

Angelman syndrome with atypical presentation mimicking cerebral palsy: diagnosis and treatment challenges

Natã N.J. Graça^{1*}, Márcio L. Duarte^{2,3}, and Márcia Fernández-Cascardi⁴

¹Department of Internal Medicine, Universidade do Oeste Paulista, Campus Guarujá, Guarujá; ²Department of Radiology, Universidade de Ribeirão Preto, Campus Guarujá, Guarujá; ³Department of Radiology, Diagnósticos da América S.A., São Paulo; ⁴Department of Pediatric Neurology - Clínica Neurosantos, Santos. Brazil

Abstract

Background: Angelman syndrome (AS) is a rare genetic disorder caused by the lack of expression of the UBE3A gene, inherited maternally, and is associated with an abnormal chromosome 15q11-q13. Affects 1 in 12,000-20,000 individuals and is more commonly diagnosed in childhood, although some cases are missed in adulthood. This condition, which affects both genders equally, often is undiagnosed due to errors or underreporting. This case involves a patient with AS, initially misdiagnosed as cerebral palsy, presenting with severe developmental delay, autistic behaviors, hypotonia, and epilepsy. **Clinical case:** We describe the case of a 3-year and 10-month-old male patient with a family history of autism spectrum disorder and attention deficit hyperactivity presented with motor delay, severe hypotonia, brachycephaly, absence of trunk control, difficult-to-control epilepsy, and severe developmental delay (unable to walk or speak). Initial observations revealed he could not sit or crawl and had difficulty swallowing. He was prescribed risperidone and had follow-ups for ongoing issues. In 2022, he experienced a tonic-clonic seizure and was diagnosed with chronic non-progressive encephalopathy and epilepsy, leading to valproic acid treatment. Subsequent seizures led to adjustments in his medication regimen, including adding clonazepam, phenobarbital, and levetiracetam. Genetic testing confirmed a deletion in the Prader-Willi/AS critical region on chromosome 15. The patient is currently stable. **Conclusions:** AS is characterized by developmental delays, speech impairment, ataxia, and seizures, along with characteristic behaviors such as inappropriate laughter. The comorbidities associated with AS, such as seizures and ataxia, significantly increase the risk of injuries and accidents, leading to higher morbidity and mortality in patients.

Keywords: Angelman syndrome. Seizures. Ataxia. Epilepsy.

Síndrome de Angelman con presentación atípica imitando parálisis cerebral: desafíos en el diagnóstico y tratamiento

Resumen

Introducción: El síndrome de Angelman (SA) es un trastorno genético raro causado por la falta de expresión del gen UBE3A, heredado de forma materna, y asociado con una anomalía en el cromosoma 15q11-q13. Su prevalencia varía en 1 de 12,000 a 20,000 individuos y es más común en la infancia, aunque algunos casos no se diagnostican incluso en la adultez. Afecta por igual al sexo femenino y al masculino, y muchos casos permanecen sin diagnóstico debido a errores o subregistro. El presente caso involucra a un paciente con SA, inicialmente diagnosticado erróneamente como parálisis cerebral, que presenta un retraso grave en el desarrollo, comportamientos autistas, hipotonía y epilepsia. **Caso clínico:** Se trata de un paciente

*Correspondence:

Natã N.J. Graça

E-mail: natannascimento1601@gmail.com

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de sexo masculino de 3 años y 10 meses, con antecedentes familiares de trastorno del espectro autista y trastorno por déficit de atención e hiperactividad que presentaba retraso motor, hipotonía grave, braquicefalia, falta de control del tronco, epilepsia de difícil control y retraso grave en el desarrollo (incapaz de caminar o hablar). Las observaciones iniciales revelaron que no podía sentarse ni gatear y presentaba dificultades para deglutir. Se le recetó risperidona y se programaron seguimientos para problemas continuos. En 2022 experimentó una convulsión tónico-clónica y se le diagnosticó encefalopatía crónica no progresiva y epilepsia, lo que llevó al tratamiento con ácido valproico. Las convulsiones posteriores provocaron ajustes en su tratamiento, incluyendo la adición de clonazepam, fenobarbital y levetiracetam. Las pruebas genéticas confirmaron una delección en la región crítica del síndrome de Prader-Willi/Angelman en el cromosoma 15. Actualmente, el paciente se encuentra estable. **Conclusiones:** El síndrome de Angelman se caracteriza por retrasos en el desarrollo psicomotor, discapacidad del habla, ataxia y convulsiones, además de comportamientos característicos como risas inapropiadas. Las comorbilidades asociadas, como las convulsiones y la ataxia, incrementan significativamente el riesgo de lesiones y accidentes, lo que eleva la morbilidad y mortalidad de los pacientes.

Palabras clave: Síndrome de Angelman. Convulsión. Ataxia. Epilepsia.

Introduction

Angelman syndrome (AS) is a rare genetic disorder characterized as autosomal dominant with a phenotype defined by the lack of expression of the ubiquitin-protein ligase E3A (*UBE3A*) gene inherited maternally in the brain. It is also associated with the presence of an abnormal chromosome 15q11-q13^{1,2}. AS has a prevalence ranging from 1 in 20,000 to 1 in 12,000 individuals. Although more common in childhood, few cases are identified in adulthood³. This condition affects males and females equally, and many cases remain undiagnosed due to diagnostic errors or underreporting⁴.

Due to its early onset, global developmental delay, and motor dysfunction, AS may initially mimic cerebral palsy (CP). However, certain features help distinguish AS from CP, including the absence of perinatal hypoxic-ischemic injury, the presence of paroxysmal laughter, minimal or absent speech, severe intellectual disability out of proportion to motor findings, characteristic electroencephalogram (EEG) abnormalities, and confirmation by molecular testing of chromosome 15q11-q13 deletion involving *UBE3A*.

Previous reports have also described cases of AS initially misdiagnosed as CP, underscoring how overlapping early motor and developmental findings can mask the underlying genetic condition. Lorenzo-Ruiz et al. (2023) documented adults who were labeled as having CP in childhood until molecular testing revealed deletions in chromosome 15q11-q13. Similarly, Liu et al.² (2022) and Triono et al.¹ (2021) reported children with hypotonia and delayed milestones who were reclassified after identification of the *UBE3A* mutation¹⁻³. These studies highlight consistent early red flags – such as inappropriate laughter, minimal or absent speech, non-progressive hypotonia, and

characteristic EEG abnormalities – that may guide clinicians toward earlier suspicion of AS.

Recognizing these distinguishing characteristics is crucial, since misdiagnosis can delay appropriate genetic counseling and multidisciplinary management. Our case involves a patient with AS, mimicked by CP, causing severe delay, stereotypical autistic behavior, hypotonia, and difficult-to-control epilepsy.

A structured comparison between AS and CP highlights that, while both share early hypotonia and developmental delay, AS exhibits distinctive behavioral (frequent laughter, minimal speech), electrophysiological (EEG patterns), and genetic (*UBE3A* deletion) hallmarks that are absent in CP. Emphasizing these red flags can guide clinicians toward earlier suspicion and appropriate testing.

Clinical case

We describe the case of a 3-year and 10-month-old male patient, born via normal delivery at 37 weeks, discharged with his mother. He denies allergies or prior surgeries. He has a family history of a cousin with autism spectrum disorder (ASD) and a sister with attention deficit hyperactivity disorder. He was referred to the Neurology outpatient clinic due to motor delay, presenting with severe hypotonia, brachycephaly, absence of trunk control, a history of difficult-to-control epilepsy, and severe developmental delay (he does not walk or speak).

The patient was first evaluated in early childhood for delayed motor development and generalized hypotonia. At the time, due to marked muscle weakness, absence of trunk control, and failure to reach expected motor milestones, an initial diagnosis of CP was made. This hypothesis was reinforced by the presence of developmental delay and abnormal motor patterns, although no history of perinatal asphyxia or brain injury was identified.



Figure 1. Clinical features of the patient with Angelman syndrome. **A:** hypotonic posture and limited trunk control. **B:** persistent smiling and laughter, demonstrating the characteristic “happy puppet” facial expression. **C:** facial hypotonia with open-mouth smiling and wide-spaced teeth, consistent with the behavioral and orofacial phenotype typical of Angelman syndrome. All identifying features were removed to preserve anonymity.

At the age of 1 year and 11 months, he could not sit up by himself, still could not crawl, and had difficulty swallowing. A videofluoroscopic swallowing study was ordered, and risperidone 0.3 mL was prescribed at night, with a follow-up in 1 month. At 2 years of age, he presented a tonic-clonic seizure with a stare that lasted for 5 min, followed by hypotonia of both upper and lower limbs in the postictal period, along with a new episode of hypotonia. The diagnostic hypothesis at that point included chronic non-progressive encephalopathy with epilepsy, and valproic acid 3 mL (20 mg/kg/day) every 12 h was introduced. In the same age, the patient developed a 3-day fever and another seizure. After 3 days, the dose of valproic acid was increased to 5 mL every 12 h, showing a positive response, although episodes of fixed staring persisted. Clonazepam 10 mg, $\frac{1}{4}$ tablet every 12 h, was added. At 2 years and 3 months of age, the dose of valproic acid was further increased to 7 mL every 12 h, clonazepam was replaced with phenobarbital 0.9 mL every 12 h, and levetiracetam 4.5 mL every 12 h was introduced.

Despite multiple therapeutic adjustments, seizure control remained suboptimal, and developmental progress continued to lag. These atypical findings – especially the absence of spasticity, the persistence of severe hypotonia, the lack of speech development, and episodes of spontaneous laughter – prompted reconsideration of the initial CP diagnosis.

A comprehensive reevaluation was performed, including genetic testing, which revealed a deletion of the critical region for Prader-Willi/ASs (OMIM #176270/#1055830), with a copy number variation indicating a 4.7 Mb deletion in chromosome 15q11.2q13.1 in heterozygosity.

Following confirmation of AS, the antiepileptic regimen was maintained, as the combination of valproic acid, phenobarbital, and levetiracetam achieved partial control of seizures. This therapeutic profile aligns with typical management patterns for AS, where valproate and phenobarbital are among the most effective agents. After diagnosis, dosages were adjusted to optimize seizure control and minimize sedation, leading to a reduction in frequency and duration of tonic-clonic episodes. Carbamazepine and vigabatrin were avoided due to their reported potential to exacerbate seizures in AS. Clinical photographs of the patient are shown in [figure 1](#), illustrating the typical behavioral phenotype of AS, characterized by persistent laughter, hypotonia, and a happy facial expression despite developmental delay.

The genetic result confirmed AS the definitive diagnosis. The patient is currently clinically stable under a multidisciplinary follow-up program for neurodevelopmental stimulation and seizure management.

Discussion

AS typically presents with speech impairment (absent or minimal), psychomotor developmental delay, movement

and balance disorders (ataxia), inappropriate laughing episodes accompanied by hand movements (happy puppet), and seizures. Patients with Angelman syndrome face significant complications due to associated comorbidities. Seizures and ataxia can lead to frequent injuries, while hyperactivity, exploratory behavior, and intellectual disability increase the risk of accidents. These combined factors elevate morbidity and mortality in AS patients⁴.

Although AS and CP may share early manifestations such as hypotonia, delayed motor milestones, and global developmental delay, several key differences help clinicians distinguish them. In AS, motor dysfunction is typically non-progressive and accompanied by disproportionate speech impairment, paroxysmal laughter, and characteristic facial features, whereas in CP the neurological findings are secondary to a defined brain injury, often with spasticity or dystonia, and no distinctive behavioral phenotype. In addition, AS demonstrates specific EEG abnormalities (high-amplitude slow waves and rhythmic theta activity) and confirmatory molecular findings involving the *UBE3A* gene at chromosome 15q11-q13, which are absent in CP.

From a diagnostic perspective, early recognition of these features is essential. A systematic diagnostic approach should include initial suspicion based on phenotype and behavioral patterns, followed by neuroimaging and electrophysiological studies, and ultimately confirmed by molecular testing. Other neurodevelopmental pathologies that may resemble AS should be excluded, including Phelan-McDermid Syndrome (22q13.3 deletion), MBD5 haploinsufficiency syndrome (22q13.1 deletion), and KANSL1 haploinsufficiency syndrome (17q21.31 deletion). Other examples of single-gene disorders include Christianson syndrome, Mowat-Wilson syndrome, Kleefstra syndrome, and Rett syndrome⁴.

Neuroimaging and EEG findings play a complementary role in narrowing the differential diagnosis. MRI may show hypoplasia of the corpus callosum, enlargement of the lateral ventricles, and cortical atrophy, whereas EEG abnormalities – pseudo arrhythmias and high-amplitude slow wave bursts – are reported in almost all AS patients^{4,5}.

Non-invasive prenatal screening (NIPS) has recently gained relevance for the early detection of microdeletions and imprinting defects associated with chromosome 15q11-q13. Although it does not replace confirmatory molecular studies, NIPS can alert clinicians and families to an elevated risk of AS during pregnancy, allowing targeted follow-up with chorionic-villus sampling or

amniocentesis. Integrating NIPS into prenatal evaluation may prevent years of diagnostic uncertainty and facilitate timely genetic counseling.

The initial evaluation of AS can be performed prenatally by examining fetuses with growth restrictions, and recent studies suggest that NIPS is highly accurate for prenatal AS diagnosis. After birth, if AS is suspected, investigation should begin with methylation tests, as the promoter region of exon 1 of *SNRPN* exhibits differential methylation, where the paternal allele is unmethylated and the maternal allele is methylated. In 80% of AS cases, including deletions, imprinting center defects, and paternal disomy, the methylated maternal allele is absent. A FISH test should be performed next to identify deletions on the maternal chromosome 15; if negative, imprinting defects or paternal disomy should be considered, confirmed by DNA marker analysis. If both tests are negative, molecular studies of the imprinting center should be pursued. If methylation tests are negative but AS is still suspected, DNA sequencing can be performed to rule out mutations in the *UBE3A* gene.

Regarding management, early intervention is essential. A tailored program should combine physical therapy, occupational therapy, orthoses, and speech therapy (verbal and non-verbal communication strategies). These improve motor function, prevent contractures, and enhance quality of life. Physical therapy, orthoses, and occupational therapy, which also assist with posture and prevent contractures, are used to improve motor activities. Speech and language therapy (verbal and non-verbal) and the use of computers help improve communication⁴.

Epilepsy management is another cornerstone. Phenobarbital, sodium valproate, and clonazepam are the most effective drugs, while carbamazepine and vigabatrin should be avoided as they may exacerbate seizures. It is important to monitor treatment response and adjust the antiepileptic regimen according to seizure control and tolerance.

This case emphasizes the need for a systematic and multidisciplinary approach – from clinical suspicion and diagnostic work-up to genetic confirmation and individualized management – to improve early recognition and outcomes in AS.

The present case illustrates the diagnostic challenges of AS presenting as CP and emphasizes the value of a structured, multidisciplinary approach. Awareness of red-flag features – such as inappropriate laughter, minimal speech, and a characteristic EEG pattern – combined with modern genetic tools like

NIPS, can lead to earlier recognition, accurate diagnosis, and improved outcomes. Strengthening clinical vigilance and integrating molecular testing into both pediatric and prenatal practice remain key take-home lessons from this case.

Conclusions

AS is characterized by developmental delays, speech impairment, ataxia, and seizures, along with characteristic behaviors such as inappropriate laughter. The comorbidities associated with AS, such as seizures and ataxia, significantly increase the risk of injuries and accidents, leading to higher morbidity and mortality in patients.

Here the initial misdiagnosis of CP delayed appropriate genetic testing and specific management, illustrating how early developmental and motor symptoms can obscure the recognition of AS.

This case underscores the clinical importance of differentiating AS from CP at an early stage. Unlike CP, AS typically lacks a history of perinatal asphyxia or structural brain injury and instead presents with distinctive behavioral and electrophysiological features, such as frequent laughter, minimal speech, and a characteristic EEG pattern.

Timely recognition of these clinical clues allows for earlier genetic testing, accurate diagnosis, and initiation of individualized multidisciplinary therapy that improves neurodevelopmental outcomes and family counseling. Increasing awareness of such atypical presentations is essential to prevent delayed or incorrect diagnoses and to optimize long-term care for affected children.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical considerations

Protection of human subjects and animals. The authors declare that no experiments on humans or animals were performed for this research.

Confidentiality, informed consent, and ethical approval. The authors have adhered to their institution's confidentiality protocols, obtained informed consent from the legal guardian of all patients, and received approval from the Ethics Committee. The SAGER guidelines were followed to the extent that they were applicable to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing or creation of the content of this manuscript.

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