening demonstrated that the topoisomerase inhibitor topotecan can activate Ube3a from the paternal allele. While the precise way in which topotecan works is not fully understood, recent studies suggest that it activates the paternal Ube3a allele by reducing the amounts of Ube3a-ATS. There are two potential ways for this to occur: firstly, by stabilizing R-loops, which are RNA-DNA hybrids, resulting in the relaxation of chromatin and the suppression of Ube3a-ATS; secondly, by inhibiting topoisomerases, which reduces the strain caused by the transcription of long RNA molecules and prevents their formation. One approach to mute the paternal allele was to utilize antisense oligonucleotides to interfere with the Ube3a-ATS transcript. While this approach was effective in saving certain adult characteristics, such as contextual fear testing, it did not prove successful in saving several others. This indicates that the mere restoration of Ube3A protein is insufficient to induce complete recovery, maybe due to variations in protein quantity or developmental stage.^[20] The successful use of this approach in adult mice indicates that the reactivation of Ube3a has the potential to rectify certain behavioral abnormalities, even when the gene has been altered for a few months during development. The extent to which antisense oligonucleotides' specificity for the target transcript reduces systemic toxicity in humans is uncertain. Other challenges that need to be addressed include the dissemination of drugs and the blood-brain barrier. Targeting major damaged pathways has shown modest efficacy in restoring several abnormalities reported in animals with Angelman Syndrome (AS). These pathways encompass many mechanisms such as calcium/calmodulin-dependent protein kinase II, Na/K-adenosine triphosphatase, activity-regulated cytoskeleton-associated protein, and neuregulin-ErbB4. Currently, there is no conclusive data to support the effectiveness of Ube3a substrate alteration in recovering AS characteristics.^[21]

IX. CONCLUSION

Angelman syndrome (AS) is a rare neurodevelopmental disorder characterized by significant cognitive impairment, developmental delays, and distinctive behavioral traits, primarily caused by the loss of the maternal UBE3A gene due to genomic imprinting. Accurate diagnosis relies on molecular testing to identify genetic abnormalities, as AS shares symptoms with other neurodevelopmental disorders, necessitating careful differentiation. The pathophysiology of Angelman syndrome primarily stems from the loss of function of the UBE3A gene, which is crucial for neuronal function and synaptic plasticity, leading to significant cognitive and motor impairments. Genetic testing, particularly DNA methylation assays, plays a vital role in diagnosing the condition, as it can identify the underlying genetic anomalies associated with this syndrome. The management of Angelman syndrome primarily focuses on symptomatic treatment, particularly for seizures and behavioral issues, while ongoing research aims to explore gene-based therapies that may offer more effective solutions in the future. Despite the challenges in clinical trials and the complexity of the syndrome, advancements in understanding the underlying mechanisms present potential avenues for improved therapeutic interventions.

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