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AN OVERVIEW OF ANGELMAN SYNDROME (AS): A RARE NEURO-GENETIC DISORDER - ETIOLOGY TO IT'S POSSIBLE TREATMENT

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ABSTRACT

Angelman syndrome (AS) is a genetic disorder that mainly affects the nervous system. A tiny head and distinct facial features, significant intellectual impairment, developmental disability, restricted to nonexistent functional speech, difficulties with balance and mobility, seizures, and difficulty sleeping are among the symptoms. Youngsters often have a cheerful disposition and a special interest in water. By the time a child is a year old, the symptoms usually become apparent. A novel mutation, as opposed to an inherited one, causes a portion of chromosome 15 to stop functioning, which causes Angelman syndrome. On that chromosome, a deletion or mutation of the UBE3A gene is often to blame. Sometimes it results from paternal uniparental disomy, which is the inheritance of two copies of chromosome 15 from the dad and none from mom. No functional form of the gene survives because the father's versions are rendered inactive through a process called genomic imprinting. The symptoms and perhaps genetic tests are used to make the diagnosis. There is currently no known treatment. The type of treatment is often supportive. People who have seizures are treated with anti-seizure drugs. Bracing and physical therapy might be helpful for walking. The lifespan expectancy of those impacted is almost normal. About 1 in 12 to 20,000 persons have AS. Both sexes experience the condition equally frequently. It bears the name Harry Angelman in honor of the British doctor who initially reported the disease in 1965. This review's main goal is to concentrate on and go over the causes, signs, diagnosis, course of therapy, and side effects of Angelman syndrome.

KEYWORDS: Angelman syndrome, Chromosome, Hyperactivity, Therapy, Seizures.

INTRODUCTION

A complicated genetic condition that mostly affects the nerve system is called Angelman syndrome (AS). It encompasses delayed development, intellectual disability, profound speech impairment, and ataxia, or difficulties with balance and mobility. The majority of impacted kids also have tiny heads (Microcephaly) and epilepsy, which is recurring seizures.[1] By the time a kid is 6 to 12 months old, delayed development is evident, and other typical indications and symptoms often surface during the early childhood years. Children diagnosed with AS usually exhibit cheerful, gregarious behaviors, often grinning, laughing, and clapping their hands.

Common traits include hyperactivity, a limited attention span, and a strong interest in water. The majority of impacted kids also have trouble falling asleep and require less sleep than normal. People with Angelman syndrome tend to get less irritable as they get older, and their sleep issues usually get better.[2] Nevertheless, the affected people spend their whole lives with an intellectual handicap, significant speech impediment, and

seizures. The characteristic facial characteristics of adults with Angelman syndrome might be characterised as "coarse." Hair and an irregular side-to-side curvature of the spine (scoliosis) are two more typical characteristics. People with the disease typically live almost normal lives.[3]

Common symptoms

A variety of symptoms that differ in intensity from individual to individual are indicative of Angelman Syndrome. Although varied combinations of symptoms may be seen by individuals with Angelman Syndrome, the disorder is commonly linked with certain similar aspects. These consist of:

1. Developmental delays

A common early indication of Angelman Syndrome is delays in development. Angelman Syndrome babies may take longer to meet developmental milestones including sitting, crawling, and walking. Usually, these delays become apparent in the first year of life. In order to encourage a child's growth and enable them to realize their full potential, early intervention programs and treatments can be extremely important.[4]

2. Intellectual disability

One of the main characteristics of Angelman Syndrome is intellectual incapacity. Angelman Syndrome sufferers may have severe cognitive deficits that impede their capacity for learning and intellectual function. There is a spectrum of intellectual impairment severity, from moderate to severe. It is crucial to offer suitable educational interventions and assistance to enable people with Angelman Syndrome to optimize their cognitive capacities.

3. Speech and Communication challenges

People with Angelman Syndrome frequently experience difficulties with speech and communication. Many people who have Angelman Syndrome are nonverbal or speak very little. They could rely on nonverbal cues like signs, gestures, or assisted communication equipment. Individuals with Angelman Syndrome can benefit from speech therapy as well as augmentative and alternative communication tools to enhance their ability to communicate and successfully express their needs and goals.[5]

4. Movement and Balance issues

People with Angelman Syndrome frequently experience problems with their balance and mobility. A stiff or unnatural walk, issues with balance, and hand flapping or other repetitive motions are a few examples. For those with Angelman Syndrome, these motor problems can make everyday activities including walking, running, and fine motor skills difficult. Mobility can be increased overall and motor skills can be improved with the help of physical and occupational therapy. Comprehending the typical indications of Angelman Syndrome is essential for prompt detection and remediation. It's crucial to speak with a healthcare provider for a thorough assessment and diagnosis if your kid displays any of these signs or if you have concerns about their development.[6]

5. Behavioral and Sleep disturbances

Angelman Syndrome sufferers frequently have behavioral and sleep issues that might interfere with their day-to-day activities. Hyperactivity and excitability, along with sleep disturbances, are two typical issues linked to Angelman Syndrome.[4]

I. Hyperactivity and Excitability

People with Angelman Syndrome are often seen to be hyperactive and excitable. They could also show signs of impulsivity, restlessness, and increased physical activity. Those who have Angelman Syndrome may find it difficult to focus and participate in activities for prolonged periods of time due to their hyperactivity. To aid in the management of hyperactivity, a controlled and encouraging atmosphere is crucial. Techniques like sensory breaks, visual timetables, and adaptable seating can help to improve concentration and reduce restlessness.[7]

II. Sleep disorders

According to estimates, up to 80% of people with Angelman Syndrome may struggle with sleep-related issues. Sleep disturbances are common in this population. These sleep problems might include short sleep duration, difficulty getting asleep, and frequent overnight awakenings. Sleep disturbances can affect general wellbeing and be a factor in daytime tiredness. Creating a peaceful sleeping environment and adhering to a regular nighttime routine can help manage sleep difficulties in people with Angelman Syndrome.[8,3]

1. Unique facial features

The existence of specific facial features that can aid in diagnosing the disorder is one of the distinguishing characteristics of Angelman Syndrome. Even while people with Angelman Syndrome don't always have these facial features, they can nonetheless offer crucial hints for a diagnosis.

The following are a few typical facial characteristics linked to Angelman syndrome[9]

- A wide mouth with a prominent, wide smile.
- Pale skin
- A small and pointed chin.
- A thin upper lip and a thick lower lip.
- Full cheeks.
- Prominent, widely spaced teeth.
- A small head size (microcephaly) in some cases.
- Almond-shaped eyes with a tendency to be deep-set.
- Strabismus

2. Other Associated Medical Conditions

People who have Angelman Syndrome frequently have a number of related medical issues that need to be managed. Epilepsy and seizures are two prevalent

medical diseases linked to Angelman Syndrome, along with eating problems and gastrointestinal problems.[10]

I. Seizures and Epilepsy

People who have Angelman Syndrome frequently experience seizures. Seizures affect around 80 percent of people with Angelman Syndrome, and they usually start in early childhood. The kind and intensity of these seizures can differ, ranging from short periods of intense gazing to longer episodes of convulsions. Regular medical assessments and adequate seizure management are crucial for people with Angelman Syndrome.[11]

II. Feeding Difficulties and Gastrointestinal issues

Digestive abnormalities and feeding challenges are also frequent in people with Angelman Syndrome. These difficulties can take many different forms, such as issues with dietary preferences and aversions, digestive issues including reflux and constipation, and difficulty nursing or bottle-feeding throughout infancy. It is imperative that caretakers collaborate closely with medical specialists to guarantee proper nourishment and manage any gastrointestinal issues. To properly address these gastrointestinal problems and eating challenges, a multidisciplinary team of experts may be required.[12]

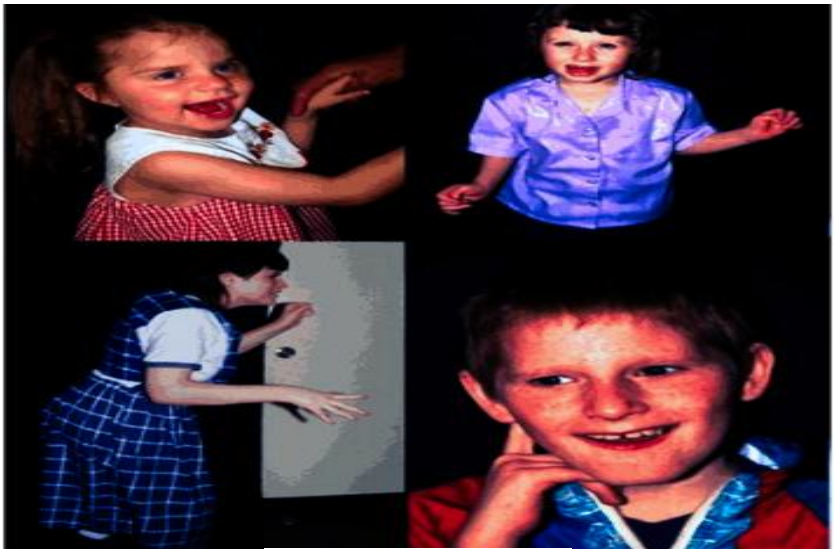

Figure 1: Symptoms of AS.

Etiology[13-17]

The lack of functioning of a gene called UBE3A causes many of the hallmarks of Angelman syndrome. The UBE3A gene is typically inherited in one copy from each parent. In most tissues of the body, both copies of this gene are active. Nevertheless, only the maternal copy—which is inherited from the mother—of a person's nerve cells—neurons in the brain and spinal cord (the central nervous system) is active. Genomic imprinting is the phenomenon that causes this parent-specific gene activation. A person will not have any active copies of the UBE3A gene in most regions of the brain if the maternal copy is deleted due to a chromosomal alteration or a gene variation, commonly referred to as a mutation.

The maternal copy of the UBE3A gene can be deleted or rendered inactive by a number of distinct genetic processes (Fig. 2). About 70% of cases of Angelman syndrome result from the deletion of a portion of maternal chromosome 15, which contains this gene (Fig. 3). A variation in the maternal copy of the UBE3A gene causes Angelman syndrome in the remaining instances (10–20 percent).

A person who receives two copies of chromosome 15 from their father (paternal copies) rather than one copy from each parent may in rare instances develop Angelman syndrome. We refer to this condition as paternal unicparental disomy (Fig. 4). In rare cases, variations or other defects in the area of DNA that regulates the activation of the UBE3A gene can also result in Angelman syndrome. These conditions are known as translocations. UBE3A and other genes on the maternal copy of chromosome 15 may be inappropriately turned off (inactivated) by these genetic alterations. In 10 to 15 percent of cases, the etiology of Angelman syndrome is unknown. Changes involving other genes or chromosomes may be responsible for the disorder in these cases. In some people who have Angelman syndrome, the loss of a gene called *OCA2* is associated with light-colored hair and fair skin. The *OCA2* gene is located on the segment of chromosome 15 that is often deleted in people with this disorder. However, loss of the *OCA2* gene does not cause the other signs and symptoms of Angelman syndrome. The protein produced from this gene helps determine the coloring (pigmentation) of the skin, hair, and eyes.

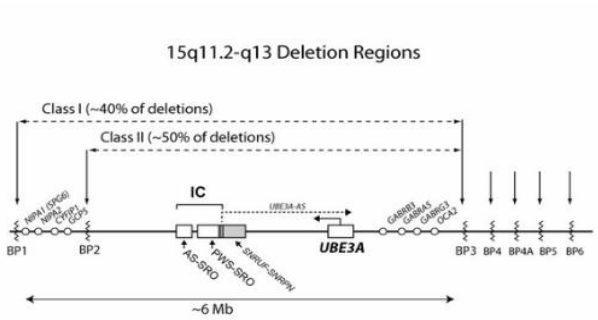

Figure 2: A schematic representation of the breakpoint areas BP1–BP6 on chromosomal region 15q11.2-q13. Ninety percent of the chromosomal deletions that cause Angelman syndrome end in area BP3 (class I and class II) after starting at BP1 or BP2. Roughly 10 percent of deletions are bigger than BP1, usually extending from BP1 to BP5, and very never going beyond BP5. The open circles indicate genes that are biparentally expressed because they are not imprinted. The two pieces of the crucial imprinting center (IC) are shown as open boxes. A shaded box represents the gene SNRUF-SNRPN, which shares some similarities with the PWS-SRO. UBE3A-AS is the designation for the SNURF-SNRPN sense/UBE3A antisense transcript.

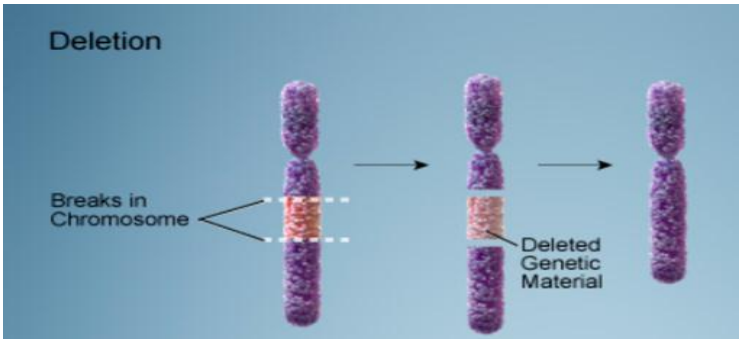

Figure 3: Segment of the maternal chromosome 15 containing *UBE3A* deleted gene.

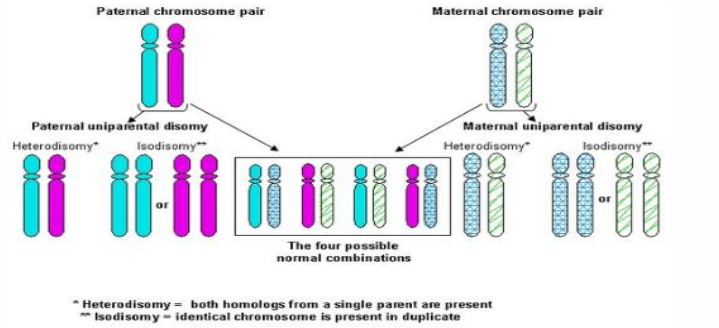

Figure 4: Uniparental disomy results in an abnormal phenotype when the chromosomes involved are imprinted, such that the genes on these chromosomes are monoallelically active.

Epidemiology

There are several estimates, but the exact prevalence of Angelman syndrome is unknown. The best available statistics are from studies of school-age children (6–13 years old) from Denmark and Sweden, where the diagnosis of AS children in medical clinics was compared to around 45,000 births during an 8-year period. The Danish research indicated a minimal AS prevalence of around 1/10,000, while the Swedish study reported an AS frequency of almost 1/20,000[39].[18] Three kids with this illness were initially noted by Warrington, England, doctor Harry Angelman in 1965.Later on, Angelman explained that he had named these instances "Puppet Children" because of an oil painting he had seen while on vacation in Italy.[19]

Diagnosis

Angelman syndrome is not present at birth. At six to twelve months, when parents start to observe developmental milestones such a lack of crawling or chattering, the disease is usually identified.[20] Around age two or three, seizures may start. Children that have a tiny head size with flatness in the back, difficulties with mobility and balance, frequent laughing, and other symptoms may also raise a doctor's suspicions about the illness.[21]

To confirm a diagnosis of Angelman syndrome, child's doctor will perform a combination of genetic tests that can include the following:

- Chromosome analysis to examine the size, shape, and number of chromosomes in a cell
- Fluorescent In Situ Hybridization (Fish) to see if any chromosomes are missing
- DNA methylation test to see if both copies of a gene — one from the mother and one from the father — are active
- Sequencing of the ubiquitin-protein ligase E3A (UBE3A): to look for a mutation in the maternal mutation of this gene, which is a rare cause of Angelman syndrome.[22,23]

Treatment

This illness can be controlled, but there is no known treatment. Care for people with Angelman Syndrome has to be thorough and interdisciplinary. Using a mix of treatments, interventions, and supporting services and resources is necessary to manage the condition's diverse symptoms and difficulties.[24]

1. Multidisciplinary approach to care

People with Angelman Syndrome adequate support requires a multidisciplinary approach to care. A group of medical specialists, including pediatricians, neurologists, geneticists, occupational therapists, physical therapists, speech therapists, and behavioral specialists, are involved in this strategy. These specialists work together to guarantee that each person's unique requirements are met in a comprehensive manner.[25] The interdisciplinary team collaborates to create a personalized treatment plan that is suited to the particular requirements of the individual with Angelman Syndrome. Frequent evaluations and follow-up visits aid in tracking development and enabling any required modifications to the treatment plan. The team may also help families and caregivers by offering advice and encouragement, enabling them to offer the most care and support at home.

2. Therapies and Interventions

People with Angelman Syndrome can enhance their overall quality of life and manage their symptoms with the use of various therapies and interventions. These might consist of:

- **Speech therapy:** Issues with speech and communication are prevalent in cases of Angelman Syndrome. Through the application of augmentative and alternative communication techniques like sign language or communication gadgets, speech therapy can assist people in improving their communication abilities.
- **Physical therapy:** Problems with balance and movement might affect motor abilities. Through exercises and treatments suited to each patient's skills, physical therapy works on enhancing strength, coordination, and mobility.
- **Occupational therapy:** The goals of occupational therapy are to improve fine motor skills, sensory integration, and everyday life abilities. Individuals benefit from this therapy by being more independent and having better participation in day-to-day activities.
- **Behavioral interventions**: Angelman Syndrome sufferers may display difficult behaviors, hyperactivity, and excitability. Applied behavior analysis (ABA) is one behavioral technique that can help control these tendencies and encourage constructive social relationships.[26]

3. Supportive Services and Resources[27-29]

It is imperative that those affected with Angelman Syndrome and their families have access to resources and supportive services. These programs might offer extra help and support in handling the difficulties brought on by the illness. Among these resources could be:

- **Support groups:** Participating in support groups and establishing connections with other families and individuals impacted by Angelman Syndrome can offer psychological assistance and a feeling of belonging.
- **Early intervention programs:** Infants and young children might get specialized assistance from early intervention programs to support their development and meet unique needs.
- **Educational support:** Angelman Syndrome persons' educational requirements are satisfied when they work with educators and school personnel to construct an individualized education plan (IEP).
- **Respite care:** Services for respite care offer caregivers short-term respite so they may take a break and yet make sure the person with Angelman Syndrome gets the right care.

Complications

The following are complications linked to Angelman syndrome:

1. **Curving of the spine (scoliosis):** This is a condition that some individuals with Angelman syndrome have over time.
2. **Hyperactivity:** Kids are impulsive, have short attention spans, and frequently put their hands or toys in their mouths. As people mature, hyperactivity often declines and medication is typically not required.
3. **Sleep disorders:** They require less sleep than the average person and have irregular sleep-wake cycles. As people age, their sleep problems may become better. Sleep problems may be managed with the use of medication and behavior therapy.
4. **Difficulties with feeding:** Infants with trouble synchronizing their sucking and swallowing issues. The baby's pediatrician can suggest a high-calorie formula to aid with weight gain.
5. **Obesity:** Children with Angelman syndrome who are older often have voracious appetites, which can result in obesity.

CONCLUSION

Because Angelman Syndrome is a complicated disorder, treatment must be provided in its whole. Angelman Syndrome has no known cure, however there are therapies and interventions that can assist those who have it manage their symptoms and enhance their quality of life in general. People with Angelman Syndrome can get the help and resources they need to maximize their health and well-being by adopting a multidisciplinary approach to care. To offer the most care and support, it's critical for families and caregivers to be aware of their options and collaborate closely with medical specialists. People with Angelman Syndrome can live happy, satisfying lives and realize their full potential with the correct therapies and support. There is no complete cure of Angelman Syndrome, more researches are needed to develop pharmaceuticals & manage this disease.

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