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CLINICAL CASE

Atypical presentation of infantile Alexander disease without macrocephaly☆

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Abstract
Background: Alexander disease is a rare form of leukodystrophy that involves mainly astrocytes; it is inherited in an autosomal recessive manner and occurs by mutations in the *GFAP* gene, located on chromosome 17q21. It can occur at any age, and its infantile form is characterized by macrocephaly, seizures, severe motor and cognitive delay, and progressive spasticity or ataxia.
Case report: An 8-month-old female was evaluated with a history of neurodevelopmental delay and unprovoked focal motor seizures. Physical examination showed normal head circumference, increased motor responses to tactile and noise stimuli, pyramidal signs and no visceromegaly. The widespread hypodense white matter was found on magnetic resonance, and lumbar puncture showed hyperproteinorrachia. Krabbe disease was ruled out by enzymatic assay and sequencing of *GALC* gene. In the reassessment of the case, abnormalities in neuroimaging lead to suspicion of Alexander disease, and *GFAP* gene sequencing reported a pathogenic mutation in exon 4 c.716G > A, which caused a change of arginine to histidine at position 239 of the protein (p.Arg239His).
Conclusions: The neuroradiology signs observed in the resonance were decisive for the diagnosis later confirmed by molecular techniques. It is important to consider that certain mutations are not associated with macrocephaly, which may cause a delay in the diagnosis.

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PALABRAS CLAVE
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Leucodristrofia;
Enfermedad de Alexander;
Resonancia magnética;
Gen *GFAP*

Presentación atípica de la enfermedad de Alexander infantil sin macrocefalia

Resumen
Introducción: La enfermedad de Alexander consiste en una forma de leucodistrofia poco frecuente que afecta principalmente a los astrocitos; tiene un patrón de herencia autosómica recesiva y es causada por mutaciones en el gen *GFAP*, localizado en el cromosoma 17q21. Puede presentarse a cualquier edad y la forma infantil se caracteriza por macrocefalia, crisis convulsivas, retraso motor y cognitivo grave y espasticidad o ataxia progresivas.
Caso clínico: Femenina de 8 meses evaluada por retraso psicomotor y crisis convulsivas motoras focales no provocadas. En la exploración física, con perímetro cefálico normal, respuesta motora incrementada ante estímulos táctiles y al ruido, signos piramidales y ausencia de visceromegalias. Se observó hipodensidad generalizada de la sustancia blanca en la resonancia magnética y punción lumbar con hiperproteinorraquia. Se descartó enfermedad de Krabbe mediante ensayo enzimático y secuenciación del gen *GALC*. En la reevaluación del caso, las alteraciones en la neuroimagen hicieron sospechar de enfermedad de Alexander, y la secuenciación del gen *GFAP* reportó una mutación en el exón 4 c.716G > A, lo que ocasionó un cambio de arginina por histidina en la posición 239 de la proteína (p.Arg239His).
Conclusiones: Los signos radiológicos en la resonancia fueron determinantes para el diagnóstico, que posteriormente se confirmó con estudio molecular. Es importante considerar que ciertas mutaciones no se asocian con macrocefalia, lo cual puede ocasionar retraso en el diagnóstico.

1. Introduction

Alexander disease (OMIM #203450) is a neurodegenerative disorder part of the infantile leukodystrophy group. It is extremely rare and mainly affects the astrocytes in the hippocampus, striatum nucleus, and neocortex.[1,2] Also, Alexander disease arises by mutations in the glial fibrillary acidic protein gene (*GFAP*), which is located on chromosome 17q21 and has an autosomal dominant pattern; it occurs most frequently in females.[3,4]

Considering the age at which the disease occurs, there are four varieties: neonatal, infantile, juvenile and adult.[5] The neonatal form begins in the first year of life; it is rapidly progressive, with seizures, hydrocephalus, severe motor and cognitive retardation and progressive spasticity or ataxia. Patients die within the first two years of life.[6] The infantile form is the most common and occurs in 51% of the cases, usually during the first two years of life, with similar symptoms and early death, although some patients survive until adulthood. One of the cardinal manifestations of this variant is macrocephaly related to megalencephaly.[7,8] The juvenile form (23%) begins between four and ten years of age. The affected patients show bulbar or pseudobulbar signs like frequent vomiting, language and swallowing problems, gradual loss of cognitive functions and the rest of the other variants-like manifestations. Survival is up to 20 to 30 years of age.[8,9] In the adult form (24%), the manifestations are highly variable, with bulbar or pseudobulbar signs, pyramidal signs, cerebellar dysfunction, dysautonomias, sleep disorders and seizures.[10–12]

This article describes a case with Alexander disease without macrocephaly. Furthermore, the main aspects of the differential neuroradiology and molecular diagnosis of leukodystrophies are revised.

2. Clinical case

Female patient of 8 months of age, with no consanguineous parents, a product of the second pregnancy, no perinatal history. She made visual contact at two months of age, social smiling at four months, failed to support the head. At seven months of age, she presented focal motor tonic-clonic seizures on the right side of the body, unprovoked origin. Treatment with magnesium valproate was initiated without improvement. Clonazepam was added, and because of the persistence of the crisis, the patient attended to our institution. During the physical examination, she showed normal head circumference (p25), appropriate eye contact, normal fundus, motor response increased to tactile and noise stimuli, hypertonia and generalized hyperreflexia, Babinski reflex and substitutes present and without visceromegaly.

Lumbar puncture showed hyperproteinorraquia. Computed cranial tomography showed widespread white matter hypodensity. The magnetic resonance imaging (MRI) of the brain corroborated the condition of generalized white substance, thalami, brain stem, basal ganglia and cerebellum (Fig. 1). Krabbe disease was discarded by enzyme assay and *GALC* gene sequencing. The case was re-evaluated when the patient was 20 months of age. The alterations in the MRI made suspicious of Alexander disease, and the sequencing of the *GFAP* gene reported a mutation in exon 4 (c.716G > A), which resulted in a change of arginine by histidine at position 239 of the protein (p.Arg239His).