Acta Scientific Otolaryngology (ISSN: 2582-5550)

Volume 4 Issue 6 June 2022

Case Report

Angelman's Syndrome: A Rare Diagnosis Causing Speech Delay

Isabela Carvalho de Queiroz, Luiza Costa Villela Ferreira, Fernando Massa Correia, Thaís Gomes Abrahão Elias and Fayez Bahmad Jr*

University of Brasilia, Brasilia, DF, Brazil

***Corresponding Author:** Fayez Bahmad Jr, University of Brasilia, Brasilia, DF, Brazil.

Received: April 05, 2022

Published: May 18, 2022

Abstract

A report is presented on a brazilian girl, with lack of speech, abnormal motor development and physical features that led to a diagnosis of Angelman's Syndrome. There was no prior family history. Awareness of this rare condition is important for the otolaryngologist and all physicians in order to provide adequate approach management to patients and improve their quality of life.

Keywords: Angelman Syndrome; Speech; Language Development; Developmental Disabilities; Otolaryngology

Abbreviations

AS: Angelman syndrome; MRI: Magnetic Resonance Imaging; VRA: Visual Reinforcement Audiometry; DPOAEs : Distortion-Product Otoacoustic Emissions; BERA: Brainstem Evoked Response Audiometry; CT: Computed Tomography

Introduction

In 1965 the English Pediatrician, Harry Angelman, described three unrelated children with similar physical abnormalities of congenital origin and profound mental retardation, including severe learning disabilities, inability to speak, epileptic seizures, jerky movements, protruding tongues and bouts of laughter giving them a superficial resemblance to puppets [1]. Therefore, he named the syndrome 'the happy puppet syndrome', later being renamed Angelman syndrome (AS) [2].

AS is a rare neurogenic disorder, with an estimated frequency of 1/15000 - 1/20000 [3,4], caused by a variety of genetic mechanisms involving the 15q11-13 chromosome. About 70% of cases are caused by a sporadic "de novo" interstitial deletion, involving the long arm region of the maternal gene UBE3A at chromosome 15q11-13 [3,5-7]. The UBE3A gene encodes E3 ubiquitin ligase, an enzyme that is mainly involved in the ubiquitin-proteasome pathway which is extremely important to all cells, especially brain neurons [4,8]. This pathway involves the degradation of selected proteins and is part of the constant protein turnover that occurs in cells [4,8], thus loss of function of UBE3A gene in neurons seems to inhibit synapse formation and experience-dependent synapse remodelling, leading to some clinical features exhibited in AS [6].

Children with AS show lack of speech, abnormal motor development, flat occiput, tongue protrusion, seizures and uncontrollable laughter, wich often leads the clinician to suspect the syndrome [6,9,10]. However, the characteristic signs and symptoms of AS evolve slowly with age, and early diagnosis of the condition can be difficult [4].

Materials and Methods

A 7-year-old girl presented with speech delay. She was born to nonconsanguineous and phenotypically normal parents with no

prior family history of mental retardation. The female child was born in 08/17/2013 by a vaginal delivery with normal APGAR score, at 39 weeks of pregnancy; she was a good feeder, and her weight gain was normal.

The patient had a typical face with prognathism, with prominent chin, wide mouth, with thin upper lip, widely spaced teeth, fair hair, light-blue irides with strabismus (Figure 1), and also she had a ataxia-like incoordination, happy demeanor with inappropriate and excessive laughter. No speech development was seen.

Figure 1: Fenotype of Angelman syndrome.

Developmental delay was suspected by the pediatrician at three months of age, and the child was referred to neuropediatrician for evaluation, as well as to early stimulation with physiotherapy and occupational therapy. Although the patient had strabismus, visual assessment demonstrated normal vision acuity. Tonic-clonic seizures began at 1 year-old, controlled with use of Levetiracetan. Eletroencefalography showed a epileptogenic activity on both temporal regions associated with a diffuse disturbance of brain electrical activity, and Magnetic Resonance Imaging (MRI) demonstrated asymmetric enlargement of the lateral ventricles, with no other additional findings.

The first audiological evaluation was performed at 11 days, with transient evoked otoacoustic emissions for neonatal hearing screening, and showed no abnormalities.

Because of the complaint of delayed speech, we performed a complete assessment of her hearing. Visual Reinforcement Audiometry (VRA) in free field suggested a normal hearing in the best ear (Figure 2), as well as Distortion-Product Otoacoustic Emissions (DPOAEs) and Brainstem Evoked Response Audiometry (BERA) were normal (Figures 3 and 4).

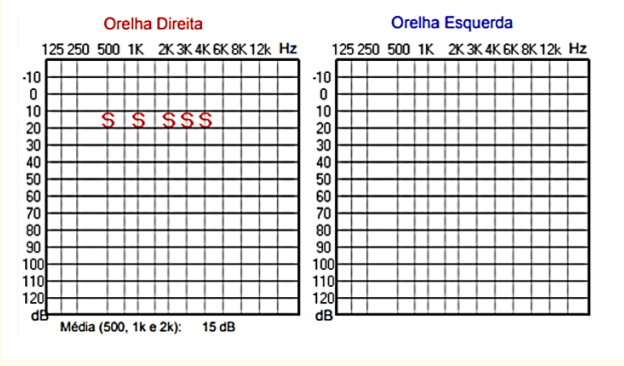

Figure 2: Visual Reinforcement Audiometry (VRA) in free field.

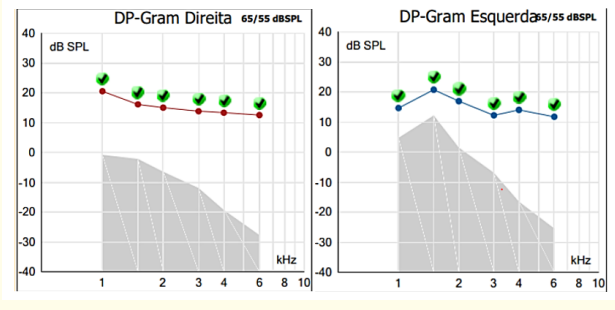

Figure 3: Distortion Product Evoked Otoacoustic Emissions (DPOAE).

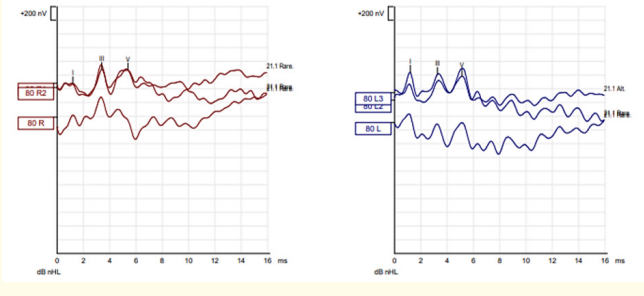

Figure 4: Brainstem Evoked Response Audiometry (BERA).

Discussion

AS is a rare neurodevelopmental disorder caused by a mutation or deletion of the maternally inherited UBE3A allele [11], and may present with severe learning difficulties, ataxia, seizures, subtle dysmorphic facial features, and a happy, sociable disposition [12]. In our reported case, developmental delayed was identified by pediatrician at the age of 3 months, and the child was promptly referred to multi-disciplinary investigation and therapy. Most children with Angelman syndrome are not able to achieve ambulation until three years of age, and some never walk and remain wheelchair-bound [8]. Our patient, however, developed deambulation by 3 years of age, despite jerky movements, as expected in this condition.

Hearing losses are not common in AS, and we found only three case reports describing patients with mild to profound hearing losses [13-15], one of them with frequent ear infections [17], and in one patient tomograms of the middle ears showed mildly decreased size of the right semicircular canals [13]. In our case there were no abnormalities in hearing evaluation until the age of 7 years, nor there were any Computed Tomography (CT) findings.

The management of this condition is mainly symptomatic and involves mutidisciplinary therapies, appropriate for the physical and neurological problems encountered in this condition [12]. As patients have general developmental delay, it is important the organization of an early, individualized, and active intervention program, right after diagnosis, wich includes physiotherapy, occupational therapy, speech and language therapy. Patient must be referred to an ophthalmologist if strabismus is suspected [8].

Epilepsy is present in 85% of patients within the first three years of life [3], with its onset varying from 1 month to 20 years [16]. Seizures are often severe and hard to control, typically most severe in early childhood but may recur in adulthood [16]. Efficacy has been reported for valproate, clonazepam, topiramate, lamotrigine and levetiracetam [6]. The most effective drugs are sodium valproate, clonazepam, and phenobarbital [3], while drugs such as carbamazepine and vigabatrin are ineffective and may cause worsening of seizures [8]. In the present case, seizures began at 1 year-old with an adequate control after use of Levetiracetan. There are reports that ketogenic diet is helpful in some children with untreatable epilepsy, as it causes a switch in brain metabolic pathways: it bypasses all malfunctioning glycolytic pathways of metabolism by supplying fat as an alternative source of energy [17-19].

There is still no curative treatment, however some novel gene-based therapies are in the development pipeline. For instance, topoisomerase inhibitors and antisense oligonucleotides are being developed to directly inhibit *UBE3A-ATS*, as well as artificial transcription factors are being developed to "super activate" *UBE3A* or inhibit *UBE3A-ATS* [18,19]. Recently, Wolter., *et al*. [11] designed 260 *Staphylococcus pyogenes* Cas9 guide RNAs that target putative regulatory regions and genes in or near *UBE3A-ATS*, which is a long non-coding RNA that silences the paternally inherited *UBE3A* allele in neurons. They found that Cas9 targeted to Snord115 genes (small nucleolar RNAs that are clustered in the 3' region of *UBE3A-ATS*), when packaged into an adeno-associated virus and administered to a mouse model of AS during the embryonic and early postnatal stages, can unsilence paternal *UBE3A*, restoring its function throughout life, providing a path towards a disease-modifying treatment for this syndrome.

Conclusion

As Angelman Syndrome is characterized by developmental delay, including speech impairment, it is essential that all physicians have a high degree of suspicion for this condition, noting its clinical presentation and assessing patients's hearing development, in an environment of multidiscipline approach, with consequent improvement in their quality of life.

Conflict of Interest

None.

Bibliography

1. Angelman Harry. "'Puppet' Children A Report on Three Cases". *Developmental Medicine and Child Neurology* 7 (1965): 681-688.
2. Ashrafzadeh, Farah., *et al*. "Angelman Syndrome: A Case Report". *Iranian Journal of Child Neurology* 10.2 (2016): 86-89.
3. Fiumara Agata., *et al*. "Epilepsy in patients with Angelman syndrome". *Italian Journal of Pediatrics* 36 31 (2010).
4. Bonello Daniela., *et al*. "Angelman Syndrome: Identification and Management". *Neonatal Network: NN* 36.3 (2017): 142-151.

5. Knoll J H., *et al*. "Angelman and Prader-Willi syndromes share a common chromosome 15 deletion but differ in parental origin of the deletion". *American Journal of Medical Genetics* 32.2 (1989): 285-290.

6. Buiting Karin., *et al*. "Angelman syndrome - insights into a rare neurogenetic disorder". *Nature Reviews Neurology* 12.10 (2016): 584-593.

7. Magenis R E., *et al*. "Is Angelman syndrome an alternate result of del (15) (q11q13)?". *American Journal of Medical Genetics* 28.4 (1987): 829-838.

8. Madaan Manik and Magda D Mendez. "Angelman Syndrome". StatPearls, StatPearls Publishing, 14 August (2021).

9. Jana Nihar Ranjan. "Understanding the pathogenesis of Angelman syndrome through animal models". *Neural Plasticity* 2012 (2012): 710943.

10. Khatri Natasha and Heng-Ye Man. "The Autism and Angelman Syndrome Protein Ube3A/E6AP: The Gene, E3 Ligase Ubiquitination Targets and Neurobiological Functions". *Frontiers in Molecular Neuroscience* 12 (2019).

11. Wolter Justin M., *et al*. "Cas9 gene therapy for Angelman syndrome traps Ube3a-ATS long non-coding RNA". *Nature* 587.7833 (2020): 281-284.

12. Clayton-Smith J and L Laan. "Angelman syndrome: a review of the clinical and genetic aspects". *Journal of Medical Genetics* 40.2 (2003): 87-95.

13. Williams C A., *et al*. "Angelman syndrome in a daughter with del (15) (q11q13) associated with brachycephaly, hearing loss, enlarged foramen magnum, and ataxia in the mother". *American Journal of Medical Genetics* 32.3 (1989): 333-338.

14. Tekin M., *et al*. "Fluorescence in situ hybridization detectable mosaicism for Angelman syndrome with biparental methylation". *American Journal of Medical Genetics* 95.2 (2000): 145-149.

15. Huang Bing and James Bartley. "Partial hexasomy of chromosome 15". *American Journal of Medical Genetics Part A* 121A.3 (2003): 277-280.

16. Larson Anna M., *et al*. "Angelman syndrome in adulthood". *American Journal of Medical Genetics Part A* 167A.2 (2015): 331-344.

17. Evangeliou Athanasios., *et al*. "Ketogenic diet in a patient with Angelman syndrome". *Pediatrics International : Official Journal of the Japan Pediatric Society* 52.5 (2010): 831-834.

18. Tan Wen-Hann and Lynne M Bird. "Pharmacological therapies for Angelman syndrome". "Pharmakologische Therapien bei Angelman-Syndrom". *Wiener medizinische Wochenschrift* (1946) 167.9-10 (2017): 205-218.

19. Tan Wen-Hann and Lynne M Bird. "Angelman syndrome: Current and emerging therapies in 2016". *American Journal of Medical Genetics Part C, Seminars in Medical Genetics* 172.4 (2016): 384-401.