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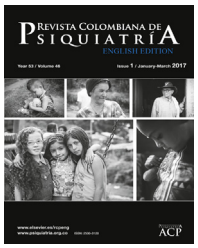

Case Report

Metachromatic leukodystrophy. Case presentation☆

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ABSTRACT

Metachromatic leukodystrophy (MLD) is a rare demyelinating disease (prevalence 1:40,000), also called arylsulfatase A deficiency (ARS-A), which may present with neurological and psychiatric symptoms. Clinical assessment may be difficult, due to unspecific signs and symptoms. A case is presented of a 16 year-old female patient seen in psychiatry due to behavioural changes, psychosis, and with impaired overall performance. She was initially diagnosed with schizophrenia, but the Nuclear Magnetic Resonance (NMR) scan and laboratory tests lead to the diagnosis of MLD.

Leucodistrofia metacromática. Presentación de caso

Palabras clave:
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RESUMEN

La leucodistofia metacromática (LDM) es una enfermedad desmielinizante rara (prevalencia, 1:40.000), también llamada deficiencia de arilsulfatasa A (ARS-A), que puede presentarse con síntomas neurológicos y psiquiátricos y cuyo diagnóstico puede plantear dificultades para el clínico, dado lo inespecífico de los signos y síntomas. Se presenta el caso de una paciente de 16 años atendida por psiquiatría por cambios conductuales, psicosis y deterioro general del funcionamiento. Inicialmente diagnosticada como esquizofrenia, se documentaron por resonancia magnética y pruebas de laboratorio en la evolución cambios que llevaron al diagnóstico de leucodistrofia metacromática.

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Introduction

Metachromatic leukodystrophy (MLD) is a demyelinating genetic disorder that can present clinically with neuropsychiatric symptoms such as psychosis, similar to those of patients with schizophrenia.[1,2] The late onset of MLD has been suggested as a model of schizophrenia, because both disorders are characterised by signs of generalised anatomical disconnection and secondary functional impairment that indicate an extensive lesion in the frontal-subcortical circuits. These signs are manifested in symptoms affecting mood, motivation, judgement and planning and changes in behaviour,[1] suggestive of the recently revived concept of diaschisis, coined by Monakow (1914), in which neurophysiological disorders distant from the focal brain lesion are observed.[3]

Currently, most patients do not undergo arylsulfatase A gene sequencing, approximately 50% of the alleles have not been identified, and it is not possible to predict clinical outcome based solely on mutation analysis.[4]

Case report

The patient first developed behavioural changes at the age of 16, characterised by marked isolation, poor performance and behaviour problems at school, and altered sleep pattern, with psychotic symptoms: soliloquy, hallucinations, disorganised behaviour (eating unpeeled bananas) and general deterioration in functioning, without recovery. We initially requested simple cranial computerised tomography (CT), electroencephalogram, complete blood count, and thyroid and metabolic profile, which were reported as normal. Paranoid schizophrenia was diagnosed. She had several admissions to a mental health unit and had to be institutionalised in a long-term care home as a result of psychotic symptoms and severe episodes of aggression towards others.

Poor pharmacological response with persistent symptoms led to a magnetic resonance imaging (MRI) scan being requested, which showed small nonspecific focal lesions in the white matter of both cerebral hemispheres, and the differential diagnosis included the possibility of ischaemic lesions in small vascular territories. Cerebral angiogram was normal, while the metabolic profile and leptospira, cytomegalovirus and Epstein–Barr virus antibodies were all negative.

The patient was treated with haloperidol and developed extrapyramidal side effects. Subsequently, with olanzapine, she had marked weight gain and with risperidone, amenorrhoea. She was then treated with aripiprazole in progressively higher doses up to 60 mg, with which her behavioural and psychotic symptoms were finally stabilised.

Three years after the first consultation, bilateral T_2 hyperintense focal lesions and bilateral FLAIR frontal/parietal subcortical lesions, nonspecific in character, most likely as sequelae, were observed (Fig. 1).

Blood count and thyrotropin, VDRL, renal function and folic acid determinations were normal, while antinuclear and anticardiolipin antibodies and the complete phospholipid profile were negative. Rheumatology ruled out autoimmune disease as a cause of the patient's behavioural disorder.

Genetic assessment revealed neurodegenerative disease and white matter disorder. Elevated lactic acid was noted, and metabolic screening for white matter disease was requested. The results showed a significant decrease in arylsulfatase A (ARSA) in leukocytes which, together with the clinical picture and the brain MRI, led to the diagnosis of MLD.

Definition

MLD is a lysosomal disease of the sphingolipidoses group, caused by a deficiency of ARSA, an enzyme related to the metabolism of sulfates, which is abundant in myelin (Table 1).[3] The low concentration of this enzyme affects the metabolism of the cerebroside sulphate and causes intralysosomal storage of sulfatide, also known as 3′O-sulfogalactosylceramide, in the white matter of the central nervous system (oligodendrocytes and glia) and peripheral nervous system, especially in the myelin sheaths that surround the nerve cells and other tissues of the body, such as lactosyl sulfatide of the kidneys, bladder and gallbladder.[1,5,6] The accumulation of this material alters the formation and destroys the myelin by an unknown pathophysiological mechanism.[7]

MLD is caused by an autosomal recessive mutation of chromosome 22q which results in an ARSA deficiency. A total of 189 mutations have been identified in the ARSA gene,[8] including substitution at amino acid 31, one substitution at position, three deletions, three donor site mutations and three donor receptor-binding site mutations.[1]

Salmon et al. reported the case of a 30-year-old woman with a diagnosis of enzymatically confirmed MLD, with cognitive changes in which bilateral hypometabolism was found in the thalamus, medial frontal cortex, frontal pole and occipital cortex, in contrast to the changes shown in Alzheimer's disease: hypoperfusion in the dorsolateral prefrontal cortex and temporal-frontal lobe.[1]

Tamagakien reported similar changes in a patient with behavioural changes.[1]

Diagnosis

MLD is suspected when metachromatic granules are found in biopsy of the conjunctiva or sural nerve.[1] Diagnosis is confirmed when low ARSA activity is documented in leukocytes or fibroblast culture.[1,9]

In ARSA pseudo-deficiency, there is a partial deficit that does not cause clinical disorders, and this can complicate the diagnosis and identification of patients with MLD. This condition can also be found in healthy subjects.[4]

The diagnosis is based on analysis of mutations, biochemistry tests and clinical assessments.[4]

The tests that can be used for the diagnosis of MLD include the following[10]:

- Blood or skin tests for low ARSA activity.
- Brain MRI.
- Lumbar puncture to test for high protein concentrations.
- Urinalysis for high sulfatide concentrations.
- Nerve conduction velocity studies.