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Angelman Syndrome: A Genetic Cause Of Absent Speech And Ataxia In Childhood – Case Report

Síndrome De Angelman: Uma Causa Genética De Ausência De Linguagem E Ataxia Na Infância – Relato De Caso

Síndrome De Angelman: Causa Genética De Ausencia De Lenguaje Y Ataxia En La Infancia. Informe De Caso

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ABSTRACT

Introduction: Angelman syndrome (AS; OMIM #105830) is a rare neurodevelopmental disorder characterized by severe developmental delay and severe intellectual disability, gait ataxia and/or limb incoordination, absence of language, and happy behavior that includes unmotivated and excessive laughter. It occurs due to *imprinting* defects with loss of gene expression at the 15q11.2-q13 *locus* of maternal origin; maternal deletion of 15q11.2-q13, paternal uniparental disomy of 15q11.2-q13 or a heterozygous pathogenic variant in UBE3A. The incidence of AS is 1:12,000 to 1:24,000 births. **Objective:** Report a child diagnosed with AS. **Case Description:** Male, 4 years old. Referred due to global developmental delay. Absent speech, gait ataxia and paroxysmal laughter. The only child of healthy, non-consanguineous couple, with no family history of other similar cases, malformations or genetic diseases. **Discussion:** The proband presented the typical AS phenotype, and the diagnosis and genetic mechanism were confirmed through molecular MLPA and Array-CGH, respectively.

Keywords: Angelman Syndrome; Genomic Imprinting; Ataxia; Absent Speech.

RESUMO

Introdução: A síndrome de Angelman (AS; OMIM #105830) é um raro distúrbio do neurodesenvolvimento caracterizada clinicamente por atraso grave no desenvolvimento neuropsicomotor (DNPM), deficiência intelectual grave, ataxia de marcha e/ou incoordenação dos membros, ausência de linguagem e comportamento feliz que inclui risos desmotivados e excessivos. Ocorre por erro na informação genética proveniente da mãe (*imprinting* genético), com perda da expressão de genes do *locus* 15q11.2–q13 de origem materna; deleção do *locus* 15q11.2–q13 materna, dissomia uniparental paterna do cromossomo 15 ou por variante patogênica em heterozigose do gene *UBE3A*. A incidência estimada da AS é de 1:12.000 a 1:24.000 nascimentos. **Objetivo:** Relatar uma criança com diagnóstico de AS. **Descrição do Caso:** Masculino, 4 anos. Referido por atraso global do DNPM. Evoluiu com ausência de fala, ataxia de marcha e risos desmotivados. Filho único de casal não consanguíneo, saudável e sem histórico de outros casos semelhantes, malformações ou doenças genéticas na família. **Discussão:** O probando apresenta o fenótipo típico da AS, sendo confirmados o diagnóstico e o mecanismo genético através de exames moleculares de MLPA e Array-CGH, respectivamente.

Palavras-chave: Síndrome de Angelman; *Imprinting* Genômico; Ataxia; Ausência de Fala.

RESUMEN

Introducción: El síndrome de Angelman (SA; OMIM #105830) es un trastorno poco frecuente del neurodesarrollo que se caracteriza clínicamente por un retraso grave en el desarrollo neuropsicomotor (NPMD), discapacidad intelectual grave, ataxia de la marcha y/o incoordinación de las extremidades, ausencia de lenguaje y comportamiento alegre que incluye risa desmotivada y excesiva. Se produce debido a un error en la información genética de la madre (impronta genómica), con pérdida de expresión de genes del locus 15q11.2-q13 de origen materno; deleción del locus materno 15q11.2-q13, disomía uniparental paterna del cromosoma 15 o por una variante patogénica heterocigótica del gen UBE3A. La incidencia estimada de SA es de 1:12.000 a 1:24.000 nacimientos. **Objetivo**: Informar sobre el caso de un niño con diagnóstico de SA. **Descripción del caso**: Niño de 4 años. Derivado por retraso global en NPMD. El paciente presentó ausencia de habla, ataxia de la marcha y risa desmotivada. Hijo único de una pareja sana, non consanguínea, sin antecedentes familiares de casos similares, malformaciones ni enfermedades genéticas. **Disción**: El probando presenta el fenotipo típico de SA, con diagnóstico y mecanismo genético confirmados mediante pruebas moleculares con MLPA y Array-CGH, respectivamente.

Palabras clave: Síndrome de Angelman; Impronta Genómica; Ataxia; Ausencia del Habla.

INTRODUCTION

Angelman syndrome (AS; OMIM #105830) was first described in 1965 by Harry Angelman, a British pediatrician who reported three children with severe intellectual disability, absence of language, excessive unmotivated laughter, and ataxic movements, whom he called "puppet children".[1] In 1967, Bower and Jeavons described two children whose clinical characteristics included delayed neuropsychomotor development, severe intellectual disability, hypotonia, ataxia, epilepsy, absence of language, and a characteristic face with a large jaw and open mouth.[2] Only in 1982 was the term "puppet children" replaced by Angelman syndrome, as the initial name was considered pejorative for the patient and their family.[3]

AS is a rare neurodevelopmental disorder of genetic origin that occurs due to the loss of function of the maternal copy of the *UBE3A* gene (*UBE3A* – OMIM *601623 – Ubiquitin-Protein Ligase E3A – *locus* 15q11.2),[4] responsible for encoding a protein that functions both as an E3 ligase in the ubiquitin proteasome pathway and as a transcriptional coactivator. The *UBE3A* gene is subject to genomic imprinting, with specific maternal preferential expression in the brain and, more specifically, in neurons, but does not occur in glial cells.[5] AS has an estimated incidence of between 1:12,000 and 1:24,000 births.[6] In Brazil, the authors did not find epidemiological data regarding AS.

The etiology of AS is not Mendelian, being explained through four distinct molecular mechanisms, which directly involve genetic counseling and recurrence risk, all involving the loss of expression of the maternally inherited *UBE3A* gene: (1) Deletion of the 15q11.2–q13 region of the maternal chromosome, occurring in approximately 70% of cases;[7] (2) Paternal uniparental disomy of chromosome 15, with the imprinting[a] pattern occurring in both critical regions of the paternally inherited chromosome 15, 2 to 3% of cases and, consequently, the *UBE3A* gene is not expressed, representing approximately 2% of cases;[7] (3) Imprinting errors in the 15q11.2-q13 region of the maternally inherited chromosome 15, promoting the non-expression of the *UBE3A* gene, occurring in 2 to 3% of cases;[7,8] and (4) Pathogenic heterozygous variant of the maternally inherited *UBE3A* gene, occurring in approximately 10% of cases.[7]

AS is characterized by clinical manifestations that mainly include severe delay in neuropsychomotor development (NPMD), severe intellectual disability, gait ataxia and/or limb incoordination, absence of language, and happy behavior that includes unmotivated and excessive laughter.[1,9,10] In addition, microcephaly, seizures, and sleep disorders are quite common.[11,12] Other findings that may also be observed are autism spectrum disorder (ASD), hyperactivity, strabismus, macrostomia, spaced teeth, open mouth, protruding tongue, prognathism, sialorrhea, feeding problems, hypotonia during childhood, scoliosis, constipation, attraction/fascination with water.[9] In relation to their relatives, hypopigmentation of the skin, hair, and light eyes may occur in cases where there is a chromosomal deletion, leading to haploinsufficiency of the *OCA2* gene (located near the gene *UBE3A*), the *OCA2* gene is responsible for encoding a protein involved in tyrosine metabolism that is related to the development of skin, hair, and iris pigmentation.[13,14]

The aim of this study is to report on a child diagnosed with AS.

CASE DESCRIPTION

Proband – male, 4 years old. Referred to the Medical Genetics service at 3 years and 11 months of age by the Family Clinic for global delay in neuropsychomotor development.

He is the only child of a non-consanguineous couple, healthy and with no history of other similar cases, malformations or genetic diseases in the family. Mother was 37 years old at the time of pregnancy. Gesta I, Para I. Pregnancy without complications and eight

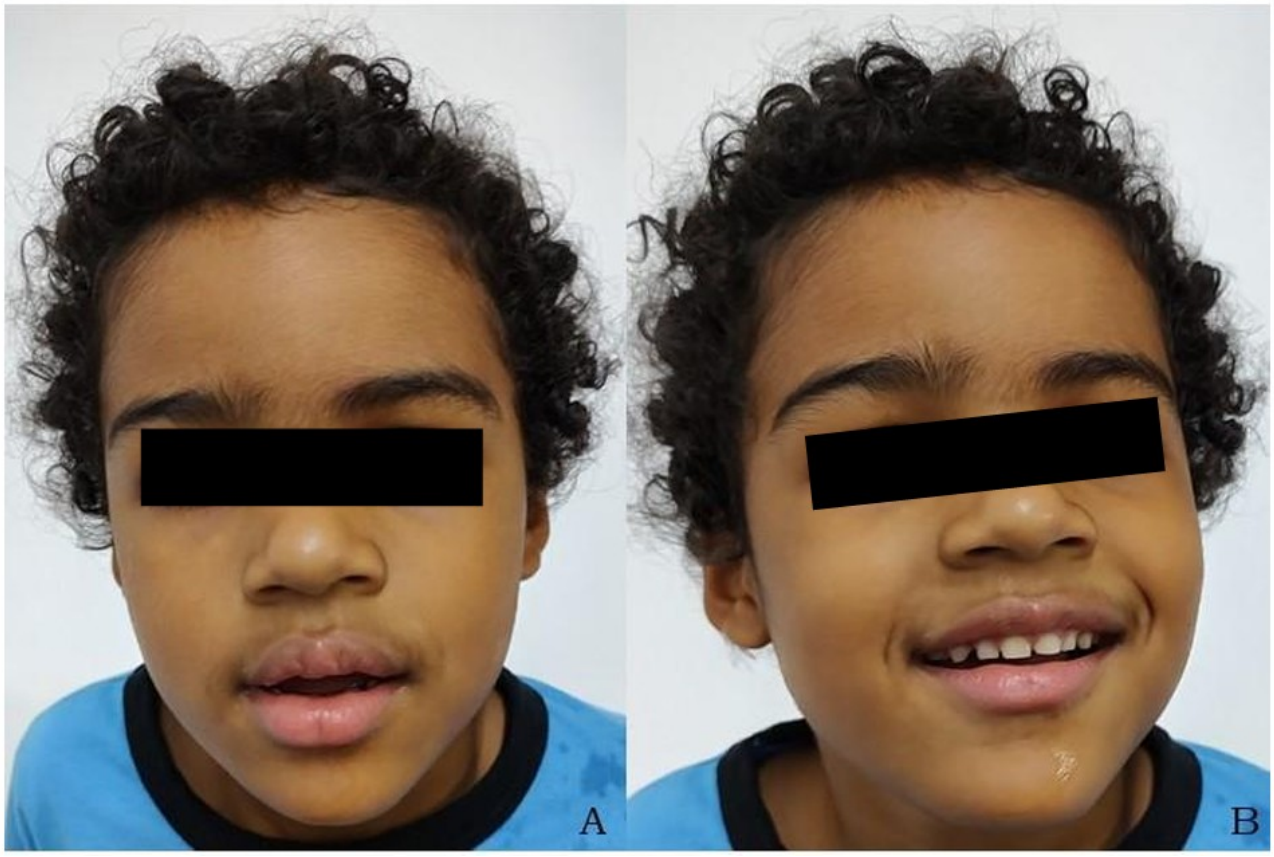
[a] ***Imprinting*** this is the term used to determine the parental origin of genes, chromosomal regions, or chromosomes that are not expressed ("silenced").

prenatal visits. Denies exposure to known teratogenic agents. Cesarean delivery at 37 weeks, without perinatal asphyxia (Apgar score[15] 8/9 at the first and fifth minute, respectively). Weighed 2,380g (below p10), measured 47cm (between p3 and p15), head circumference 34cm (between p15 and p50). Small for gestational age.[16] No perinatal complications. Normal neonatal screenings. Discharge from the maternity ward at 72 hours of life.

At 15 months of age, the parents reported to the pediatrician that the infant was not speaking or walking, and he was then referred to neuropediatrics and otolaryngology.

Physical and morphological examination at the first evaluation, in Genetics, showed normal height (50th percentile), normocephaly (between 15th and 50th percentiles). Hypotonia. Black and curly hair, broad forehead, hypertrichosis on the forehead, synophrys, long eyelashes, epicanthus, square nasal base, depressed nasal bridge, short philtrum, macrostomia with open mouth, thick and everted lips, spaced teeth, sialorrhea, prognathism, unmotivated laughter (Figure 1). Ataxic gait on tiptoes, unstable, in a position of flexion of the wrists and elbows. Absence of language, hyperactivity and easily excitable, ASD, sleep-wake cycle alterations, fascination with water and crumpled paper.

Figure 1 - Photos of the proband – broad forehead, hypertrichosis on the forehead, synophrys, short philtrum, thick and everted lips (A). Macrostomia, open mouth, spaced teeth, sialorrhea (B).



Complementary exams: normal magnetic resonance imaging of the skull, cervical spine, thoracic spine and lumbosacral spine. Normal electroencephalogram, brainstem evoked potential, echocardiogram and total abdominal ultrasound. Normal amino acid chromatography. Karyotype 46, XY.[20] Molecular research for fragile X syndrome negative. Comparative array genomic hybridization (array-CGH)[b] of peripheral blood revealed a 2,068kb deletion in the 15q11.2-q12

[b] **Array comparative genomic hybridization (array-CGH)** is a molecular biology technique used to identify chromosomal microdeletions or microduplications (sizes smaller than 5,000 Kb) that cannot be identified by karyotyping.

region or arr 15q11.2-q12 (24141964_26210817)x1 encompassing 101 genes, including the *UBE3A* gene. Methylation analysis using the MLPA (Multiplex Ligation-dependent Probe Amplification)[c] technique of the 15q11.2 region of peripheral blood revealed an altered methylation pattern, detecting only the unmethylated allele, thus confirming the presence of the paternal allele and the absence of the maternal allele in the analyzed chromosomal region.

DISCUSSION

Chart 1 shows the described phenotype of AS correlated with the phenotype of the proband, who obtained positive findings in more than 50% of the parameters, a child with developmental delay, absence of speech, gait ataxia, typical wrist and elbow flexion position, unmotivated laughter, and facial dysmorphisms characteristic of AS. On the other hand, the proband does not present hypopigmentation of the skin, hair, and iris, which is reported in the literature as observed only in cases of deletion, a molecular mechanism identified in the proband. In this study, however, the deletion did not involve the *OCA2* gene (*OCA2* – OMIM *611409 – Melanosomal Transmembrane Protein – locus 15q12-q13.1) responsible for encoding a protein that corresponds to the mouse mutant “pink eye dilution” (p). Protein plays a role in regulating the pH of melanosomes.[17]

[c] **MLPA (Multiplex Ligation-dependent Probe Amplification)** is a molecular biology technique that allows the evaluation of alterations in DNA methylation, a process that regulates gene expression (epigenetic defects).

Chart 1 – Angelman syndrome phenotype according to the OMIM "Clinical Synopsis", correlated with the proband's phenotype.

Phenotype	*Proband*
Obesity (older children)	**NO**
Facial dysmorphia (Head and Neck)	
Postnatal microcephaly	**-**
Brachycephaly	**-**
Occipital plane	**-**
Occipital sulcus	**-**
Prognathism	**+**
Strabismus	**-**
Ocular hypopigmentation	**-**
Refractive errors (astigmatism, hyperopia, myopia)	**NO**
Macrostomia	**+**
Protruding tongue	**-**
Sialorrhea	**+**
Spaced teeth	**+**
Scoliosis	**NO**
Skin hypopigmentation (observed only in cases of deletion)	**-**
Neurological (Central Nervous System)	
Delay at DNPM	**+**
Severe intellectual disability	**+**
Absence of speech	**+**
Ataxia with jerky arm movements	**+**
March with a broad base	**+**
Clumsy, unstable	**+**
Limb tremor	**-**
Hypotonia	**+**
Convulsions	**-**
Hyperreflexia	**-**
Typical position of flexion of the wrists and elbows	**+**
Alteration of the sleep-wake cycle	**+**
Electroencephalographic changes	**-**
Mild cortical atrophy identified on CT scan or MRI	**-**
Neurological (Psychiatric and Behavioral)	
Unmotivated laughter	**+**
Easily excitable	**+**
Attraction/fascination with water	**+**
Attraction/fascination with crumpled items (paper, plastic)	**+**

Caption: Not observed (NO), Present (+), Absent (-).

AS is a rare neurodevelopmental disorder and usually occurs as a result of a *de novo* genetic alteration, that is, a sporadic case.[18] Thus, the authors emphasize that clinical suspicion of AS should be considered by pediatricians in all children who present with clinical signs including developmental delay, intellectual disability, absence of language, gait ataxia, seizures, and behavioral changes such as unmotivated laughter, ASD, and/or hyperactivity. Considering that the pediatrician is, in most cases, the first medical professional to evaluate children with AS, it is essential that they are attentive to clinical signs suggestive of the syndrome. Given the relevance of early diagnosis of Angelman syndrome for clinical and therapeutic management, it is imperative that the general pediatrician be trained to identify its main signs and symptoms. Diagnostic suspicion allows for timely referral to a medical geneticist, who will perform etiological confirmation through appropriate molecular tests and the early institution of multidisciplinary interventions that will have a positive impact on the functional prognosis and quality of life of the patient and their family.

The reported proband presents the typical AS phenotype, confirmed through molecular tests that initially included the MLPA technique, demonstrating an altered methylation pattern of the 15q11.2 chromosomal region with the detection of only the unmethylated allele. Subsequently, array-CGH was performed, which demonstrated the genetic mechanism involved, identifying a heterozygous deletion in the 15q11.2-q12 region of the maternal chromosome encompassing 101 genes, including the *UBE3A* gene, which represents most AS cases. Thus, identifying the molecular mechanism responsible for causing AS in the proband was fundamental for conducting genetic counseling for the family and estimating the risk of recurrence, which in this case is less than 1%.[19]

Therefore, the authors emphasize that for all children suspected of having Angelman syndrome, the first test that should be requested is specific methylation PCR for AS. The deletion of the 15q11.2 chromosomal region can be identified by array-CGH or FISH (Fluorescence In Situ Hybridization).[20] On the other hand, karyotyping does not have the resolution capacity to detect chromosomal microdeletions (smaller than 5,000Kb), as was the case with the proband reported in this study, in which a loss of genetic material of 2,068Kb in size was identified.

There is no specific treatment for AS; the therapeutic approach is based on the symptoms presented by the patients. The follow-up should be carried out jointly by doctors from various specialties, and multidisciplinary rehabilitation therapies should ideally begin as early as possible. The proband is monitored by a pediatrician and geneticist, and undergoes therapies including speech therapy, occupational therapy, psychology, psychomotor therapy, and physiotherapy.

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