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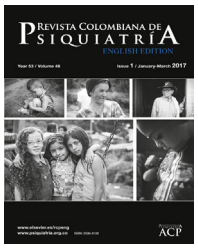

Review Article

Psychiatric disorders secondary to neurometabolic disorders☆

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ABSTRACT

Some diseases secondary to inborn errors of metabolism are associated with psychiatric disorders or minor neurological symptoms. The existence of some cases with exclusively psychiatric symptoms represents a diagnostic and therapeutic challenge. The aim of this article is to describe seven treatable neurometabolic disorders that should be taken into account in the psychiatric consultation as they manifest with psychiatric symptoms that mask the organic origin of the disorder. Homocysteine metabolism and urea cycle disorders, Wilson's disease, Niemann-Pick disease Type C, acute porphyria and cerebrotendinous xanthomatosis are described. Following an analysis of the literature, a list of psychiatric symptoms associated with these disorders are proposed, ranging from insidious changes in affective state and thought to atypical symptoms such as visual hallucinations, as well as paradoxical effects of antipsychotics or behavioural disorders in children and adolescents associated with loss of autonomy. The most frequently associated neurological signs, such as alterations in the state of consciousness, motor behaviour and balance disorders, catatonia or progressive cognitive deficit are also listed. Emphasis is placed on the importance of considering resistance to antipsychotic treatment as a warning sign to suspect organicity, as well as the significant improvement in psychiatric impairment when effective and early treatment is established.

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Trastornos psiquiátricos secundarios a enfermedades neurometabólicas

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RESUMEN

Hay algunas enfermedades secundarias a errores innatos del metabolismo que se asocian a trastornos psiquiátricos o síntomas neurológicos menores. La existencia de algunos pacientes con signos únicamente psiquiátricos representa un desafío diagnóstico y terapéutico. El objetivo del presente artículo es describir 6 enfermedades neurometabólicas tratables que se presentan con síntomas psiquiátricos que camuflan su origen orgánico, con el propósito de que se las tome en cuenta en la consulta psiquiátrica. Se describen los trastornos del metabolismo de la homocisteína y del ciclo de la urea, la enfermedad de Wilson, la enfermedad de Niemann-Pick tipo C, la porfiria aguda y la xantomatosis cerebrotendinosa. El análisis de la literatura lleva a proponer una lista de síntomas psiquiátricos asociados con dichas afecciones, que abarcan desde los cambios insidiosos del afecto y el curso del pensamiento hasta síntomas atípicos, como alucinaciones visuales, efectos paradójicos de los medicamentos antipsicóticos y trastornos del comportamiento de niños y adolescentes que conllevan degradación de la autonomía. Asimismo se listan los signos neurológicos más frecuentemente relacionados, como las alteraciones del estado de conciencia, los trastornos de la conducta motora y el equilibro, la catatonia o el déficit cognitivo progresivo. Se hace hincapié en la importancia de considerar la resistencia al tratamiento antipsicótico como una señal importante para sospechar organicidad y la mejoría significativa de la alteración psiquiátrica cuando se instaura un tratamiento eficaz y precoz.

Introduction

Neurometabolic disorders (NMDs) are also known as inborn errors of metabolism or congenital errors of metabolism. Depending on the evolution time and systems affected, they may present acutely with non-specific symptoms such as digestive and respiratory disorders, rapid neurological decline of unknown origin, or through late-onset clinical manifestations of recurrent episodes of somatic decompensation. They may also present with behavioural disorders or diverse psychiatric symptoms.

Psychiatric manifestations are considered an unusual form of presentation that complicate diagnosis, precisely because of their rarity.[1]

NMDs have a genetic origin. The majority present a deficit relating to the conversion of a substrate that inhibits the production of one or several enzymes. The metabolic mechanisms and processes are complex and diverse, but share one common denominator: the wide range of organic disorders. In various NMDs, the absence of an essential product from birth or the accumulation of a product have a damaging effect on neurodevelopment, which explains the frequency of neurological or psychiatric signs, as well as anomalies in different organs or viscera.

These conditions are well known by paediatricians in their most severe forms, thus enabling early diagnosis and, if possible, timely treatment. However, late-onset manifestations may also be detected, accompanied by discreet symptoms or symptoms that go unnoticed. The interest surrounding knowledge of these entities, particularly among psychiatrists, lies in the fact that some diseases can emerge with psychiatric and neurological signs that remain silent for many years.

Recent advances in enzyme therapy and the proven efficacy of other therapies—such as regimens of oral vitamins or specific medicines—facilitate the treatment of these entities and significantly improve patients' quality of life.

This article is confined to NMDs that present with schizophreniform manifestations.

Neurometabolic diseases in Latin America

Studies on the psychiatric manifestations of NMDs in the Latin American population are few and far between.

In a study on a paediatric Mexican population, 72 patients with hyperammonaemia were reviewed, in whom an inborn error of metabolism was only proven in 11 cases. The most common clinical symptoms were drowsiness, lethargy, irritability, developmental delay and refusal of food, as well as seizures, stupor, hypotonia and vomiting.[2] In an Argentinean study between 1970 and 2003, NMD-related conditions were diagnosed in a group of psychiatric patients, with cases of Wilson's disease, Krabbe disease and homocystinuria being detected.[3] Finally, one case report was found concerning an adult Mexican patient with acute porphyria and a history of hallucinations, irritability and depression.[4]

Neurometabolic disorders and psychiatric disorders

As well as the neuropsychiatric disturbances of schizophrenia, some schizophreniform disorders are associated with organic conditions.[5] NMDs have been described among these causes. In a study of 268 schizophrenic patients, an organic cause was identified that was able to explain the psychiatric

symptoms in 6% of cases.[6] Due to limited symptom explorations in the mental disorder patient population, this prevalence is considered likely to be underestimated.[7] Individually, each neurometabolic disorder is rare. However, the cumulative incidence of NMDs is relatively high, at around 1 in 1500 to 1 in 5000 live births.[8]

The six entities described below may present as psychiatric diseases, eclipsing the suspicion of an organic origin and delaying diagnosis and, thus, timely treatment.

Homocysteine metabolism disorders

Disorders of homocysteine metabolism are diverse. The most widely known are cystathionine beta-synthase (CBS) deficiency, methylenetetrahydrofolate reductase (MTHFR) deficiency and disorders of cobalamin (vitamin B_{12}), folic acid or pyridoxine transport or metabolism.[9]

CBS normally metabolises homocysteine using vitamin B_{12} and folic acid. A deficiency thereof is related to homocystinuria. It has a prevalence of around 1 in 350,000 births and has an autosomal recessive inheritance pattern. Homocysteine accumulation gives rise to varying symptoms, including skeletal abnormalities and the Marfan morphotype. Thromboembolic disorders may also arise. *Ectopia lentis* and severe myopia are reported in 85% of cases. Mental disability is common. Psychiatric signs affect up to 50% of said patients, mostly in relation to mood disorders, anxiety and obsessive compulsive disorder.[10] Psychotic symptoms have also been described and may be present without any other symptom. Despite having no psychiatric history or risk factors, cases of patients with visual hallucinations, agitation and a poor response to antipsychotics have been reported.[11,12]

MTHFR deficiency is a recessive autosomal abnormality caused by a mutation in the MTHFR gene (1p36.3).[13] The presence of a MTHFR allele polymorphism has been associated with the appearance of schizophrenia and early-onset bipolar disorder.[14] *De novo* signs of bipolar disorder and schizophrenia may precede somatic symptoms. Such cases represent 2.8% of cases of this type of NMD.[15] Diagnosis is generally early and founded on neurological symptoms such as hypotonia, developmental delay, microcephaly, epilepsy and gait and coordination disorders, or severe symptoms such as recurrent episodes of apnoea and coma.[16] Schizophrenic disorders have been described as possible late-onset symptoms that present with colourful symptoms which contrast with previous social functioning.[17–19] Polymorphic hallucinations—often visual—may occur, along with delusional interpretations, aggression, paranoid ideation or catatonia.[20–22] Behavioural disorders in these NMDs have a generally insidious onset[23], though sudden onsets have also been described following a surgical intervention.[24]

While folic acid deficiency has been associated with certain symptoms of depression[25], cobalamin deficiency has been linked to the onset of psychosis.[26,27]

Diagnosis is made using amino acid chromatography and a homocysteine test. Treatment consists of the administration of folic acid and vitamin B_{12} or a low-methionine or high-cysteine diet.

Urea cycle disorders

The metabolism of the urea cycle consists of nitrogen elimination *via* the intracellular organelles. The absence of one of the six enzymes involved in this cycle disrupts proper functionality and causes ammonaemia. The prevalence of urea cycle disorders (UCDs) stands at 1 in 8000 births. The severity of the disorders is related to the degree of enzyme deficiency. There are mild forms that generally involve nausea, vomiting and headaches in patients exposed to a high protein intake.[28] Corticosteroids and valproic acid exacerbate the symptoms.[29] Psychiatric signs are common and may comprise mood disorders or auditory or visual hallucination episodes.[30] The condition may follow an acute or subacute course.[31,32]

Cases have been reported of psychiatric patients presenting acute and very intense symptoms, such as states of agitation, confusion and loss of autonomy, coma and convulsions.[33,34]

The combination of acute visual hallucinations and vomiting in the context of medication intake or a high-protein diet should point to a UCD, for example, in people taking protein supplements. Special care should be taken if psychiatric manifestations emerge following the administration of valproic acid.[35,36] To confirm the suspected diagnosis, an ammonia blood test may be carried out. Prompt diagnosis is vital, due to the risk of a fatal outcome. Treatment consists of restricting the patient's protein intake.[37]

Acute porphyria

Porphyrias are a group of eight diseases that cause the accumulation of porphyrin or its precursors. Its manifestations are intermittent, neurovisceral and cutaneous, and may occur separately or together. δ-Aminolevulinic acid (δ-ALA) and porphobilinogen (PBG) accumulate mainly in the liver and bone marrow. Prevalence is estimated at around $5.4/10^6$ people. Symptoms generally appear in adulthood, though there are reports of prepubescent cases.[38] A symptomatic triad has recently been recognised, comprising abdominal pain, peripheral neuropathy and mental changes.[39] Acute hepatic porphyrias may have gastrointestinal manifestations alongside neurological and psychiatric symptoms. In the acute phase, psychiatric recurrences have been reported in 24–70% of cases.[40–44] The most common clinical symptoms are delusions, hallucinations and thought or mood disorders. Depressive manifestations are predominant, although cases of disorientation, mutism and echolalia have been reported in adolescents.[39] Some authors report that a delusional presentation may occur in up to 40% of these patients.[42] Moreover, patients who have already been diagnosed may experience severe psychiatric episodes—such as suicide attempts—during an acute crisis.[45] Certain psychotropic medicines may exacerbate these crises.[46]

Crimlisk[47] described three illustrative cases of neuropsychiatric porphyria manifestations, including one regarding three adults who presented with somatic complaints—such

as intense headache, seizures, fever and abdominal pain—at the onset of the condition, preceding the psychiatric symptoms. One of the cases was diagnosed during an episode of decompensation and abdominal pain, with high urine concentrations of δ-ALA and PBG successfully identified. It must be stressed that laboratory results may come back negative, particularly in asymptomatic periods.[48]

The disease should be suspected in the presence of polymorphic psychotic symptoms with asymptomatic intercritical periods that present with similar and recurrent somatic complaints during crises.[49] Definitive diagnosis is based on δ-ALA and PBG blood and urine tests. Treatment consists of a human hemin injection and carbohydrate infusions.

Wilson's disease

Wilson's disease is an autosomal recessive entity caused by a mutation in the ATP7B gene, which encodes an intracellular copper-transporting protein (CPx-type ATPase).[50] Prevalence is estimated at 1 in 30,000 inhabitants, although some studies have found a high frequency (1 in 10,000) in specific populations.[51,52]

Psychiatric symptoms may occur in the early stages of development.[53] It is estimated that half of patients present psychiatric disorders, and approximately 20% of them have no organic symptoms.[54]

Psychiatric manifestations have three predominant signs: personality changes, irritability and aggressive behaviour.[55] Mood disorders with both depressive and manic manifestations have also been described[56] as well as, less frequently, a form of presentation similar to schizophrenia, with severe episodes of catatonia.[54]

In a retrospective study performed on a sample of 282 patients with Wilson's disease, a frequency of 2.4% was found regarding the expression of psychiatric symptoms.[57] Previous studies had reported up to 10% of cases.[58] The existence of hallucinations has been described in a number of reports.[59,60] Early diagnosis is particularly important, as the condition can have cognitive, learning-related and academic consequences that may be attenuated if timely treatment is administered.[61]

The treatment of psychiatric disorders poses a significant challenge in these patients, since the use of antipsychotics may exacerbate the symptoms. This eventuality may prompt suspicion of the disease in the absence of other organic symptoms, much like the exacerbation of adverse neurological effects that we would expect to find to a lesser degree with the use of second-generation antipsychotics.[62]

Diagnosis is achieved using magnetic resonance imaging, which reveals hyperintense signals in the thalamus and lenticular bodies. Measuring blood copper levels, or even the existence of the classic Kayser–Fleischer ring in the ophthalmology exam, enables easy diagnosis and detection, but prove that the disease is at an advanced stage.[63] Treatment is based on copper chelation.[64] Electroconvulsive therapy has proven effective in the event of intense symptoms or side effects to antipsychotics.[65]

Niemann–Pick disease type C

Niemann–Pick is an autosomal recessive disease characterised by sphingomyelin deposits in various organs. Type C (NPC) presents with abnormalities relating to the cellular processing and transport of low density lipoproteins. 95% of cases are associated with a NPC1 mutation and 4% with a NPC2 mutation.[66]

These mutations cause an anomaly in the transport of intracellular cholesterol and lead to accumulation in the lysosomal compartment. Early symptoms are mostly neurological. Neonates may present with jaundice, splenomegaly, ascites and severe hepatic or pulmonary diseases caused by infiltration.[29] The condition classically presents during mid to late childhood, with ataxia and vertical supranuclear gaze palsy. These may coexist alongside dysarthria, dysfunctional dysphagia, deafness or cataplexy. Although systemic insufficiencies generally precede psychiatric symptoms, 15% of patients are reported to have late symptoms of cataplexy with or without narcolepsy, disorientation, psychosis or progressive dementia, even after 70 years of age. Psychotic symptoms include paranoid delusions, auditory or visual hallucinations and thought disorders with ideas of reference.[67] Other late psychiatric manifestations include bipolar disorders or obsessive compulsive disorder.[66] When said symptoms are the first to appear, this may be a prime opportunity for the early identification and treatment of the disease.

Some cases of schizophrenia spectrum disorders with no neurological signs have been reported in adolescent or adult patients,[68,69] as well as autism spectrum disorders.[70,71] In most cases, visual hallucinations are a symptom that makes up a very sizeable part of the patient's subjective complaint.[72] One of the signs on which attention should be focused is supranuclear gaze palsy, since it is an early sign that is present in almost every case.[73] To assess it, the patient is asked to follow the examiner's finger with their eyes, but cannot do so spontaneously without guidance.[74]

Diagnosis is made by means of a skin biopsy and fibroblast culture, DNA sequencing for NPC1 or NPC2 mutations or oxysterol detection.[29] Treatment options include the use of non-steroidal anti-inflammatory drugs (NSAIDs) alone or in combination with miglustat. Though not curative, this medicine has been shown to decelerate the evolution of the disease.[75]

Cerebrotendinous xanthomatosis

Cerebrotendinous xanthomatosis (CTX) is a disease that affects bile acid synthesis caused by an autosomal recessive mutation in the CYP27A1 gene. The condition causes a deficiency of the mitochondrial enzyme P450 sterol 27-hydroxylase, which leads to an accumulation of cholestanol in various visceral tissues—including the brain—and the formation of xanthomas.[76] The prevalence has been estimated at 1 in 50,000 among the Caucasian population, although other authors have reported a prevalence of up to 8.7 in 10,000 depending on the type of mutation.[77,78]

The clinical presentation is variable and includes chronic diarrhoea starting in childhood, along with psychomotor retardation, juvenile cataracts and progressive neurological disorders such as epilepsy and Parkinsonism.[79] In the forms that present during adolescence, neurological signs such as progressive spastic paraparesis, cerebellar ataxia and polyneuropathy appear at the forefront, as well as cognitive impairment and psychiatric symptoms.[80,81] Tendon xanthomas are a clear sign that should prompt diagnostic suspicion. Magnetic resonance imaging shows a typical hyperintense signal in the dentate nuclei of the cerebellum.[76]

Acute episodes have been described as schizophreniform-type outbreaks, although psychomotor agitation, attention deficit hyperactivity disorder (ADHD) and cognitive impairment are more common.[82] A bimodal/bitemporal pattern has been observed in the onset of these symptoms: early outbreaks in the form of non-specific behaviour and personality disorders, alongside learning difficulties and mental retardation, and late phases expressed as dementia with frontalization symptoms, an upsurge in behavioural, personality or mood disorders, and even psychotic manifestations with notable disorganised thinking.[83] Diagnostic confirmation is attained by identifying the CYP27A1 mutation and measuring plasma cholestanol.[84] Treatment is based on chenodeoxycholic acid, the effects of which are greater the earlier it is instituted.[85] Dietary changes may also help to prevent the exacerbation of symptoms.[81]

Discussion

Schizophrenia spectrum disorders are associated with various neurological, immune, neurometabolic, genetic and endocrine diseases. However, the pursuit of organic disorders in psychiatric diseases is not usually a priority, but should be systematic, particularly in children. There is still lots to be learned about the prevalence of organic disorders in this group of patients. The prevalence of schizophrenia in the general population is known to be around 1%, but the incidence of the associated aetiological factors is unknown.[13,18,20,86] In some case series, the early-onset forms of schizoaffective disorder show a strong association with underlying organic aetiologies.[87] Severe psychiatric symptoms such as catatonic states in children and adolescents, which are mostly related to schizophrenic disorders, coincide with organic diseases in 10–15% of the cases reported.[88] In this sense, genetic associations such as the 22q11 microdeletion—present in 1–2% of schizophrenic patients—should be taken into account.[89,90]

One of the greatest difficulties stems from distinguishing between causality and comorbidity.[91] The presence of psychiatric symptoms in paediatric populations may discourage clinicians during the exploration of important neurological signs, mislead diagnosis and cause a delay in the detection of the underlying organic disease.[92,93]

Taking into account the database found in the literature, we propose a list of warning signs that may help clinicians to direct their search for a chronic organic disease, in particular a NMD:

- Resistance to antipsychotic treatment.
- Paradoxical response to antipsychotics.
- Severe neurological adverse effects after administering some form of antipsychotic: akinesia, dystonia, dysarthria, ataxia, convulsions, catatonia, impaired consciousness and coma.
- Rapid onset of psychiatric disorders in patients with a history of convulsions or developmental delay.
- Early-onset of psychiatric symptoms alongside mental retardation or progressive cognitive impairment in children with previous normal development, since cognitive impairment is not directly related to childhood schizophrenia.
- Onset of catatonia associated with atypical elements.

A biological assessment of the neurometabolic anomalies detected would be advisable for all patients, particularly in cases of high NMD suspicion, and even more so in children and preadolescents.[94]

Conclusions

The literature review shows that it is not unusual for certain organic diseases such as NMDs to be associated with psychiatric disorders, particularly schizophrenia spectrum disorders. The early detection of these cases is thus extremely important, especially when they are treatable or improvable conditions, as in the case of NMDs. The utility of systematically exploring atypical elements in psychiatric disorders is indispensable both due to its usefulness in public health and because this is a legitimate right of all patients with psychiatric symptoms, whose quality of life may be improved. More studies are required in Latin America in order to better understand the implications on our local population.

Conflicts of interest

The authors have no conflicts of interest to declare.

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