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CASE REPORT OF ANGELMAN SYNDROME- A CHILD WITH PATHOGENIC VARIANT c.678dup, p.(Leu227iLefster4) IN THE EXON 7 OF UBEZA GENE

Danilo Nonkulovski[1], Aspazija Sofijanova[1], Sonja Bojadzieva [1] ,
Ilija Kirovski[1] , Olivera Jordanova [1]
University Clinic for Pediatric Diseases, Faculty of Medicine,
Ss. Cyril and Methodius University in Skopje, North Macedonia

Abstract

Angelman syndrome is rare and belongs to the group of genetic imprinting disorders where pathogenic mutations in the active gene are responsible for the disease, while pathogenic mutations in the inactive gene do not cause the disease. It's usually caused by problems with a gene located on chromosome 15 called the ubiquitin protein ligase E3A (UBE3A) gene. Some of pediatric patient don't have a family history of the disease.

We present to you a 2 and a half year old female child with seizures which are difficult to control and recur in clusters, alternating with periods without attacks. Due to suspicion of epilepsy sent for genetic diagnosis. The presence of a pathogenic variant c.678dup, p.(Leu227iLefster4) in the in exon 7 of UBEZA gene in heterozygous form was proven. T

here is a change in the reading frame (frameshift), i.e. replacement of the amino acid leucine at position 227 with the amino acid isoleucine and termination of the protein after 4 amino acids. This variant has not been published in the literature so far. Family studies showed that the c678dup variant in the UBEZA gene was not present in the child's parents. Additional analysis confirmed the biological connection of the parents with the child. These findings confirm that the pathogenic c678dup variant in the child arose de novo. Anticonvulsant therapy was prescribed and ketonic diet

Early diagnosis of Angelman syndrome and appropriate therapy enables a better quality of life for children

***Keywords*:** Angelman syndrome, epilepsy, seizures, UBE3A gene.

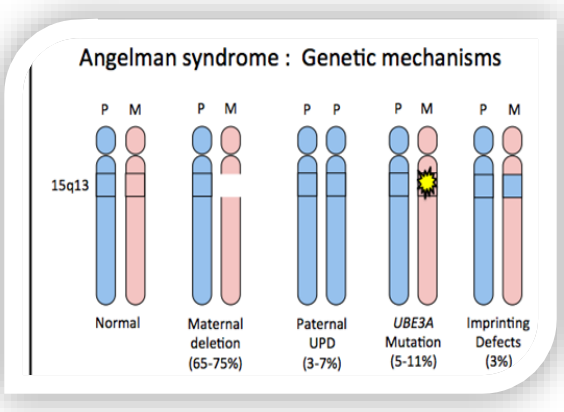
Introduction

Angelman syndrome is a genetic disease that mainly affects the nervous system. The name of this disease is Dr. Harry Angelman first reported this situation in 1965. This condition is rare, can occur in any fetus, and belongs to a group of imprinted diseases in which pathogenic mutations are present in an active gene responsible for the problem. Mutations in the inactivating gene do not cause disease [1,2].

This condition is caused by a problem in the ubiquitin protein ligase E3A (UBE3A) gene located on chromosome 15. Some pediatric patients have no family history of the disease (Picture 1).

Genetic testing is very important. It can cause growth retardation, intellectual disability, developmental delay, speech disorder and ataxia. Most children also have epilepsy (epilepsy) and microcephaly[3,4].

Babies with Angelman syndrome appear normal at birth but often have feeding problems in the first few months of life. They also show growth retardation between 6 and 12 months. Seizures usually begin between the ages of 2 and 3.



Picture 1. Genetics of Angelman syndrome
Image courtesy Genetics 4 Medics

Children with Angelman syndrome usually appear cheerful, cheerful, and often smile, laugh, and clap their hands. ADD and ADHD are common. Many children also have trouble sleeping and need less sleep than usual. Gastrointestinal, orthopedic and eye problems often also occur [5,6].

Angelman syndrome is rare. Approximately 1 in 12,000 to 20,000 people are affected. It affects people assigned male at birth equally as those assigned female at birth. Autism spectrum disorder is a neurodevelopmental disorder that is often diagnosed in childhood. Autism spectrum disorder used to be known as autism, and many people still use that term. But autism spectrum disorders include many conditions on the spectrum.

Autism spectrum disorder changes the way your child interacts and communicates. There is no cure for autism, but symptoms will decrease over time. Many of the symptoms of Angelman syndrome are caused by the activity of the UBE3A gene [7].

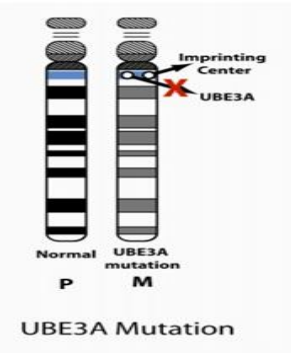
These changes occur early in fetal development, before the baby is born. Gene mutations are changes in the DNA sequence. DNA sequence provides brain with the information it needs to do its job. Babies can develop genetic disorders if part of their DNA is defective or damaged.

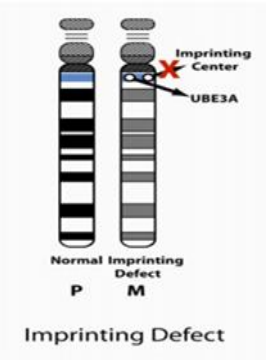
Most people get one copy of the UBE3A gene from their parents. Both copies of this gene are "on" (active) in most tissues of your body. However, in some parts of your brain, only the copies from your parents (maternal copy) are valid. If the parent's copy of the UBE3A gene is lost due to a chromosomal mutation or genetic mutation, that part of your brain will no longer have a copy of the gene. This causes the characteristic symptoms of Angelman Syndrome, a neurodevelopmental disorder.

A person may develop symptoms of Angelman syndrome because part of the UBE3A gene is malfunctioning or missing (about 70% of patients).

Mutations in UBE3A can also cause Angelman syndrome (about 11% of cases). Mutations in the UBE3A gene are often persistent (dominant), meaning they are not beneficial (passive)[8,9].

The UBE3A gene is located on chromosome 15 and encodes a protein called ubiquitin protein ligase E3A. Two copies of the UBE3A gene are usually inherited, one from each parent. However, only the copy inherited from the mother is active in certain areas of the brain. This cospecific gene activation is the result of a phenomenon known as genomic imprinting (GHR:UBE3A) (Picture 3,4).





Picture 2. UBE3A Mutation Picture 3. Imprinting Defect

*ANGELMAN SYNDROME Foundation

In rare cases, children do not receive one copy of chromosome 15 from their parents and relatives (for example, they may receive two copies of chromosome 15 from the other biological parent), leading to the development of Angelman syndrome. In about 10 to 15 percent of patients, doctors cannot determine the cause of Angelman syndrome. Mutations in other genes or chromosomes may be responsible for these conditions.

People with Angelman syndrome tend to live nearly normal lives, but there is no cure for the disease. Treatment focuses on maintaining health, sleep, and growth [10,11].

Definitive diagnosis is almost always made with a blood test. This genetic test can identify chromosomal abnormalities that indicate Angelman syndrome in children. Combination genetic testing can detect chromosomal abnormalities associated with Angelman syndrome.

These tests can examine:Parental DNA samples. The test, called DNA methylation testing, examines three of the four genetic abnormalities known to cause Angelman syndrome [12].

Removal of chromosome. Chromosome microarray (CMA) can show whether part of a chromosome is missing. Gene mutation. Angelman syndrome can occur when a person's mother's copy of the UBE3A gene is active but mutated, but this is rare. If the DNA methylation test is normal, we examinated UBE3A gene sequencing to look for the mutation inherited from the parent [13,14].

Targeted massively parallel sequencing of exogenous protein-coding genes in the human genome (WES) using second-generation sequencing (NGS) technology and bioinformatic processing of genes associated with patient condition. PCR amplification of exon 7 of the UBE3A gene and direct sequencing with the BigDye Terminator Sequencing kit according to the Sanger method and analysis on the AB-PRISM 3500 automatic analyzer.

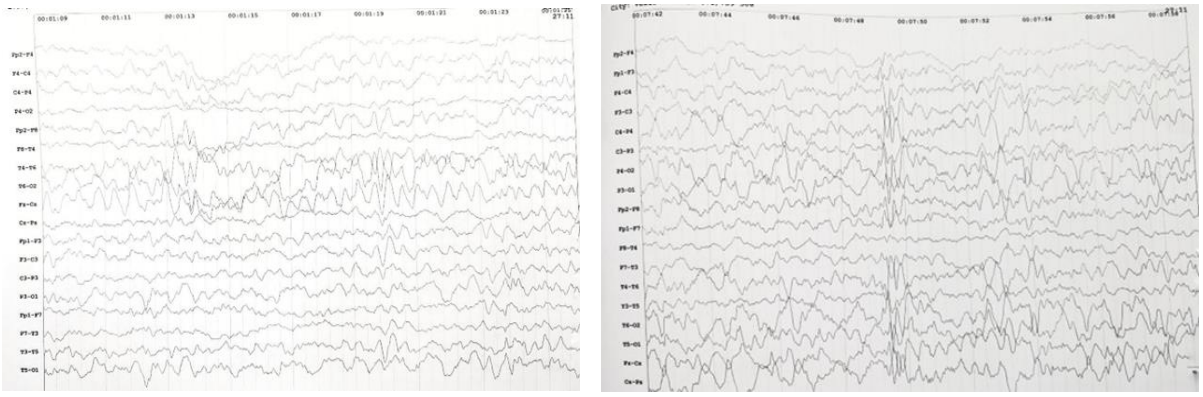
Case report

We present 2 and a half year old female child, first child from the first in a row regular and orderly controlled pregnancy. Born in 42 GN±2 weeks, with s.c. with cephalic presentation, with RT=3350 g; RD= 52 cm. APGAR 9/9. It cried immediately after birth and was not blue. Lactation established in the maternity ward. It did not manifest physiological jaundice.

Vaccination started in the maternity ward (HB and BSG). At the first hospitalization the child has several short-term afebrile attacks that occurred at a time interval of 1 hour and were manifested by a fixed look and contraction of the whole body and placed on Depakine therapy. Sir.Depakine 2x100mg.

During the second hospitalization, she is somnolent and febrile. Placed on parenteral antibiotic therapy with third-generation cephalosporin, antipyretic and anticonvulsant therapy per os as well as vitamin therapy. Lumbar puncture was performed with the finding of clear cerebrospinal fluid under pressure with lymphocytic predominance and EEG with a finding in addition to encephalitis. Included virostatic and systemic corticosteroid in parenteral therapy.

During the stay, she was febrile with seizures which are difficult to control and recur in clusters, alternating with periods without attacks , for which Diazepam i.v. was given on two occasions. and due to severe anxiety on one occasion a sedative, rectally. (Picture 4,5).



Picture 4,5. EEG demonstrating basic brain activity with present alpha wave appearance of bihemispheric pathological outbreaks more pronounced on the right

Realized additional analyzes of viral markers with the finding of positive CMV IgG and Hepres IgG.After the therapy carried out in this way, there was an improvement in the general condition and a decrease in fever on the seventh day of stay.Performed a control lumbar puncture with an orderly finding.On the tenth day of stay with the reappearance of fever due to which additional analyzes were taken with the finding of elevated inflammatory markers.

Continued with antiviral and anticonvulsant therapy. After one week on the control EEG, there is present extended brain activity in addition to encephalopathy. Due to suspicion of epilepsy sent for genetic diagnosis. Genetic analysis in the child showed the presence of a pathogenic variant c.678dup, p.(Leu227iLefster4) in UBE3A in a heterozygous form. Testing of the child's parents did not show the presence of the c.678dup variant, indicating that the child's change occurred de novo. Pathogenic changes in UBE3A are associated with Angelman syndrome which is inherited in an autosomal dominant manner.

Additional analysis confirmed the biological connection of the parents with the child. These findings confirm that the pathogenic c678dup variant in the child arose de novo. Anticonvulsant therapy was prescribed and ketonic die and control by a neurologist.

Discussion

Angelman syndrome belongs to the group of genetic imprinting disorders where pathogenic mutations in the active gene in Angelman syndrome gene inherited from the mother are responsible for the disease, while pathogenic mutations in the inactive gene in Angelman syndrome gene inherited from the father do not cause the disease. In certain areas of the brain, only the copy inherited from the mother is active [15,16].

The UBE3A gene is located on chromosome 15 and encodes a protein called ubiquitin protein ligase E3A. Ubiquitin protein ligase is an enzyme that breaks down other proteins in cells. It plays an important role in the normal development and functioning of the nervous system, for example, it helps maintain the balance of connections. and protein degradation at synapses where communication between cells in the brain occurs [17,18].

Angelman syndrome is characterized by severe motor and intellectual retardation, ataxia, hypotonia, epilepsy, absence of speech and characteristic facial appearance. Variant c.678dup, p. It is a missense variant in exon 7 of the UBE3A gene (Leu227iLefster4) in which the readthrough is changed, i.e. the amino acid leucine at position 227 is replaced by the amino acid isoleucine and Protein termination. After 4 amino acids. So far this change has not been published in the literature [19,20].

In 85% of patients develop epilepsy in the first three years of life , but less than 25% develop epilepsy in the first year[21,22] .

The age of onset of epilepsy has been defined as ranging from 1 month to 20 years . Epilepsy is usually very severe. Seizures of all types have been described and are often difficult to control and recur in clusters, alternating with periods without seizures. The most common type is atypical absence, generalized tonic-clonic, atonic, or myoclonic seizures; 50% of deletion patients have more than one

type of epilepsy. Among the main seizure patterns, there are also partial seizures, mainly occipital seizures and clonic unilateral seizures. It has been shown that febrile seizures often precede the diagnosis of Angelman syndrome and that even a slight increase in body temperature leads to complications . Based on their experience, stated that myoclonic seizures are the most common seizure type (seen in 25% of patients between 4 months and 5 years), followed by atonic seizures (23%).

Generalized tonic-clonic seizures (21%) and atypical absences (12%) were observed around 3 years. Less frequently in their series, seizures occur in the first year of life (9%), flexion spasm (5%) and focal seizures occur in the first year of life (5%). Infantile spasms are a feature of Wester Syndrome and are associated with "hyperarrhythmic" EEGs [23,24].

Different antiretroviral drugs have been used and antiepileptic drugs have been described in Angelman syndrome patients. There is now a lot of evidence that some drugs work better than others and give abnormal EEG in the absence of anxiety, physical weakness, tremors and vomiting. The ketogenic diet helps some children with epilepsy. Piracetam is said to be effective in controlling distal myoclonus .Gene therapy is the process of using a genetically modified gene to deliver the missing gene (UBE3A) directly into the appropriate cell type. This is usually done using adeno-associated virus (AAV), which is widely used and very safe, but can also be done using lentiviruses. The investigational gene therapy GTX-102 shows potential to reduce disease severity and improve function in children and adolescents with Angelman syndrome, according to interim data from Phase 1/2 clinical trials.

Conclusion

Angelman Syndrome is a rare and complex neurodevelopmental disorder that causes developmental delay, intellectual disability, speech impairment, and movement problems. It is caused by problems in a gene called UBE3A that occurs during fetal development. Early diagnosis of Angelman syndrome and appropriate therapy enables a better quality of life for children.

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