A Case Report of Angelman Syndrome

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ABSTRACT

We describe a case of a female pediatric patient showing recurrent seizures, socialization problems and speech development delay. She was born preterm, due to fetal heart rate alterations and spent a few days in neonatal intensive care. She has presented evolutionary global neurodevelopment delay and from the first year of life, she presented sleep disorders referred to as difficulties in initiating sleep and frequent waking up with irritability. She shows 2 kinds of seizures referred to as one-side of the face and the ipsilateral arm contractions and brief falls of the head and trunk backwards. Complementary test were done, such as Video/EEG recording, neuropsychological evaluation and genetic studies to the patient and her mother.

INTRODUCTION

Angelman Syndrome (AS) is a neurodevelopmental disorder caused by an absent or non-functioning maternal allele of chromosome 15q11-q13 [1]. These disorder was first described in 1965 by Harry Angelman [2]. AS is a severe neurodevelopmental disorder, with a prevalence estimate ranging from 1 in 20,000 to 1 in 12,000 [3]. The typical AS phenotype is characterized by Intellectual Disability (ID), lack of speech, hyperactivity, ataxic gait, microcephaly, sleep disturbances, frequent laughter/smiling and an apparently happy demeanor [4-6], high prevalence of epilepsy, and feeding problems [6]. Epilepsy occurs in 80% of cases, usually involving multiple seizure types and starting in early childhood [7,8]. High rates of autistic symptoms are also reported, estimating the prevalence of Autism Spectrum Disorder (ASD) from 24 to 81% [9]. AS could be due to UBE3A mutations, uniparental disomy and imprinting defects [2,6], but deletions are the predominant cause and are found in 68–75% of patients [6]. Otherwise, the spectrum of the 15q13.3 deletion syndrome overlaps that of AS, sharing features such as epilepsy/abnormal EEG, hyperactivity and widely spaced teeth [10]. CHRNA7 encodes α7 subunit of neuronal nicotinic acetylcholine receptor protein, among several, it is expressed the pre and post-synaptic region where it regulates both GABA and glutamate neurotransmitters in the hippocampus, it was also detected in the rat striatum dopaminergic neurons. CHRNA7 involves in Ca2+ regulation, which suggested as the prime candidate for the seizure phenotype [11].
Interestingly, OTU domain-containing deubiquitinating enzyme (OTUD7A) localized within the recurrent 15q13.2q13.3 deletion encodes for a deubiquitination enzyme expressed in the brain. Deubiquitination enzymes generally oppose the action of ubiquitin ligases, such as UBE3A, by specifically cleaving ubiquitin linkages. Possibly, a heterozygous deletion of OTUD7A leads to a disruption of the ubiquitination pathway and contributes to the phenotypic overlap between patients with AS and patients with the 15q13.3 deletion syndrome [10,11]. Considering the potential upcoming treatments in AS, it is important to get a more detailed view of all the health issues in AS, with a focus on epilepsy and neurodevelopmental outcomes as these are likely to be the target of future interventions [12,13].

CASE PRESENTATION

The patient is a 4 years-old female and first sibling of a twin member offspring from parents not related by blood. The mother was 35 years old and the father 36 years old at the time of conception. She was born preterm by cesarean section at 33.5 weeks gestation due to fetal heart rate alterations causing termination of pregnancy. She spent 23 days in neonatal intensive care, the first 18 days with intermittent assisted ventilation, and was diagnosed with respiratory distress in the newborn. She has presented evolutionary global neurodevelopmental delay. With rehabilitation treatment she got cephalic support at 6 months, clumsy prehension at 8 months, digital clamp at 12 months, seating by herself at 12 months, putting objects in her mouth at 14 months, standing and first steps at 24 months, more stable at 3 years, first words at age 3. She does not say simple sentences and does not control sphincters. She communicates with vocalizations, emits few words (mom, dad). She goes up and down the stairs with support, without alternating her feet. She does not jump, and she cannot stand on one foot. Handles objects awkwardly, has a clumsy digital clamp. She also shows ataxic gait with flexed arms, open mouth with excessive drooling, strabismus, hypopigmented skin, light hair and eye color and Hyperactive lower extremity deep tendon reflexes. An electroencephalogram was performed which resulted: during the vigil a record was obtained with eyes open all the time, in these conditions the proper organization of the basic activity according to age was not identified. A notable global slow anomaly was found in the temporal and frontal regions of the left hemisphere. An active paroxysmal interictal disorder was fond that focuses on the anterior temporal territory of the left hemisphere. Prolonged monitoring evolutionary Video/EEG recording was performed using Micromed Software System Plus Evolution Equipment, 32 extracranial recording electrodes were placed. In 24 hours of continuous monitoring Video/EEG without reduction of anti-epileptic medication. This study shows a significant decrease in the frequency of discharge of the interictal electroencephalographic epileptiform patterns characteristic of Angelman Syndrome: rhythmic delta pattern anterior regions, posterior theta pattern and epileptiform discharges in posterior regions that were significantly exacerbated with ocular closure. The Predominant ictal activity in these 24 hours record were the generalized non-motor crisis with poli-spine 3Hz pattern corresponding to a
typical absence seizure pattern which one were unseen by the mother or the nurse, and myoclonic seizures of one-side of the face and the ipsilateral arm. Also generalized atonic seizures of the upper limbs and trunk where found.

In the neuropsychological evaluation, a performance corresponding to a developmental age of approximately 18 months and a developmental coefficient of 35, which corresponds to a severe level of psychomotor development, influenced by motor, language and behavioral limitations, was shown during the neuro-psychology session, with greater affectation of language and behavior.

**DISCUSSION**

**Background**
- Prenatal: Fetal suffering.
- Perinatal: preterm, spent 23 days in neonatal intensive care and was diagnosed with respiratory distress in the newborn.
- Postnatal: Neurodevelopmental delay, sleep disorder and socialization problems

**Clinical findings**
- Neurodevelopmental delay
- Seizures described before
- Dysmorphic according to Angelman Syndrome.
- Clinical Characteristics according to Angelman Syndrome

**Complementary tests**
- Video/EEG recording: This study shows patterns characteristic of Angelman Syndrome, the electrical characterization of the two kinds of seizures described above and the electro-clinical evidence of typical absence seizure unnoticed until these recording.
- In the neuropsychological evaluation: showing a severe level of psychomotor development, influenced by motor, language and behavioral limitations

**Genetic studies**
1. A normal karyotype study of the patient and her mother
2. Fluorescence in Situ Hybridization (FISH) study showing amicrodeletion of the chromosome 15q11.2-13.3 region which extends about 4.8Mb involving the region of UBE3A, OTUD7Aand CHRNA7 genes. The same study was also performed on the mother and no alteration were found.

**TREATMENT**
An intensive, personalized, comprehensive, multidisciplinary and interdisciplinary neurorestaurative treatment program was also incorporates, which included:
- Physical rehabilitation, special education and speech therapy program. Non-invasive brain stimulation, 20 sessions of electrical mode, language stimulation protocol.
- Pharmacological readjustment: change of anti-epileptic medication, given by the gradual withdrawal of lamotrigine and the incorporation of valproic acid because the typical absence seizure.

**CONCLUSION**
This is a typical case of Angelman Syndrome, having the most common characteristics. The prenatal, perinatal and postnatal background and the clinical findings are according with this syndrome and with the complementary exams for example: Video/EEG recording the patterns characteristic of Angelman Syndrome and the genetic test that was interpreted as a de novo microdeletion of the region of UBE3A gene and a 15q13.3 deletion syndrome. Early stimulation help with the socialization issues and the characteristics of the ASD were not predominant in our patient but may be common in this syndrome. In addition, the speech developmental delay was one of the problems that make the patients to search for medical attention, fact that is very frequent. The disorder in question is very uncommon, it might be on the interest to the scientific community, health care professionals and medical science students. Angelman Syndrome do not pose a severe risk for the patient’s live but indeed heavily affect its quality and also the life of the parents.

**REFERENCES**


