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American Journal of Biopharmacy and Pharmaceutical Sciences

Review Article *Biomedical and Pharmaceutical Sciences*

Angelman syndrome: A genetic challenge for physical and learning disabilities

Bassy Kuruppan Alias[1], Lini K. Simon[1]

[1]Department of Pharmacy Practice, Veerashaiva Vidhyavardhaka Sanghas Togari Veeramallappa Memorial College of Pharmacy, Bellary, Karnataka, India.

***Corresponding author:**
Bassy Kuruppan Alias, Department of Pharmacy Practice, Veerashaiva Vidhyavardhaka Sanghas Togari Veeramallappa Memorial College of Pharmacy, Bellary, Karnataka, India.

bassyalias@gmail.com

Received: 24 January 2023
Accepted: 20 September 2023
Published: 18 December 2023

DOI
10.25259/AJBPS_6_2023

Quick Response Code:

ABSTRACT

Angelman syndrome (AS) was first reported in 1965 by Dr. Harry Angelman. It is a condition of neurodevelopment characterized by, a lack of speech, distinctive behavior, seizure, intellectual capacity, and cheerful disposition. The cause of AS is a lack of production by maternal imprinted genes (UBE3A) on the 15q11-q13 chromosome. The complications of AS are strabismus, atrophy of the optical nerve, and blindness, which are rarely reported. There is a possibility of complications in the laboratory diagnostic tests for AS. One method is to evaluate with DNA methylation analysis of AS/Prader-Willi Syndrome (PWS) imprinting center (IC). On cytogenetic analysis, at least 50–60% of patients had a maternally induced de novo mutation of chromosome 15q11-13 with more serious clinical phenotypes such as microcephaly, seizures, language impairment, and motor difficulties. Multiexonic or whole gene deletion is identified by array-comparative genomic hybridisation (CGH) in some cases and laboratory and methodology may vary such deletions. Diagnosis of AS can be suggested by unsteady movements before walking. Based on the patient's medical history, electroencephalogram (EEG) data, clinical symptoms, and the presence or absence of a chromosome 50 deletion, a diagnosis of AS is made. Incidence estimated for AS is approximately 1 in 12,000–20,000 birth lives, but the epidemiological measures of life expectancy remains unknown. The clinical features of AS phenotype include seizures, sleep disturbance, intellectual disability, and movement disorders such as tremor and ataxia, anxiety, expressive language is limited, behavioral changes, pleasant demeanor, and easily manipulated laughs, EEG abnormalities were discovered in around 100% of the patients. The researcher identified problems with inflammation at the injection site caused by a higher dose of a drug and they monitored proteins in the individual's blood and cerebrospinal fluid as an additional safety precaution. Genetic counseling for families with one child with AS to address the likelihood of recurrence can be a challenging subject that frequently requires specialist advice.

Keywords: Angelman syndrome, Maternal imprinted genes, Genetic disorder, DNA methylation, Denova mutation

INTRODUCTION

Angelman syndrome (AS) was first reported in 1965 by Dr. Harry Angelman.[1] It is a condition of neurodevelopment characterized by a lack of speech, distinctive behavior, seizure, deficit intellectual capacity, and cheerful disposition.[2] The cause of AS is a lack of production by maternal imprinted genes (UBE3A) on 15q11-q13 chromosome.[3] Uniparental disomy (UPD) and imprinting center (IC) defects are the other genetic causes. The estimated prevalence of the AS is about 1:20000 births.[4] The earliest characteristic behavior of the syndrome is sustained social smiling, growing as early as 1-3 months of constant laughter, giggles, and smiles which may not be seen after. Intellectual disability is a challenge in AS.[1] Ataxia and seizure accompanied by certain electroencephalogram (EEG) deviations are examples of neurological symptoms.

In 2005, Williams *et al*.[1] proposed a set of concurrent criteria for the detection of AS, which include a list of symptoms such as (a) frequent, (b) consistent, and (c) associated features. AS differential diagnosis includes disorders with a monogene such as Rett syndrome (MECP2), Christianson syndrome (SLC9A6), Pitt Hopkins disorder (TCF4), Klecfstra disorder (EHMT1), Mowat–Willson syndrome (ZEB2) or HERC2 deficiency syndrome.[5] Most of the children are identified over a longer duration, 3-7 years while the bizarre gait and exceptional behavior become evident. Most walk by the age of 2 years and 6 months to 6 years and have features such as jerky and atactic gout associated with raised and pronated form arms. If not encouraged for walking, severe ataxia can be a reason to lose walking ability, for people having severe ataxia in AS. Development of scoliosis during adolescence is particularly a challenge for people who cannot walk.[1] The complications of AS are strabismus, atrophy of the optic nerve, and blindness, which are rarely reported. About 40% of adults, mostly females, reported thoracic scoliosis. Vagal hypertonia associated with disturbances in cardiac rhythm is noted.[6] There is a possibility of complications in the laboratory diagnostic tests for AS. One method is to evaluate with DNA methylation analysis of AS/PWS IC. One of three mechanisms of AS is present, if there is any abnormality in DNA methylation: (a) UPD, (b) large common deletion, and (c) IC deletion. If there is an abnormality in DNA methylation, further examinations are recorded to confirm the distinct genetic process. In those cases, the common later one is to achieve microsatellite, fluorescent *in situ* hybridisation (FISH) or microarray chromosome study to find out whether 15q11.2-q13 is deleted. If deletion is eliminated, the following stage is to prevent paternal UPD by extra microsatellite or microarray test. In the end, if DNA methylation is normal, UBE3A gene mutation analysis is the next stage and can identify a specific percentage of each.[1] Most patients develop seizures at an early young age, which requires anticonvulsant medication. Visual assessment is important if ocular problems develop. Ocular surgery can be needed if the patient is found with strabismus. Behavioral treatment should be considered in intellectually disabled patients. Physical therapy is required for non-ambulatory. Occupational therapy is needed for oral motor control skills.[6]

THE GENETIC BASIS OF THE DISORDER

Different clinical phenotypes are detected in AS patients, each with contrasting genetic mechanisms. Clinical phenotype with severe intellectual disability, speech retardation, and behavioral phenotype is caused by a variety of underlying genetic mechanisms.[6] On cytogenetic analysis, at least 50–60% of patients have a maternally induced *de novo* mutation of chromosome 15q11-13 with more serious clinical phenotypes such as a microcephaly, seizures, language impairment, and motor difficulties. A fraction of patients, around 2–5% have UPD for chromosome 15 either from the father and/or from the mother.[7] Trisomy rescue, genetic issues, mitotic duplication, and the post-fertilization fallacy are the mechanisms of UPD formation.[6] The risk of recurrence is unknown, although it might be modest if the postulated mechanism is right and both parents have normal chromosomes.[7] In about 75% of parental UPD chromosome 15 cases, show somatic segregation error, and this type of patient have fewer recurrences of microcephaly, ataxia, motor problems, and seizures. In around 2-5% of patients, genetic changes in the IC result in microcephaly, hypopigmentation, ataxia, motor problems and seizures. Some patients have a higher level of speech abilities.[6]

In chromosome microdeletions, proximal BP1, BP2, and the more distal BP3 (break points of 3 chromosomes 15q11.2-q13) approximately 90% of deletion is found and approximately 5–7 Mb is the deletion span. Around 40% of deletion cases fall in class I deletion and extended from BP1 to BP3. Class II deletion comprises 50% of deletions and extends from BP2 to BP3. Less than 10% of deletion extends from BP1 to BP2 to more distal at BP4, BP4A, BP5, or BP6. The BP1, BP2, and BP3 are distinguished by little copy repeats, containing duplicates of some pseudo genes and further sequences. Reduced copy repeats are derived from the HERC2 gene, containing HECt domain and RCcl domain protein 2. Doornbas *et al*.[8] and Rosenfeld *et al*.[9] reported that microdeletion includes regions between BP1 and BP2, BP3 and BP4, and the distal syndrome of microdeletion involving 15q13.3 is reported by Masurel–Paulet *et al*. in 2010.[10]

Approximately 3–7% of AS is caused by paternal UPD of 15 chromosomes with the occurrence of seizures. In 2000, a report by Robinson *et al*.[11] indicated that somatic segregation errors led to UPD. This mechanism is less common.

A fraction of individuals with defects in imprinting caused by the IC and with a bipartite structure and managing cis imprint resetting and maintain with 15q11.2-q13 imprint domain. Without any changes in the DNA frequency and primary epimutation, imprinting defects could be found. More than 40% of individuals found to have somatic mosaicism with an imprinting defect are a significant cause in the post-zygotic loss of maternal imprint.

Protein truncating mutation is the most found UBE3A mutation in AS and reported in more than 60 mutations. Frameshift mutation is also found in around 60–70% of AS. Missense and nonsense mutation is found in approximately 25% with gross deletions, splicing defects, and complex rearrangements. Multiexonic or whole gene deletion is identified by array-CGH in some cases and laboratory and methodology may vary such deletions.[1]

GENETIC DIAGNOSIS AND SCREENING

The phenotype seems to be normal in newborn babies. Feeding problems and hypotonia in muscle may be present in the first 6 months. A developmental delay is observed at the age of 6 months. Usually, non-specific features emerge at the age of 6 months to 2 years, so the diagnosis is often difficult. Diagnosis of AS can be suggested by unsteady movements before walking.[6]

Based on the patient's medical history, EEG data, clinical symptoms, and presence or absence of a chromosome 50 deletion, a diagnosis of AS is made. Although ataxic cerebral palsy is a differential diagnosis, the degree of intellectual disability is significantly less severe, usually no abnormal facial traits and speech are present.[7]

Cytogenetic approach

On a standard chromosomal examination, a cytogenetically detectable chromosome rearrangement influences the 15q 11.2-13 regions through large deletion, translocation, or inversion. However, a common deletion of 5–7 Mb normal chromosome analysis is missed.

Molecular testing

Deletion, UPD, or imprinting defects can be detected by DNA methylation and confirmed in about 78% of the patients. Around, 60–75% of patients identify 4–6 Mb deletion of 15q11.2-q13 through FISH studies with D15S10 and/or SNRP probe CGH may detect a smaller deletion.[6]

Through DNA methylation, about 80% of cases can be performed to confirm AS. There is a disadvantage to that. That is, there is no discrimination between chromosome removal, IC defect, and paternal UPD. If there is abnormality in DNA methylation, the next step is to achieve microsatellite, FISH, or microarray. Deletion of the 15q11-q13 chromosome can be detected by chromosome study in the cells and is applicable in 70% of cases. If the DNA methylation is normal, the next step is analysis of mutation in UBE3A. UBE3A mutation analysis is identified either as a single test, ordered specifically or as a whole exome sequencing. But now, more often the use of a whole exome sequencing panel that carries intellectual deficiency is a group of many genes known to cause.[1]

For the diagnosis of AS, typical EEG patterns can be helpful in patients with mental retardation, and in the West Syndrome, Hypsarrhythmia, or in Lennox–Gastaut, petit mal variant pattern includes differential diagnosis.

Rett syndrome confirms that AS diagnosis in a section of children without any genetic confirmation and having MECP2 gene mutation.

Heterozygous deletions or truncating of ZFX1B gene mutation on 2q22 will cause Mowat–Wilson syndrome. Its features are mental retardation and microcephaly. Alpha–thalassemia, X-linked is caused by XNP gene mutation on Xq13 or syndrome of mental retardation (ATR-X). Mental retardation, seizures but positive speech development are common features. Patients with global developmental delay, mental retardation (moderate to profound), delay of speech, and conditions in 22q13 deletion syndrome, that is, Phelan–Mc Dermid syndromes.[6]

PREVALENCE

Incidence estimated for AS is approximately 1 in 12,000–20,000 birth lives, but the epidemiological measures of life expectancy remain unknown.[12] AS is reported in childhood, in several studies. Dr. Harry Angelman first described AS in 1965. A clear picture was given on health issues of children with AS, but on adults, only a limited number of studies are available.

After the first 20 years of Angelman description by Dr. Harry Angelman, it was rarely reported. The phenotype has been widely reported and generated to both cytogenetic and molecular genetic abnormalities on chromosome 15 and characteristics of EEG findings reported by Boyd *et al*.[13] these observations lead to an increased number of patients diagnosed with Angelman and to be diagnosed in younger ages. In 1995, Michael B. Petersen reported the frequency of AS as high as 1 in 10,000–20,000.[1]

INHERITANCE PATTERNS AND CLINICAL FEATURES

The cause of AS is the deletion of maternal chromosome 15 or by paternal UPD, but most of the cases are not inherited. There is no history of the disorder in the family of affected individuals. During the formation of eggs and sperm, these genetic changes occur or in early embryonic development as random. Rarely, a genetic change for AS can be inherited, like a variation in the UBE3A gene.

The clinical features of AS phenotype include seizures, sleep disturbance, intellectual disability, and movement disorders such as tremors and ataxia, anxiety, expressive language limited expressive language, behavioral changes, pleasant demeanor, and easily manipulated laugh, EEG abnormalities were discovered around 100% of patients.[14] In AS, epilepsy and sleep dysfunction caused by reduced expression of the GABA receptor gene distinctly GABRB3 on 15q11-13, alongside UBE3A, and may be secondary to haploinsufficiency.[12] Triphasic delta activity is present with moreover the anterior region and the likelihood of triphasic waves increases with age shown in EEG of AS in children and adults.[6] Epilepsy and sleep dysfunctions are the most common features in AS individuals

and the interaction between these is not well understood, also, the occurrence of visual impairment coexisting with pathology remains unclear. In ophthalmologic examination, a strabismus and/or a pale fundus were identified. Obesity is a vital health problem in adults along with AS. Moreover, weight management is a complication that involves different elements including genetic predisposition, limited access to exercise, and challenging food behaviors.[12]

CURRENT DEVELOPMENT

For AS, the U.S. Food and Drug Administration had decided to start a gene therapy as a clinical trial by February last year. It is a genetic condition caused by deletion or lack of production by maternal imprinted genes (UBE3A).[15] Hence, they aimed to activate a paternal copy of the gene and the gene therapy named GTX-102. For this clinical trial, five children with AS started to receive gradually increasing doses through injection in the lower back. Biopharmaceutical company Ultragenyx in Novato, California, is running the trial in collaboration with Florida-based biotech start-up GeneTx and the dosing started at 3.3 mg and increased up to 20, and in some instances 36 mg, which is when side effects began. In May and June, regulatory bodies in the United Kingdom and Canada gave permission to the companies to start testing the drug using 3.3 mg in younger children and 5 mg in children aged between 8 and 17. All five individuals were observed with leg weakness, which was severe enough to prevent independent walking in two children by July. The trial was officially paused in November by the FDA. The researchers identified problems with inflammation at the injection site caused by a higher dose of drug and they monitored proteins in the individual's blood and cerebrospinal fluid as an additional safety precaution. After the trial paused, the children showed improvement in communication, motor skills, and sleep.

In the new trial, included eight children in between the age of 4 and 8 years. In that four were not previously treated with GTX-102 and they received 4 monthly doses of 2 g of drug. Another four will not receive the therapy. Both the groups were examined at the start of the trial and after 128 days, at which the control group could also start to receive the therapy. In the second phase, eight children with AS will continue to be treated with the lower dose of GTX-102. The primary endpoint is the clinical global impression of improvement scale for AS, which is designed to identify changes in the development of children based on the interview with parents. The clinical trial is to be held in New York and the researchers hope to start enrolling children by this month.[6]

CONCLUSION

AS is an exceptional genetic disorder of chromosome 15, characterized by intellectual disability, speech impairment, seizures, and a unique behavioral pattern. Research and understanding of the genetic basis of AS are growing, but the treatment remains largely symptomatic. Gene therapy provides a promising avenue for potential therapeutic interventions. The clinical trials of gene therapy for AS are in the early stages, and although there have been setbacks, the pursuit of effective treatment continues. The community of scientists, clinicians, patients, and their families are committed to furthering our understanding of AS and developing effective treatments. More research is required to understand the full complexity of AS, as well as to develop and optimize targeted therapies.

Ethical approval

The Institutional Review Board approval is not required.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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How to cite this article: Alias BK, Simon LK. Angelman syndrome: A genetic challenge for physical and learning disabilities. Am J Biopharm Pharm Sci 2023;3:9. doi: 10.25259/AJBPS_6_2023