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CLINICAL VARIANT OF NASU-HAKOLA DISEASE ASSOCIATED WITH FRONTOTEMPORAL DEMENTIA AND ABSENCE OF OSTEODYSPLASIA. CASE REPORT

Isabelly de Arruda Cardoso Slavec

Thaís Laura Almada da Fonseca

Aline Mizuta Kozoroski Kanashiro

Elder Yanaze Oda

Yasmin Coelho

Maria Luiza Ferri Cury

Bárbara dos Reis Dal Lago Rodrigues

INTRODUCTION

Nasu-Hakola disease (NHD), a genetic condition, has dementia syndrome as one of its main symptoms. In a descriptive study published in 2020, 1.5 million Brazilians aged 60 or over were estimated to be living with dementia in 2016[1]. According to the definition established by the Brazilian Academy of Neurology, dementia is a syndromic diagnosis, which encompasses cognitive and/or behavioral decline, with interference in activities of daily living (ADL), consequently generating functional deficit in relation to the patient's previous state, and without better explanation by major psychiatric disorder or *delirium*[2].

The diagnosis of dementia syndrome is clinical and its causes can be classified as neurodegenerative or secondary. Among neurodegenerative diseases, the most common is Alzheimer's dementia[3], while other prevalent diseases are dementia caused by Lewy bodies (DLB) and frontotemporal dementia (FTD), with FTD being considered the second most prevalent cause of dementia in people under 65[4]. The main symptom of frontotemporal dementia is a gradual cognitive and behavioral decline, such as inappropriate social behavior, loss of empathy and even compulsive behavior[4].

DNH is a dementia of secondary etiology that presents with a clinical picture typical of FTD. This condition occurs due to the presence of a pathogenic variant on chromosome 6. In addition to systemic alterations, such as bone deformities, the patient may develop neurological alterations, with cognitive decline present even at a pre-senile age (under 65). Therefore, due to the severe impairment of functionality, it is relevant to consider DNH as a differential diagnosis of dementia in patients under the age of 60[5].

MATERIALS AND METHODS

A case report was made of a patient who was seen and monitored on an outpatient basis by the neurology team at the Mato Grosso do Sul Regional Hospital between 2023 and 2024. The patient in question started being monitored at a late stage, when she was no longer able to answer for her civil acts, and the informed consent form (ICF) was signed by her legal guardian, her husband. At the time, it was explained to the patient's spouse and other family members present at the consultation through the ICF that the purpose of this report is solely scientific, with the aim of encouraging academic discussion on the subject. In addition, it was emphasized that the patient's name and other personal data would not be disclosed. The case report was approved by the ethics and research committee of the hospital where the treatment took place.

CASE PRESENTATION

Patient L.S., female, 46 years old, until the age of 43 healthy, housewife. In 2020, she began to show a slow and gradual cognitive decline, characterized by memory loss , impairment of executive function, spatial disorientation, as well as an inability to judge, disinhibition, inattention and mood swings. She developed behavioral changes with infantilization, psychosis and episodes of bilateral tonic-clonic epileptic seizures. The patient began to neglect her own hygiene, as well as losing autonomy for functional activities and sphincter continence. No movement disorders were reported.

The patient›s family history was positive for the disease, with five siblings having a similar condition. The presence of familial consanguinity was ruled out and the genetic investigation for Huntington's disease was null. Exome testing identified the presence of a homozygous variant in the *TREM2* gene, a condition of autosomal recessive inheritance.

At the last outpatient visit, the patient was already showing significant cognitive deterioration, with temporo-spatial disorientation, severe speech impairment, anarthria, dysphagia and the need for an alternative feeding route (gastrostomy). In addition, the neurological examination showed an apraxic gait, an inexhaustible glabellar reflex, palmar grasp and grappling.

Magnetic resonance imaging of the skull showed significant global volumetric reduction, thinning of the corpus callosum, hypersignal in T2/FLAIR periventricular, semi-oval and cerebral hemispheres, preserved cerebrospinal fluid flow.

DISCUSSION

Nasu-Hakola disease (NHD) occurs due to the presence of a pathogenic variant on chromosome 6, specifically in the *POLH* and *TREM2* genes (triggering receptor expressed in myeloid cells 2), associated with autosomal recessive conditions, Xeroderma Pigmentosum, and NHD or Sclerosing Leukoencephalopathy type 2, respectively[5].

In a case report that reviewed the literature in several databases, including Pubmed, those patients with a mutation in the *POLH* gene generally manifested a clinical picture with bone alterations and deformities, such as bone cysts, a greater propensity to fractures, even in the first decades of life, and few developed cognitive impairment[5,6].

Although classically Sclerosing Leukoencephalopathy type 2 manifests itself with bone and cognitive alterations, the literature reports some cases in which, depending on the mutation in the *TREM2* gene, only neurological impairment was present[5,6,7]. The triggering receptor expressed in myeloid cells (*TREM2*) is widely present in microglia, for example, with a central function as an immune regulator. That said, the clinical manifestations can vary with early-onset Alzheimer's disease, late-onset Alzheimer's disease, the development of Frontotemporal Dementia, as well as the presence of epileptic seizures[5].

In the case described, the neurological impairment was more pronounced. Rapid progression to severe cognitive impairment and the presence of epilepsy were observed, in line with other cases found in the literature. The patient's positive family history is noteworthy, although it was not possible to assess the exomes of other family members.

CONCLUSION

The cognitive impairment seen in the case reported here and in others found in the medical literature is a reminder of the need to investigate dementia that begins at a pre-senile age, given the extent of the emotional and functional impairment and even the economic impact. It is therefore very important to consider this pathology as a differential diagnosis, with a view to genetic family counseling and family support in diagnosed cases.

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