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Case Report
Relato de Caso

Language, neurodevelopment, and behavior in Angelman syndrome: a case report

Linguagem, neurodesenvolvimento e comportamento na Síndrome de Angelman: relato de caso

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Keywords

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ABSTRACT

Purpose: This study aimed to present findings on language, behavior, and neurodevelopment in a girl diagnosed with Angelman Syndrome, evaluated when she was three and eight years old. **Methods**: The following evaluation instruments were used: Observation of Communication Behavior, Early Language Milestone (ELM) Scale, and Denver Developmental Screening Test, 2nd edition (DDST-II). **Results**: In this case report, presence of AS phenotype signals such as wide mouth and wide-spaced teeth, tongue thrusting, strabismus, up slanting palpebral fissures, and sialorrhea are verified. Expressive and receptive deficits were verified in the language assessment, with the absence of orality and loss of comprehension with very similar performances in both evaluations. The ELM and DDST-II tests indicated severe impairment of all abilities evaluated at both three and eight years of age. Performance was quite similar in both evaluations in all areas of child development. Little progress was observed over time despite the great therapeutic and educational investment. **Conclusion**: The presence of a complex scenario such as AS demands high complexity clinical needs, a situation that is worsened due to scarcity of therapeutic resources that could minimize the harmful impacts of AS and culminate in increased quality of life for the AS population and their families.

Palavras-chave

Síndrome de Angelman
Linguagem Infantil
Desenvolvimento Infantil
Desempenho Psicomotor
Comportamento

RESUMO

Objetivo: O objetivo deste estudo é apresentar achados de linguagem, comportamento e neurodesenvolvimento de uma menina com diagnóstico da Síndrome de Angelman, avaliada aos três e aos oito anos. **Método**: Os instrumentos de avaliação foram Observação do Comportamento Comunicativo, *Early Language Milestone Scale* (ELM) e Teste de *Screening* de Desenvolvimento DENVER-II (TSDD-II). **Resultados**: No caso apresentado, verifica-se a presença dos sinais fenotípicos da SA, tais como boca larga, dentes espaçados, língua protuberante, estrabismo, fissuras palpebrais ascendentes e sialorreia. Na avaliação de linguagem, foram verificados déficits expressivos e receptivos, com ausência de oralidade e prejuízos na compreensão. O TSDD-II e a ELMS indicaram grave comprometimento de todas as habilidades avaliadas aos três e aos oito anos. O desempenho encontrado, nas duas avaliações, foi muito semelhante em todas as áreas do desenvolvimento infantil. Ao longo dos anos, verificou-se pouca evolução, apesar do grande investimento terapêutico e educacional. **Conclusão**: A presença de um quadro complexo como a SA demanda necessidades clínicas de alta complexidade, situação agravada frente à escassez de recursos terapêuticos que possam minimizar os impactos deletérios da síndrome, culminando em comprometimento da qualidade de vida da população com a SA, bem como de suas famílias.

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INTRODUCTION

Angelman syndrome (AS) is a rare disorder first described in 1965. It significantly compromises all areas of child development, with an impact on the quality of life of children and their families[1]. Its prevalence is estimated to be 1:15,000 live births[1,2].

The main etiological factor of AS is deletion in chromosome 15q11-q13[1-5], resulting in lack of expression of the maternal ubiquitin-protein ligase E3A (UBE3A) gene, which is essential for synaptic development and neuronal plasticity[1]. Other genetic polymorphisms of different sub-molecular classes of chromosome 15 have been described in the literature; however, they present lower prevalence, and maternal deletion occurs in 70-80% of the cases[1,3,6].

The most common clinical findings were particularities such as frequent and decontextualized smiling and laughter, a characteristic that composes a differential diagnostic criterion compared with other syndromes manifested with global developmental delay. Intellectual disability is usually severe in all cases described in the literature[2,5]. Motor behavior is characterized by difficulties in controlling and planning, impacting the acquisition and execution of gross and fine motor skills, with presence of ataxic gait and/or limb tremor[1,3,7,8]. Additional abnormalities are observed in this syndrome, such as wide mouth, wide-spaced teeth, upslanting palpebral fissures, prognathism, strabismus, scoliosis, aggressiveness, and anxiety[1,3,5]. Sleep disorders have also been described as traits in this syndrome[1,5].

Communication is also particularly affected in AS. It is extremely restricted and compromised: the skills are slowly acquired and pre-intentional behaviors do not progress typically. Communicative and linguistic deficits are attributed to intellectual changes, which hinder the acquisition of communicative abilities, and there are motor changes suggestive of speech apraxia in childhood[7-10]. Authors have pointed out that regardless of the molecular sub-class of genetic changes language skills are severely compromised, suggesting that the lack of the UBE3A gene may be essential for the development of these skills[3].

Diagnosis is complex, involving clinical, neurological and genetic analyses. As the unique clinical characteristics of AS do not appear before the first year of life, the definite clinical diagnosis is usually postponed[8]. The role played by speech-language pathologists in the diagnostic process and case management is fundamental so that communication skills and other clinical signs can be observed and verified, contributing to the early detection of signs suggestive of AS. However, there are still limitations in the evaluation and treatment of the linguistic aspects of children with this syndrome, because many of the instruments available for their language assessment do not allow assess restricted communicative abilities in this population[3,7]. In addition, the standardized methods available for the therapeutic process in children who present atypical behaviors associated with severe intellectual impairment present some limitations, resulting in unmet clinical needs and a consequent negative impact on development and quality of life[1,3].

Therefore, this study aimed to present findings on language, behavior, and neurodevelopment of a girl diagnosed with AS, evaluated when she was three and eight years old.

CASE PRESENTATION

The legal guardian signed an Informed Consent Form (ICF) prior to study commencement, and the other ethical principles (CAAE: 42356815.1.0000.5417) were in compliance with Resolution 466/12 of the National Council of Ethics in Research (CONEP).

The girl in this case report was first assisted when she was three years old and reassessed when she was eight. The information presented ahead was provided by her mother during anamnesis. The girl's record showed a 37-year-old mother and a 40-year-old father when she was born. No inbreeding was reported. During the gestational period, the mother had anemia, and reduced fetal movement was observed. The girl was born through a Cesarean section at 38 weeks of gestation with 2,450 g weight and 43 cm height. Apgar score at the first and fifth minutes was nine. After birth, the girl presented hypotonia, inactivity, respiratory changes, and cyanosis, requiring oxygen therapy and a 2-day stay in Intensive Care Unit (ICU).

During childhood, the girls present frequent and unimpressive crying and sleep disorder: she usually slept only three hours a night, and only five years later started to sleep better with the use of medication. She presented repetitive behaviors and mannerisms. At one year and eight months of age, epileptic seizures began, and she began to make continuous use of medication to control them. Electroencephalography (EEG) revealed a generalized epileptiform discharges, severe disturbance of background activity, and hypsarrhythmia. The diagnosis of AS was reached when the child was one year and nine months old, through a genetic examination that indicated deletion in chromosome 15q11-q13. At the same time, the therapeutic processes (physical, speech-language and occupational therapies) were started, showing limited progress. At the rehabilitation institution, a multidisciplinary evaluation was performed, and intellectual disability was diagnosed. At three years old, the rehabilitation team requested a speech-language pathology diagnostic evaluation.

The mother reported that, since early childhood, the girl had an interest in people (her parents), preference for toys with wheels, and fascination by water games and plastic containers, which she manipulated in a repetitively and unconventionally. Regarding communicative behavior, she said that the child utters only meaningless vowel sounds, and does not seem to understand simple orders, and seems to understand only two words: "not pap" (for food, in an immediate and concrete context), in addition, she does not use gestures to communicate. To draw the attention of others, the girl seeks eye contact, and there are situations of self-harm and/or throwing of objects. She uses people as instruments. Despite the treatments she has undergone, communication has not evolved. In her history of neuropsychomotor development, she sat with support at one year and six months, stood up at two years and six months, and walked at three years of age. Changes in balance have been described, and they have been accentuated more recently

with the evolution of scoliosis. She does not perform activities of daily living independently and has got no sphincter control. She accepts to be touched and affection only from her parents.

The child has attended regular school since she was 4 years old. In this environment, she is monitored by a teacher of the special education program, but cannot keep up with the activities. In her out-of-school hours, she attends a specialized institution, a special school, and physical, speech-language and occupational therapies weekly (two speech-language therapy and occupational therapy meetings and three physical therapy sessions). As reported by her mother, the speech-language therapeutic process focuses at attention, interaction, symbolic play, and language functionality. At 3 years of age, alternative supplemental communication procedures were started, but with little evolution. In physical therapy, the focus is on the maintenance of gait and static and dynamic balance, whereas in occupational therapy, the objective has been based on activities that favor independence in her daily routine.

Speech-language pathology assessments were performed when she was three and eight years old using the following instruments: Observation of Communication Behavior/clinical evaluation, Early Language Milestone (ELM) Scale[11], and Denver Development Screening Test (DDST-II)[12]. Behavioral observation was carried out in a structured environment and in semi-directed situations, thus the ludic and interactive activities were proposed with several pre-selected toys and in concrete conditions to verify the communicative abilities of the child through actions with objects and the evaluators, who were present during the assessments. The ELM scale was used to obtain information on language behavior regarding its expressive and receptive aspects, allowing comparison between them, and on visual abilities. Although this scale is intended for application in children aged 0-36 months, it is also used in cases where language behavior is incompatible with chronological age; therefore, it was eligible for application in this case. The DDST-II was used to verify the child's performance in the main areas of child development (personal-social, fine motor-adaptive, language, and gross motor), allowing an overall assessment of the child, in addition to providing information on language and communication.

In the Observation of Communication Behavior conducted at three years of age, the child showed maintenance of eye contact with the mother and limited attention to specific objects and sound stimuli, without interaction with the evaluators or presence of orality. Behaviors of flapping and repetitive manipulation were observed, but without any function to the objects available in the evaluation environment. When she was eight years old, assessment showed the following behaviors other than those observed at the age of three years: eye contact with the evaluator, undifferentiated vocalizations with no contextual meaning, absence of flapping, and the presence of decontextualized laughter. At both ages, she did not show imitation of gestures or oral productions, and was not able to follow simple orders.

Chart 1 shows signs and symptoms of AS compiled from the literature[1-5,7-9] and the phenotypic characteristics presented by the evaluated child. The findings presented in this chart and the other clinical and genetic findings corroborate the diagnosis of AS.

Table 1 shows the results of the evaluations performed at three and eight years of age using the ELM and DDST-II tools. The developmental assessments in the areas of language (expressive and receptive), gross motor, fine motor-adaptive, and personal-social were performed at two moments with an interval of five years between them, and the performance levels observed in the two assessments were very similar in all areas of development to that of a child aged <14 months.

Chart 1. Signs and symptoms of Angelman syndrome (AS)

Characteristic Signs and Symptoms	Problems observed in this case report
Intellectual disability	(+)
Communicative deficit / absence of speech	(+)
Decontextualized laughter and smiles	(+)
Neuropsychomotor development delay	(+)
Hypermotor behavior	(+)
Hypotonia	(+)
Ataxia	(+)
Balance changes	(+)
Oral motor apraxia	(+)
Skull circumference changes	(+)
Microcephaly	(+)
Seizures	(+)
Sleep disorders	(+)
Fascination by water, paper and plastic	(+)
Aggressiveness	(+)
Abnormal EEG patterns	(+)
Hypopigmentation	NO
Scoliosis	(+)
Wide mouth	(+)
Wide-spaced teeth	(+)
Prognathism	NO
Tongue thrusting	(+)
Strabismus	(+)
Deep-set eyes	NO
Upslanting palpebral fissures	(+)
Sialorrhea	(+)

Caption: NO: not observed, (+) present, (-) absent

Table 1. Performance comparison in development areas at three and eight years of age

ELMS		
Areas	3 years old	8 years old
	Age range of performance	
Auditory Expressive	4 months	7 months
Auditory Receptive	14 months	14 months
Visual	9 months	9 months
DDST-II		
Areas	3 years old	8 years old
	Age range of performance	
Personal-social	5 months	6 months
Fine motor-adaptive	7 months	9 months
Language	6 months	7 months
Gross motor	12 months	14 months

DISCUSSION

Angelman syndrome (AS) is a complex clinical condition that, in spite of having relatively well-defined phenotype and etiology[2,3], still presents restricted clinical needs, including diagnosis and therapeutic treatment, that along with the severity of the cases, have shown little evolution over time[1,5].

Genetic examination conducted in the child in this case report revealed deletion in chromosome 15q11-q13. However, there are cases in which the genetic tests do not show conclusive results and in which there is presence of genetic polymorphisms, requiring comprehensive analysis of the clinical and laboratory characteristics so that clinical diagnosis of greater significance can be achieved and interventions can be started[1,3,6].

In the present case, the main phenotypic signs of AS (Chart 1) were verified: severe intellectual disability, lack of speech, delayed acquisition and development of motor skills, decontextualized laughter, scoliosis, wide mouth, wide-spaced teeth, tongue thrusting, sialorrhea, upslanting palpebral fissures, microcephaly, seizures and sleep disorder, corroborating the specific scientific literature[1-5,7,8]. Gestational history without complications is common in AS patients[5,8]. In this case report, anemia during the gestational period may be an occasional finding.

There was a 5-year interval between the assessments; however, little progress was observed in this case even though the child underwent rehabilitation programs in the areas of speech, physical and occupational therapy and attended a regular and a specialized school. Improvement was observed only in hyperactivity, self-aggression, sleep disorder, and epileptic seizures, but through drug treatment. The literature describes the need for studies on the implementation of protocols and therapeutic methods focused specifically on the etiology and clinical manifestations that favor the development of children with AS[1,7,10], considering that there are great clinical-therapeutic, social and emotional investments with limited return[1,10].

Communication is one of the areas drastically affected in this syndrome, with expressive and receptive deficits and absence of oral production or production of isolated vowel sounds without communicative intention. The extent of communication impairment is associated with cognitive issues[7,9], because they are conditions with presence of severe intellectual disability, which impairs the understanding of symbolic language and interferes with the development of abilities such as joint attention and other neurocognitive processes. Nevertheless, the communication skills of individuals with AS are also associated with motor issues. Quinn and Rowland[9] reported that children with AS present primitive vocalizations, with reflex utterances of isolated vowel sounds or laughter, tending to produce central and low-pitched vowels, with few high-pitched vowels, and rare consonant-vowel combinations. Thus, the difficulties with motor planning and execution also extend to the articulating organs of speech, characterizing a condition of childhood apraxia of speech that, when combined with the condition severity, hinders the development of oral communication, especially regarding speech. Additionally, the receptive aspects are affected and the ability to understand contexts is precarious[7], which are consistent with the findings of this case.

The use of alternative communication methods is common in cases with deficits in expressive language, thus they can be introduced by different procedures with the use of images, graphic signals, and/or gestures[10,13]. The choice of the method to be used in AS cases is complex because of the extent of the impairments. However, authors who compared the use of oral, graphic and gestural methods concluded that graphic methods were more effective and accurate[10]. Training using gestures, with parents acting as self-administrators of the technique in their children, demonstrated being a viable method for communication, though with limited results[13]. However, the results of these studies are often inconclusive, since the improvements were subtle and there were limitations to the instruments available to measure scores related to improvement of the conditions, and many analyses are performed using subjective methods, including parent report[7,10,13]. Since these are rare cases, the therapeutic procedures described were performed in single cases. In addition, authors[7] have suggested that the acquisition of gestures and other communication skills occur very slowly, and intentional behaviors may not progress as expected as in children with typical development. The process of acquisition and development of communication skills is complex even with the use of alternative communication procedures[7]. The communication pattern of the child in the present case corroborates the findings in the literature, as the pre-intentional behaviors were not noticed, as described in the results of the evaluations. In the therapeutic process of this child, alternative communication procedures are being used, but with little progress and, according to the mother, the girl does not seem to understand the language, does not show interest in interaction with figures and/or objects, and does not pay attention to the stimuli, throwing whatever is put in her hand (*sic*). The family refers to maintaining therapeutic procedures so that the child does not lose what she has already achieved, especially when it comes to walking and staying in an educational environment.

Thus, there are no treatments focused on the etiology underlying AS, and current treatments are symptomatic for sleep disorders and seizures, but therapies for the presently prescribed behavioral interventions have little empirical support[1].

The role of speech-language pathologists in the assessment and intervention team is fundamental, since they are the professionals qualified to verify intentionality and communicative and verbal comprehension functionality, even in children without orality; from these skills, the therapeutic process can be outlined. In addition, these professionals should be aware of the behavioral phenotype that will favor both the referral for medical diagnosis and the search of evaluation and intervention procedures that enable improvement in the activities of daily living and quality of life of individuals with AS and their families.

The presence of a severe and chronic condition, as in the cases of AS, undoubtedly results in a substantial burden on caregivers, with psychological, behavioral and physiological effects on their everyday life and health. Thus, studies are being conducted to verify the level of stress of these caregivers as a result of the presence of AS in the family routine[6].

Further studies are needed to search for technologies that can improve methodologies to benefit these individuals and their families.

FINAL COMMENTS

Presence of a complex condition, such as in Angelman syndrome (AS), highly demands equally complex clinical needs, which are not met and culminate in cases with little evolution over time.

Although the diagnosis of AS occurred early in this case report and the family invested in several therapeutic procedures, the results of the evaluations showed little progress, corroborating the findings in the literature regarding the course of this syndrome and its impact on child development. Therefore, the prognosis is often unfavorable, because clinical manifestations drastically affect and prevent full child development. This situation is aggravated by the scarcity of therapeutic resources that can minimize the deleterious impacts of AS, justifying the need for further studies and the development of new therapeutic measures so that scientific evidence can be improved, optimizing the performance of children with AS and other serious developmental disorders.

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REFERENCES

1. Wheeler AC, Sacco P, Caco R. Unmet clinical needs and burden in Angelman syndrome: a review of the literature. Orphanet J Rare Dis. 2017;12(1):164. http://dx.doi.org/10.1186/s13023-017-0716-z. PMid:29037196.
2. Cote-Orozco JE, Mera-Solarte PD, Espinosa-Garcia E. Neuropsychiatric phenotype of Angelman syndrome and clinical care: report of seven cases. Arch Argent Pediatr. 2017;115(2):e99-e103. http://dx.doi.org/10.5546/aap.2017.e99.
3. Wang K, Li YT, Hou M. Applicability of genetic polymorphism analysis for the diagnosis of Angelman syndrome and the correlation between language difficulties and disease phenotype. Genet Mol Res. 2016;15(2). http://dx.doi.org/10.4238/gmr.15027945.
4. Le Fevre A, Beygo J, Silveira C, Kamien B, Clayton-Smith J, Colley A, et al. Atypical Angelman syndrome due to a mosaic imprinting defect: case reports and review of the literature. Am J Med Genet A. 2017;173(3):753-7. http://dx.doi.org/10.1002/ajmg.a.38072. PMid:28211971.
5. Kocaoğlu Ç. Two sisters with angelman syndrome: a case series report. J Pediatr Neurosci. 2017;12(4):388-385. http://dx.doi.org/10.4103/JPN.JPN_55_17. PMid:29675084.
6. Adams D, Clarke S, Griffith G, Howlin P, Moss J, Petty J, et al. Mental health and well-being in mothers of children with rare genetic syndromes showing chronic challenging behavior: a cross-sectional and longitudinal study. Am J Intellect Dev Disabil. 2018;123(3):241-53. http://dx.doi.org/10.1352/1944-7558-123.3.241. PMid:29671635.
7. Grieco JC, Bahr RH, Schoenberg MR, Conover L, Mackie LN, Weeber EL. Quantitative measurement of communication ability in children with Angelman Syndrome. J Appl Res Intellect Disabil. 2018;31(1):e49-58. http://dx.doi.org/10.1111/jar.12305. PMid:27990716.
8. Dagli, AI, Mueller J, Wiliams CA. Angelman syndrome. Seattle: University of Washington; 1998. GeneReviews.
9. Quinn ED, Rowland C. Exploring expressive communication skills in a crosssectional sample of children and young adults with Angelman Syndrome. Am J Speech Lang Pathol. 2017;26(2):369-82. http://dx.doi.org/10.1044/2016_AJSLP-15-0075. PMid:28384804.
10. Hyppa Martin J, Reichle J, Dimian A, Chen M. Communication modality sampling for a toddler with Angelman syndrome. Lang Speech Hear Serv Sch. 2013;44(4):327-36. http://dx.doi.org/10.1044/0161-1461(2013/12-0108). PMid:24124202.
11. Coplan J. The early Language Milestone Scale. Austin: Pro-Ed; 1983.
12. Frankenburg WK, Doods J, Archer P, Bresnick B, Maschka P, Edelman N, et al. Denver II training manual. Denver: Denver Developmental Materials; 1992.
13. Calculator SN. Description and evaluation of a home-based, parent-administered program for teaching enhanced natural gestures to individuals with Angelman Syndrome. Am J Speech Lang Pathol. 2016;25(1):1-13. http://dx.doi.org/10.1044/2015_AJSLP-15-0017. PMid:26847597.

Author contributions

ATHT and DYC were responsible for collection and analysis the data, literature review, and writing of the manuscript; PAPC and SRVH contributed to data analysis and revision of the manuscript; DACL was responsible for collection and analysis of the data and writing of the manuscript.