Case Report

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Neurodegeneration with brain iron accumulation associated with late-onset psychiatric symptoms

Neurodegeneração com acúmulo de ferro no cérebro associada a sintomas psiquiátricos de início tardio

Neurodegeneración con acumulación cerebral de hierro asociado con síntomas psiquiátricos de inicio tardío

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ABSTRACT:

Introduction: The neurodegeneration with brain iron accumulation (NBIA) is a heterogeneous group of rare genetic disorders that lead to accumulation of iron in the basal nuclei, which leads to numerous neurologic disorders. This condition has been associated with many genes, PKAN2 being the most common. The treatment remains mostly symptomatic and the approach based on a multidisciplinary team is recommended. **Case report:** The case presented is from a 67-year-old male with iron accumulation bilaterally in the pale globes and has been having delirium for 8 months, as well as visuospatial and executive dysfunction and behavioral alterations. The patient's MRI showed abnormalities and the "eye of the tiger" sign. Furthemore, the treatment of choice was the administration of atypical antipsychotic medication, which partially controlled the patient's condition. **Discussion:** The most recurrent location of brain iron accumulation is in the basal ganglia and it is mainly linked with mutations in the pantothenate kinase 2 (PKAN2), which leads to psychiatric manifestations of insidious progression and can be inferred when the "eye of the tiger" sign is found in a MRI. **Conclusion:** The patient was diagnosed with late onset psychotic disorder, mild cognitive deficit and parkisonian syndrome. Genetic tests were not

performed to diagnose the etiology. Therefore, the case is considered a NBIA of unknown cause with atypical characteristics and probable mutation linked to PANK2.

Keywords: neurodegeneration, brain iron accumulation, NBIA, PKAN2

RESUMO:

Introdução: A neurodegeneração com acúmulo cerebral de ferro (NBIA) é um grupo heterogêneo de doenças genéticas raras que levam ao acúmulo de ferro nos núcleos basais, o que leva a inúmeros distúrbios neurológicos. Esta condição tem sido associada a muitos genes, sendo o PKAN2 o mais comum. O tratamento permanece majoritariamente sintomático e recomenda-se a abordagem baseada em equipe multidisciplinar. **Relato de caso:** O caso apresentado é de um homem de 67 anos com acúmulo de ferro bilateralmente nos globos pálidos e há 8 meses apresentando delirium, além de disfunção visuoespacial e executiva e alterações comportamentais. A ressonância magnética do paciente mostrou anormalidades e o sinal de "olho de tigre". Além disso, o tratamento de escolha foi a administração de medicação antipsicótica atípica, que controlou parcialmente o quadro do paciente. **Discussão:** A localização mais recorrente do acúmulo de ferro cerebral é nos gânglios da base e está principalmente ligada a mutações na pantotenato quinase 2 (PKAN2), que leva a manifestações psiquiátricas de progressão insidiosa e pode ser inferida quando o "olho do tigre " é encontrado em uma ressonância magnética. **Conclusão:** O paciente foi diagnosticado com transtorno psicótico de início tardio, déficit cognitivo leve e síndrome parkisoniana. Não foram realizados testes genéticos para diagnosticar a etiologia. Portanto, o caso é considerado um NBIA de causa desconhecida com características atípicas e provável mutação ligada ao PANK2.

Palavras-chave: neurodegeneração, acúmulo de ferro no cérebro, NBIA, PKAN2

RESUMEN:

Introducción: La neurodegeneración con acumulación cerebral de hierro (NBIA) es un grupo heterogéneo de trastornos genéticos raros que conducen a la acumulación de hierro en los núcleos basales, lo que conduce a numerosos trastornos neurológicos. Esta condición se ha asociado con muchos genes, siendo PKAN2 el más común. El tratamiento sigue siendo

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mayoritariamente sintomático y se recomienda el abordaje basado en un equipo multidisciplinar. **Caso clínico:** Se presenta el caso de un varón de 67 años con acumulación de hierro bilateral en globos pálidos y delirio desde hace 8 meses, así como disfunción visoespacial, ejecutiva y alteraciones de la conducta. La resonancia magnética del paciente mostró anormalidades y el signo del "ojo del tigre". Además, el tratamiento de elección fue la administración de medicación antipsicótica atípica, que controlaba parcialmente el estado del paciente. **Discusión:** La localización más recurrente de la acumulación de hierro cerebral es en los ganglios basales y se relaciona principalmente con mutaciones en la pantotenato quinasa 2 (PKAN2), lo que conduce a manifestaciones psiquiátricas de progresión insidiosa y puede inferirse cuando aparece el "ojo del tigre". El signo " se encuentra en una resonancia magnética. **Conclusión:** El paciente fue diagnosticado de trastorno psicótico de inicio tardío, déficit cognitivo leve y síndrome parkisoniano. No se realizaron pruebas genéticas para diagnosticar la etiología. Por tanto, el caso se considera un NBIA de causa desconocida con características atípicas y probable mutación ligada a PANK2.

Palabras clave: neurodegeneración, acumulación de hierro en el cerebro, NBIA, PKAN2

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Introduction

The neurodegeneration with brain iron accumulation (NBIA) consists in a heterogeneous group of rare genetic disorders characterized by the accumulation of iron in the basal nuclei, mainly in the pale globe and in the substantia nigra, resulting in variable neurological disorders, including neuropsychiatric, visual and extrapyramidal symptoms [1, 2]. The ten genes known for being associated to the types of NBIA are ATP13A2,

C19orf12, COASY, CP, DCAF17, FA2H, FTL, PANK2, PLA2G6 e WDR45 [3, 4]. The type 1 neurodegeneration with brain iron accumulation, also known as neurodegeneration associated to the pantothenate kinase (PKAN2), previously known as Hallervorden-Spatz disease, consists in the most common form of presentation, corresponding to 35-50% of the cases [5, 6].

In this group of diseases, generalized brain atrophy and cerebellar atrophy are frequently observed, but are clinically characterized by progressive dystonia, dysarthria, spasticity, parkinsonism, neuropsychiatric manifestations, optic atrophy and retinal degeneration. Although the cognitive decline occurs in some genetic types, the cognition is frequently spared [4, 5].

The exact etiology of PKAN2 is not known. A proposed hypothesis is that the abnormal peroxidation of the lipofuscin to neuromelanin and the deficient cysteine dioxygenase lead to the abnormal iron accumulation in the brain, specifically in the pale globe and in the pars reticulata of the substantia nigra, leading to axonal and neuronal damage [7].

The genotype-phenotype association is not well comprehended, and the main characteristics, such as progression rate, starting age and signals and symptoms, are highly variable, even between siblings and individuals with identical mutations [8].

The treatment remains mainly symptomatic. An approach of a multidisciplinary team involving physiotherapists, occupational and speech therapists can be necessary to better the functional abilities and the quality of life. In the present study, we report the case of a 67-year-old patient with iron accumulation in the pale globes bilaterally with an eight month evolution with delirium involving the themes of debts, persecutory and mystical-religious.

Case Report

67-year-old male, married, 8 years of study, progressing in 8 months with delirium in the themes of debts, persecutory and mystical-religious; progessive worsening of the executive and visuospatial dysfunction; psychomotor agitation and heteroaggressiviness; behavioral alterations with self care compromising, social isolation, skinpicking; affective dullness; hyporexia and insomnia. Previous psychiatric history with

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hospitalization when he was 30 years old because of a confused state, without other reports.

After discharge, he did not use any medication and was not accompanied by a psychiatrist. Previous morbid story of arterial hypertension with good control in monotherapy with captopril. Familiar history: father and sister died through self-extermination; mother with depression and brother with dementia to enlighten.

Hospitalization was necessary because of the severity and intensity of the psychiatric symptoms, with no success in the ambulatorial approach. In the physical examination, he presented parkinsonism; bilateral fine tremor, more intense to the right, and intention tremor in hands.

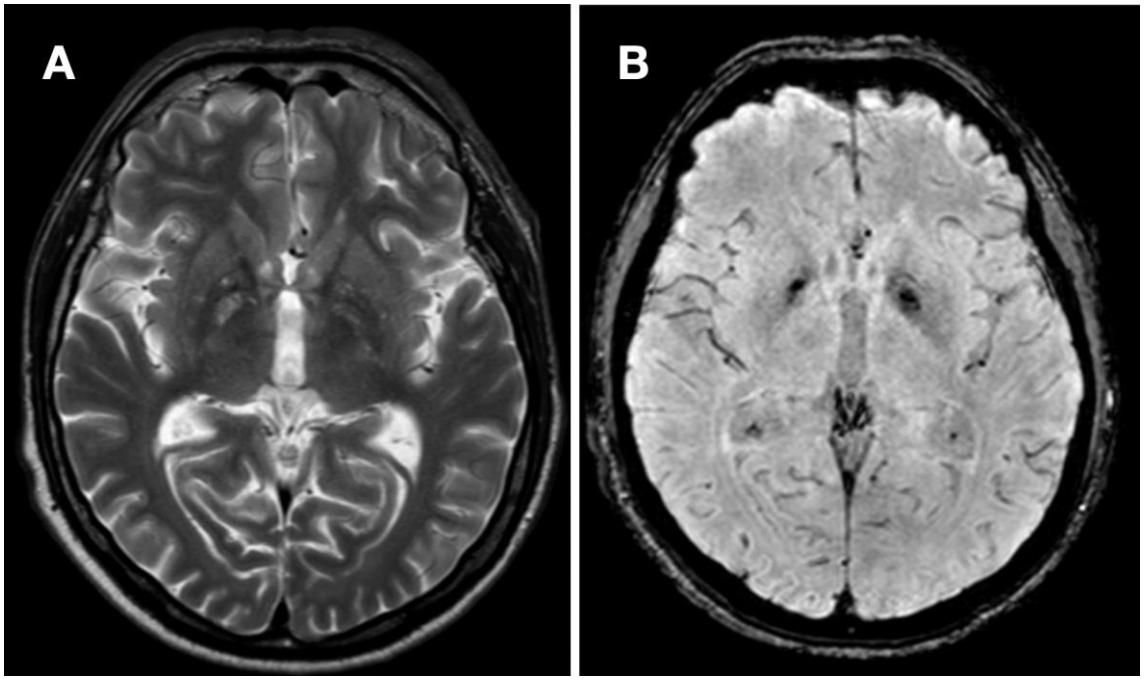

Figure 1. Magnetic resonance imaging (MRI) of the encephalon. A) T2 with hyperdensity in the pale globe, more importantly to the right. B) SWI with anomalous iron deposition in the pale globes, more intense to the left. Intermediate stage of formation of the "eye of the tiger" sign.

Wilson's disease, neuroacantosys and the juvenile form of Huntignton disease were discarded. Besides, despite the lack of genetic testing, every subtype of NBIA listed in the Table 1 was also considered.

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Tabela 1. Subtypes of neurodegeneration with brain iron accumulation. (Adapted of Nassif D, Pereira JS, Spitz M, Capitao C, Faria A. Neurodegeneration with brain iron accumulation: a case report. Dement Neuropsychol. 2016;10(2):160–164)

NBIA Subtypes e Mode of inheritance
Autosomal Recessive
Neurodegeneration Associated with Phospholipase 2
Neurodegeneration Associated with Mitochondrial Membrane Protein
Neurodegeneration Associated with Fatty Acids Hydroxylase
Neurodegeneration Associated with Coenzyme A Synthase Protein
Kufor Rakeb Syndrome
Woodhouse-Sakati Syndrome
Aceruloplasminemia
Autosomal Dominant
Neuroferritinopathy
X-linked Dominant
Neurodegeneration Associated with Beta Helix Protein

Finally, the partial control of the condition using atypical antipsychotic. Initially risperidone was used, worsening the extrapyramidal symptoms and the apathy; replaced by olanzapine with good adaptation.

Despite the medication, the reverberant delirious speech about debts was maintained, as well as motor symptoms and partial dependency on instrumental activities and independence for basic ones. In the absence of antipsychotics, he returned to the original state.

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MOCA test: 22/30, visuospatial, executive, verbal fluency and abstraction compromising. MEEM 27/30. Therapeutic plan: maintain the administration of atypical antipsychotic, comorbidity control, multidisciplinary team approach and refer to family support.

Discussion

The neurodegeneration with iron accumulation (NBIA) characterized by abnormal iron accumulation in the basal ganglia, mainly in the pale globe and substantia nigra, with progressive extrapyramidal manifestation. The most common form of NBIA is through the mutation associated with the pantothenate kinase 2 (PKAN2), responsible for 35-50% of NBIA cases [8, 9].

The neurodegeneration associated with the pantothenate kinase 2 is a recessive autosomal disorder caused by mutations in the PANK2 gene localized in the chromosome 20 p13. The atypical form (commonly related to PANK2 missenses mutations) starts in the second or third life decade, characterized by psychiatric manifestations, focal dystonia (with or without parkinsonism), cognitive damage and late gait dysfunction, such as through an insidious progression [10, 11, 12].

The global prevalence of this mutation was estimated of being 1:1.000.000, no related with race or genre [8, 9, 11, 13]. Alterations in the basal ganglia are strongly associated with psychotic symptoms in the elderly [14], being the reported psychiatric symptoms most linked with the compromising of the pale globe dementia, maniac symptoms and compulsions [15]. The "eye of the tiger" sign in the MRI in the atypical form was associated with the PANK2 mutation [16, 17].

Conclusion

The diagnosis of late onset psychotic disorder, mild cognitive deficit and parkinsonian syndrome was made syndromically. Genetic tests were not performed to effectively diagnose the etiology, awaiting evaluation from medical genetics and neurology. It is considered as NBIA of unknown cause, with atypical characteristics and probable mutation linked to PANK2.

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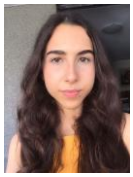

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