NEUROIMAGING HIGHLIGHT

Alpha-Mannosidosis: A Novel Cause of Bilateral Thalami and Dentate Nuclei Hyperintensity

Maria J Malaquias, Eduarda Pinto, Jorge Oliveira, João P Freixo, Carla Caseiro, Marina Magalhães

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Alpha-mannosidosis is a rare autosomal recessive lysosomal storage disorder caused by mutations in the *MAN2B1* gene.[1] To date, a total of 154 variants have been identified in 191 patients worldwide.[1] Symptoms usually begin in childhood, but milder forms may present only in adulthood. The most frequent systemic findings include skeletal abnormalities (81%), facial dysmorphia (70%), deafness (67%), immunodeficiency (recurrent respiratory tract infections; 53%), and organomegaly (namely, hepatosplenomegaly; 41%).[2] Nervous system involvement not only includes intellectual disability (>90%) but also psychomotor developmental regression, behavioral alterations and ataxia.[2] Brain magnetic resonance imaging (MRI) data is limited, with leukodystrophy and cerebellar atrophy representing the most frequently reported abnormalities.[3] Clinical-imaging descriptions are relevant to prompt recognition of this potentially treatable entity.

Herein is presented the case of a 49-year-old female patient born from healthy consanguineous parents. Birth and perinatal periods were unremarkable and motor and language acquisitions followed normal milestones. At the age of 7, psychomotor regression was noticed after a normal first year at primary school, as well as gait impairment and speech and learning difficulties. Around the same period, hearing loss was also perceived. At the age of 14, the patient presented bilateral tonic–clonic seizures. In subsequent years, the clinical picture was dominated by intellectual disability and the girl was never capable of attending school or working. At the age of 42, she was referred to our Neurology Department for the first time, due to cognitive deterioration, aggressiveness, and frequent falls. Medical history included hepatosplenomegaly, metrorrhagia, and early menopause. Bone abnormalities and past recurrent infections were denied. Neurological examination revealed cognitive delay, poor spontaneous speech, axial, and appendicular choreo-dystonic movements, axial instability, and ataxic gait. Facial dysmorphia was also notorious, comprising low set ears, prognathism, and high forehead. Brain MRI showed symmetrical T2-weighted images hyperintensity of superior aspects of both thalami (Figure 1A, B – arrows) and dentate nuclei (DN) of cerebellum (Figure 1C, D – arrowheads). Periventricular white matter hyperintensity on T2-FLAIR sequence was mild (Figure 1E, F) and no cerebellar atrophy was shown. During the 7 years of follow-up, the patient presented progressive cognitive deterioration, as well as motor and behavioral fluctuations. In 2020, clinical exome analysis identified a novel homozygous variant in *MAN2B1* (NM_000528.4:c.1061C>T, p. Ser354Phe), initially classified as having uncertain clinical significance. Biochemical studies subsequently established a causal association by showing reduced alpha-mannosidase enzymatic activity in total peripheral blood leukocytes (1 nmol/h/mg protein; reference value 77–413) and abnormal urinary levels of mannose-rich oligosaccharides. In view of these findings, the new *MAN2B1* variant was reclassified as likely pathogenic.

This study reports a childhood-onset case evaluated in adulthood of alpha-mannosidosis exhibiting rare neurological features (epilepsy and choreo-dystonic movements) and a novel *MAN2B1* variant. Additionally, thalami and DN hyperintensity here described have not been previously reported, including in one series of 13 patients.[2] Previous brain MRI descriptions of alpha-mannosidosis comprised cerebellar and cortical atrophies, leukodystrophy, basal ganglia and thalami T2 hypointensity, corpus callosum thinning, Virchow–Robin spaces and widened perioptic cerebrospinal fluid spaces.[3–5] In recent quantitative studies, Majovska et al. did not confirm basal ganglia and thalami T2 hypointensity, suggesting that T2 hypointensity seen in these locations is due to adjacent white matter T2 hyperintensity and not to gray matter iron deposition, as formerly believed.[3,5] The range of differential diagnoses of thalami and DN hyperintensity in neuropediatric genetic/metabolic disorders is narrow and includes cerebrotendinous xanthomatosis, Canavan disease, L2-hydroxyglutaric, and type 1 glutaric acidurias, Alexander´s

From the Neurology Department, Centro Hospitalar Universitário do Porto, Porto, Portugal (MJM, MM); Neurorradiology Department, Centro Hospitalar Universitário do Porto, Porto, Portugal (EP); Center for Predictive and Preventive Genetics (CGPP), Institute for Molecular and Cell Biology (IBMC), Instituto de Investigação e Inovação em Saúde (i3S), Universidade do Porto, Porto, Portugal (JO, JPF); Unidade de Bioquímica Genética, Centro de Genética Médica Doutor Jacinto Magalhães, Centro Hospitalar Universitário do Porto, Porto, Portugal (CC); Neurology Department, Hospital Padre Américo, Centro Hospitalar do Tâmega e Sousa, Penafiel, Porto, Portugal (MM)

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Correspondence to: Maria J. Malaquias, Neurology Department, Centro Hospitalar Universitário do Porto, Largo do Prof. Abel Salazar, Porto 4099-001, Portugal. Email: mariajcmalaquias@gmail.com

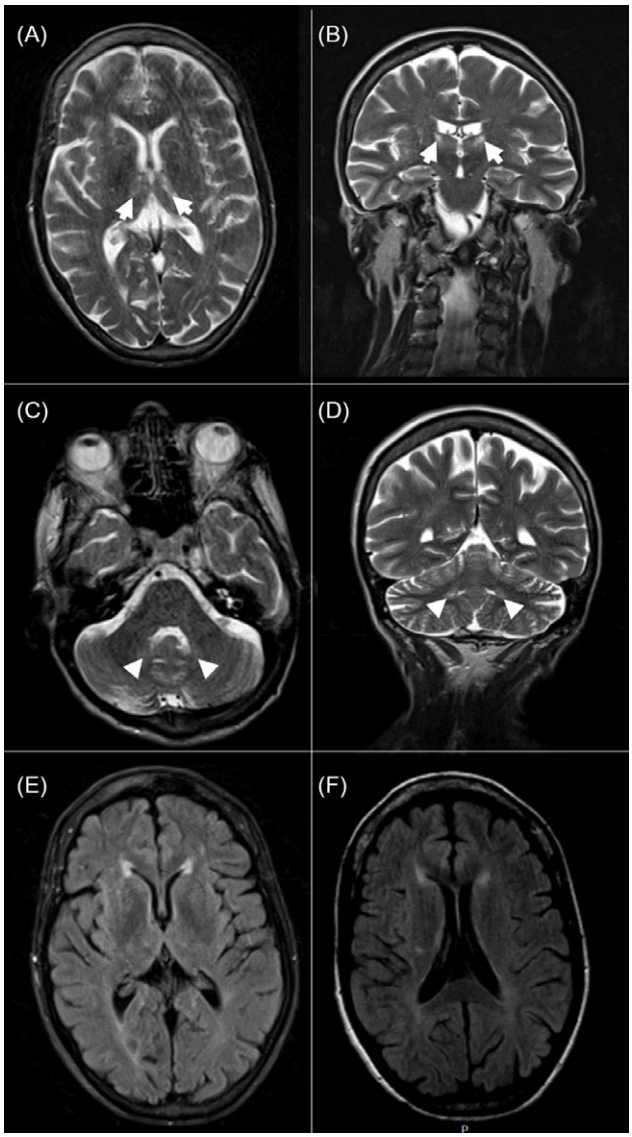

Figure 1: *T2-weighted images performed at 49 years of age, showing symmetrical hyperintensity of superior aspects of both thalami (A, B – arrows) and dentate nuclei of cerebellum (C, D – arrowheads). Periventricular white matter hyperintensity on T2-FLAIR sequence was mild (E, F).*

disease, Leigh syndrome, and Wilson disease.[6–8] We additionally propose that alpha-mannosidosis, traditionally regarded as a white matter disease, should be considered in the approach to central gray matter (thalami and DN) hyperintensity.

Disclosure

The authors report no disclosures relevant to the manuscript.

Statement of Authorship

A. Research project conception and execution,
B. Manuscript preparation,
C. Writing of the first,
D. Draft, review and critique.

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MM: A, B, C, D

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