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(CASE REPORT)

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Absence of typical images and progressive psychiatric manifestations may suggest the diagnosis of neurodegeneration associated with pantothenate kinase deficiency

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Abstract

Neurodegeneration associated with pantothenate kinase deficiency is a rare disease. To confirm its diagnosis, studies are needed that are often not available in all countries and times (as in this case). Clinical case: In the Child Psychiatry ward of the "Juan Manuel Márquez" Pediatric Hospital, an adolescent was treated with psychiatric disorders of psychotic functioning level with little response to treatment, extrapyramidal manifestations and other progressive neurological dysfunction. The classic image of "tiger eyes" was evidenced by magnetic resonance imaging of the skull, at the beginning unilateral, and at 10 months it was performed again, verifying the bilateral image, in addition to significant cognitive, language, communication and loss of skills deterioration. With regression, affective symptoms and sleep disorder. Conclusions: Although neurodegeneration associated with pantothenate kinase deficiency is a rare disease and in the present case it could only be considered probable, it should be included in the differential diagnosis of children and adolescents with the progression of clinical manifestations, including extrapyramidal dysfunction. dementia, even in the absence of a tiger-eye image at the onset of manifestations or its unilateral presence. Psychiatric manifestations were the cause of admission from the start, and their persistence and poor response to treatment may be a manifestation that alerts to the presence of this disease.

Keywords: Psychotic disorders; Cerebral iron accumulation; Cognitive impairment; Extrapyramidal symptoms; “eyes of the tiger” image

1. Introduction

At present, there are many diseases whose cause is still unknown or when it is known, the use of laboratory investigations generally available only in developed countries is required for confirmation. However, in both cases, given the limitations to carrying out the "golden test" for diagnosis, patients considered as possible or probable carriers of these conditions must receive treatment to try to reduce clinical manifestations and be treated with the best quality, possible at any time.

Hallevorden-Spatz (HS) disease, in recent years better known as pantothenate kinase-associated neurodegeneration (PKAN), is included among those that require research that is often not available for study. Confirmation in all patients. However, the appearance of progressive dysfunction of symptoms and signs, evidence of extrapyramidal involvement,

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dementia, and some neurological manifestations that may be associated and the verification of magnetic resonance images (MRI) called "in tiger eyes", mainly beginning in childhood or adolescence, justify considering its diagnosis as possible or probable. (1-3)

This article refers to a patient treated in the Child Psychiatry service of the "Juan Manuel Márquez" Paediatric Hospital, who was diagnosed as a probable patient with PKAN and in the first MRI studies an image similar to the description of eyes was verified. tiger, but unilateral, and in an evolutionary study, it was described as bilateral, which we have not found reported in the literature and is the main reason for the presentation, together with the predominance of mental manifestations.

2. Case Presentation

Male patient, 19 years old, with white skin colour, who was admitted for the first time to the Psychiatry ward of the "Juan M. Márquez" Paediatric Hospital at the age of 16, presenting with a fixed gaze, insomnia, loss of communication, language, eating, bathing and dressing without help, with hallucinatory behaviour and motor clumsiness.

Personal pathological history: moderate intellectual disability with greater affectation in socialization and language and also bronchial asthma. In the family pathological history, it was collected that a maternal uncle had a diagnosis of intellectual disability and alcoholism and a paternal uncle was schizophrenic.

It was also specified that the patient was required to attend a special education school and achieved some basic skills (feeding, bathing, dressing and others under supervision). His interests were: watching music videos, and dolls, going for walks, going to the beach, and parks, playing with his brothers, and helping with simple household chores. Family members also reported that he had been treated with carbamazepine for two years and that it was suspended due to a medical prescription due to elevated liver enzymes.

Before admission, he travelled to the United States to meet with his father and brother. During his stay in that country, he went to work with his father and acquired the ability to repeat some English words with difficulty. Five months after his trip, his maternal grandfather, with whom he was very emotionally identified, died and the symptoms that led to his return to Cuba and his admission to our room began. He was diagnosed on admission as having an acute psychotic disorder based on the fact that he was found to have a hallucinatory attitude, unmotivated laughter, perseveration in the train of thought, hypothymia, dysphoria, hypobulia, hypokinesia, mixed insomnia, anorexia, and loss of hygienic and aesthetic habits. , recreational and mutism. Elevated blood pressure figures, left hemiparesis, and the administration of haloperidol intramuscularly, he presented neuroleptic malignant syndrome were also confirmed. Computed tomography of the skull was performed, in which no alterations were found, and he was discharged after 46 days with a diagnosis of depressive adjustment disorder with psychotic symptoms and extrapyramidal syndrome.

The subsequent evolution was torpid, he presented five admissions in a period of three years, with intervals of two months of the apparent improvement in symptoms and signs and hospital stays of up to five months, with cognitive deterioration, changes in mood, with periods of excitement psychomotor and insomnia, alternated with psychic and motor slowdown and mutism. In addition, he evolved presenting with dysarthria, loss of vocabulary, self-validation, impaired communication, hyperkinesia, stereotypes, sphincter relaxation, maladjusted and regressive behaviour (he played with faeces), and a total loss of his interest. In the magnetic resonance images (MRI) of the skull performed in 2020, diffuse cortical atrophy was reported, without other alterations.

Consultations were made by various specialities and the probable diagnosis of neurodegeneration associated with pantothenate kinase was raised. Fasting and postprandial lactic acid determinations were made, finding an increase in levels. High-field magnetic resonance images of the skull were also performed again, which showed a hypointense lesion at the level of the right basal ganglion with central hyperintensity, similar to the “tiger-eye image”. Evolutionary follow-up by images was carried out and the MRI was repeated at 10 months and the bilateral “eyes of the tiger” images were verified (Figure 1, 2), for which the probable diagnosis of neurodegenerative disease due to associated iron accumulation was considered to pantothenate kinase deficiency, but confirmatory tests could not be performed because this possibility was not available in our country.

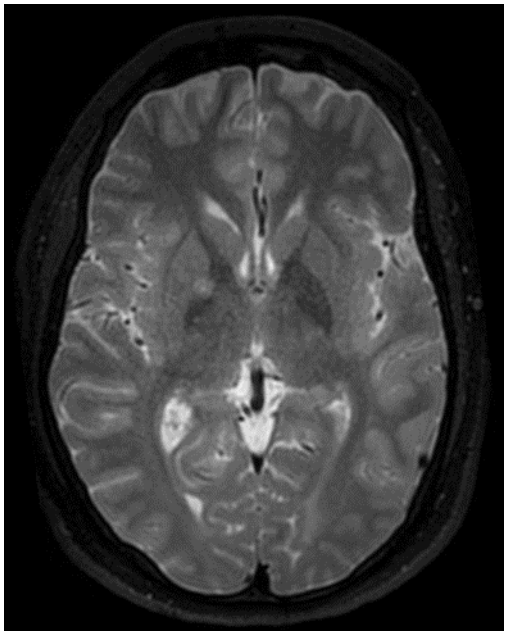

Figure 1 High field MRI, T2WI, axial section, hypointense lesion at the level of the right basal ganglia with hyperintensity central

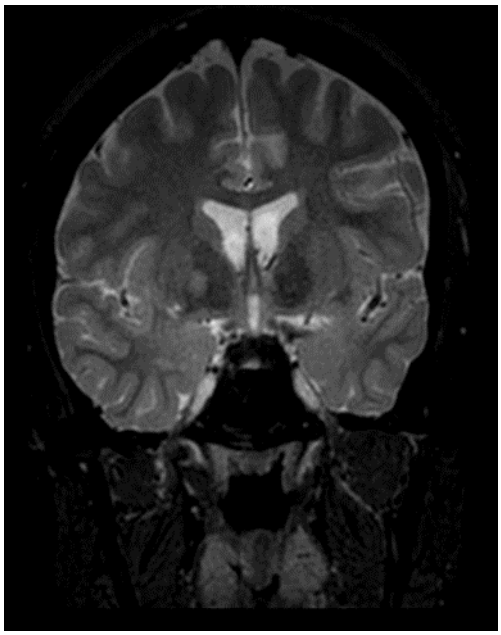

Figure 2 High field MRI, T2WI, coronal section, hypointense lesion at the level of the right basal ganglia with central hyperintensit

He currently has symptomatic treatment with atypical, anti recurrence and antiparkinsonian antipsychotics; plus folic acid, coenzyme Q, vitamin C, E, B12, biotin and melatonin. The evolution has been unfavourable as expected in this neurodegenerative disease with no known specific treatment to date.

3. Discussion

In the spectrum of diseases that share the accumulation of iron in the brain and mainly in the basal ganglia (NBIA for the acronym of neurodegeneration with brain iron accumulation), which are caused by genetic defects, PKAN is included. They are a heterogeneous group of rare diseases that cause progressive deterioration, are life-threatening and difficult to diagnose, in which numerous genes have been identified. Excessive oxidative stress caused by iron accumulation in the brain causes neuronal damage and cell death (1-4).

PKAN is a low-incidence neurodegenerative disorder, with an estimated prevalence of 1-3/1,000,000 inhabitants, characterized mainly by extrapyramidal symptoms and cognitive impairment. Movement disorders present progressively, sometimes with painful dystonia, a variable degree of pyramidal, cerebellar, and peripheral nerve involvement, and dysautonomia, in addition, there is a regression of mental functions and premature death (5-10). The age of onset, severity and cognitive compromise are variable. It is related in most of the cases studied to a mutation in the PANK gene located on chromosome 20 (20p13) (2, 3, 8-10).

It is an autosomal recessive disease, and the presentation can be sporadic or have a familial character (4). Some authors consider two forms of presentation: the classic or typical which is characterized by an early age of onset, before the age of six, with intense symptoms, with rapid evolution and the main manifestations are ataxia and extrapyramidal symptoms and signs such as dystonia, chorea and parkinsonism (5, 10-12). The atypical form is more heterogeneous with a later onset, slow evolution and psychiatric manifestations such as depression, impulsiveness, aggressiveness, and communication disorder and evolves with less deterioration of motor function (3, 5). In both cases, the clinical manifestations are associated with the "eyes of the tiger" sign that is evident in a head MRI. Evolutionarily, neuroaxonal degeneration occurs and the survival of patients with atypical PANK is estimated at 12 years after diagnosis (not so in the typical way, which can only be 5 years), the loss of motor skills can occur in a period from 15 to 40 years. (1, 3, 5 – 9)

The "eyes of the tiger" sign on MRI denotes symmetrical iron accumulation in the medial region of both globus pallidus, with a central region of hyperintensity surrounded by a rim of hypointensity on coronal images of the globus pallidus on T2-weighted sequences, which would be pathognomonic for PAKN (1, 5-8). There are characteristic axonal

thickenings in the central and peripheral nervous system called spheroids (3, 5-10). The fact considered unusual in the results of the MRI studies of this patient, that this typical image did not appear in the first study and that the first unilateral “eye of the tiger” image appeared 16 months later, delayed the classification of the diagnosis from possible to probable and required imaging follow-up, this characteristic sign of the disease appearing bilaterally 10 months later. In the reviewed literature, there are no cases with these characteristics, which is unusual and novel.

The diagnosis of aceruloplasmin is based on the absence of ceruloplasmin in the serum, which in combination with the resonance findings supports the accumulation of iron (8-11), a determination that could not be made, therefore it is an objective limitation in this case.

On the other hand, in this patient, all admissions were for serious psychiatric disorders. The onset in the adolescence of psychiatric disorders with significant psychotic and affective symptoms, and progressive cognitive, communication, language, and behavioural impairment leading to regression are indicative of an atypical form and are grounds for considering this diagnosis as possible. causes in children and adolescents in which manifestations of mental disorders associated with progressive neurological dysfunction appear. We cannot say with certainty whether language disorder and moderate intellectual disability diagnosed before the age of five are independent entities or early symptoms of the disease, but it was striking in this case.

The treatment is palliative, as has been imposed in the case presented, although it has not been possible to verify. Other diagnostic possibilities that required specific treatment were ruled out and drugs used in diseases with mitochondrial dysfunction were indicated due to the involvement of PKAN in the production of coenzyme A in the mitochondria (3, 6, 10,12-14).

The frequency according to age and sex of the different types of BAD in this study match with that reported by other authors. It is suggested that the most frequent age of onset of BD in childhood and adolescence is between 15 and 19 years, there would be no differences between the sexes, the onset would be abrupt, of a complete depressive or manic episode and a higher prevalence of symptoms psychotics. This also match with what was found in this work (1, 2, 3, 7, 10, 11, 12, 13, 14).

According to Diller and Birmaher (6), in 16 open studies and 9 double-blind studies with more than 1, 200 participants reviewed by them, it is suggested "that monotherapy with lithium, valproate or carbamazepine has similar results in the treatment of non-psychotic episodes of mania and mania with mixed features, where the response of manic symptoms ranged from 23% to 55% (41% in the open studies and 40% in double-blind studies)".

In the reviewed bibliography, few studies were found on the maintenance treatment of TB patients in this evolutionary period, with which to be able to compare our results, however, in some works, it is stated in a general way that the treatment with which clinical improvement of the acute episode was achieved, its duration depends on individual biological factors such as severity and the number of previous episodes, family history of the disease and response to medications and the occurrence of relapses (4, 6, 7, 8, 14, 15), which was strictly adhered to in all our patients.

In contrast to what was previously stated, some authors point out that when the patient is clinically stable, an attempt should be made to suspend the psychotropic drugs used in the acute episode (atypical or typical neuroleptics) and add that when there is a recurrence, symptoms or the patient is not responding at levels adequate to the stabilizing agent alone, the association with neuroleptics will be maintained (5, 6, 13).

Another study on maintenance treatment with antipsychotics in children with Bipolar Disorder, where atypical antipsychotics were used, resulted in improvement in more than 50.0% of the patients (6). Some authors point out normothymic properties for maintenance treatment of atypical antipsychotics, Quetiapine with 71% used from 10 to 17 years of age6 and which has shown positive results in Bipolar Depression as well as Aripiprazole with use from 10 to 17 years of age. 17 years and Olanzapine with use from 13 to 17 years of age. It is suggested that more Valproate alone or in combination with Risperdal is used in maintenance treatment, which also confers discrete antidepressant properties, or Quetiapine with Valproate or Lithium (4, 5, 6, 7, 8, 15, 16, 17).

In TB-I patients with manic episodes or mixed features, a significantly higher response rate was observed with Risperidone (68.5%) than with Lithium (35.6%) and sodium valproate (24%) (6,18). This approach is similar with what was found in the present study.

The goals of long-term maintenance treatment are to reduce cycling frequency and emotional instability, maximize patient functioning, as well as achieve patient adherence to treatment (4, 6, 7, 8, 10, 16, 17, 18, 19).

The use of lithium is widely recommended in the literature as a first-line mood stabilizer, but monitoring of serum levels is necessary to avoid toxicity and the development of hypothyroidism and leukocytosis with its use, so it is dangerous to use it without blood control, especially in children and adolescents (6, 7, 8, 10, 18, 19).

In Cuba, its use is limited by difficulties in carrying out therapeutic control by performing lithemia tests.

It should be noted that it has been found in the literature that about 25.0% of patients abandon treatment in the first month, 44.0% in the first trimester, and 60.0% within the initial six months. therefore, the continuity of the studies becomes difficult (6, 7, 12, 14, 19, 20). The percentage of patients who abandoned the present study is lower than that found by the authors referred to.

Despite Fluphenazine being an antipsychotic of the typical neuroleptic type, its use in Bipolar Disorder has not been sufficiently studied, although its effectiveness in other acute psychotic disorders in doses from 2.5 mg to 10 mg (21). Juan Manuel Márquez Pediatric Hospital has been used in cases refractory to treatment with Risperdal and Haloperidol.

In patients using Valproate and Lithium as the only medication, percentages of positive response as mood stabilizers ranged from 30.0% to 50.0%, reaching 73.5% in some cases, the first and 42 0.0% to 63.0% in the second. Carbamazepine and Lamotrigine between 34% and 54%. Of the antipsychotics, Quetiapine has shown the highest response rates, higher than 80.0%. It is followed by Risperidone in around 50.0% of patients and Olanzapine whose response rate is 40.0% (6, 8, 19).

There is some evidence that olanzapine may prevent further episodes of mood disorders in patients who have responded during an acute manic or mixed episode and who have not previously had a satisfactory response to lithium or valproate (1, 4, 5, 6, 19). Studies have shown that prophylactic treatment with Lithium Carbonate was effective, since it decreased the frequency, severity and duration of the episodes, with a decrease in the number of admissions and a reduction in hospital stays (6, 7, 14, 18, 19).

Other studies have found highly diverse results, with the following medications being more associated with a good patient evolution as monotherapy: the antipsychotics, Quetiapine, Aripiprasol, Asenapine and Olanzapine and Haloperidol to a lesser degree, as well as their combined treatment with anti-recurrence agents such as Valproate and Lithium, the latter also as monotherapy, in addition to Topiramate and Lamotrigine (5, 6, 7, 8, 19). The results of the current work match with this approach, although an association of satisfactory clinical status was also found in patients who used carbamazepine alone or in combination with Risperdal.

In the reviewed literature, the effectiveness of Olanzapine, Risperdal and Haloperidol in achieving a good patient evolution is widely described. Of the anti-recurrences, Lithium and Valproate are reported as the most effective (1, 4, 5, 6, 7, 8, 12, 17, 18, 19, 22, 23), similar to our results.

It is noteworthy that medications used alone or in combinations are well tolerated by patients and that allowed an acceptable recovery at discharge, at 3 months and 6 months, however at one year they are almost 50% linked to an unsatisfactory evolution. This raises questions about what the cause will be: the drugs used or a group of factors, such as the natural history of the disease itself, biological vulnerability, the presence of psychiatric or medical comorbidity, the use of other types of drugs, age of the patient, the stage of development he is in or the character traits. responsibility of the family in the control of the treatment, the management of the patient and the disease, their socioeconomic, intellectual and cultural level, the presence of psychiatric diseases in family members directly related to the care of these patients and the characteristics of the dynamics familiar. The school or work environment and their cooperation in the patient's pharmacological and non-pharmacological treatment and social support networks may also influence them.

4. Conclusion

The diagnosis of PKAN, although it is a rare disease, should be considered in the differential diagnosis of children and adolescents with the progression of clinical manifestations, including extrapyramidal dysfunction, and dementia, even in the absence of tiger eye MRI at the onset of manifestations or its one-sided presence. In the case presented, psychiatric manifestations were the cause of admission from the beginning and its persistence and poor response to treatment may be a manifestation that alerts us to the presence of this disease.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare that they have no conflict of interest.

Statement of ethical approval

The present research work does not contain any studies performed on animals/humans subjects by any of the authors.

Statement of informed consent

All data published here are under consent for publication.

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