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CLINICAL CASE REPORTS

Early Onset Psychosis in an Adolescent with Copper Metabolism Alterations: Primary or Secondary Psychosis?

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ABSTRACT

Primary psychotic disorders in adolescents are uncommon in adolescence and require careful investigation of alternative etiologies. Wilson's disease (WD) is one of the metabolic disorders that should be considered in the differential diagnosis. We report the case of a 15-year-old male who was admitted to an Inpatient Psychiatric Unit due to new-onset psychotic symptoms characterized by disorganized behavior and thought processes, psychomotor agitation and near-total insomnia. The patient was diagnosed with a brief psychotic disorder and later investigated for WD, based on an elevated urinary excretion of copper. He had a Ferenci Score of 5, but after genetic investigation with both parents, the diagnosis was not confirmed. We discuss the hypothesis that abnormalities in copper metabolism may have played a role in the onset and persistence of the psychiatric symptoms, given the essential role of copper in central nervous system functioning, affecting different pathways that have been associated with a wide range of psychiatric disorders.

Keywords: adolescent; copper metabolism; early-onset psychosis; psychiatry; psychosis

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INTRODUCTION

Primary psychosis in adolescents is not common and requires careful investigation of alternative etiologies, namely neurologic, infectious, genetic, autoimmune, rheumatologic, endocrine, nutritional, metabolic, iatrogenic causes and inborn errors of metabolism. Wilson's disease (WD), an autosomal recessive genetic disorder of copper metabolism, is one of the metabolic conditions that should be considered in the differential diagnosis.[1]

Copper is an essential trace element, and is an important cofactor for many enzymes required for cellular respiration, iron oxidation, pigment formation, neurotransmitter biosynthesis, antioxidant defense, and connective formation.[2]

In WD there is a shortage of functional *ATP7B*, a copper-transporting protein, found primarily in the liver, that promotes biliary copper excretion when copper levels are excessive, this being the principal homeostatic mechanism regulating copper metabolism. As a result, copper accumulates to toxic levels that can damage tissues and organs, most frequently resulting in hepatic and neuropsychiatric manifestations.[3]

The most common psychiatric manifestations of WD are mood disorders and behavioral disturbances, particularly irritability, aggression and antisocial behavior, whereas psychotic symptoms are a relatively rare presentation.[4]

CASE DESCRIPTION

We report the case of a 15-year-old male who was admitted to a Child and Adolescent Inpatient Psychiatric Unit due to new-onset psychotic symptoms characterized by disorganized behavior and thought process, tangential thought, persecutory, nihilist and reference delusions, and auditory verbal hallucinations, including command hallucinations. These symptoms were accompanied by significant anxiety and psychomotor agitation, occasionally resulting in self-injury. The patient also reported near-total insomnia. Symptoms onset was abrupt, approximately 15 days prior to admission. Laboratory investigations revealed a normal complete blood count, apart from a mild neutropenia of 2,88 x 10^9/L. Total bilirubin was slightly elevated, at 0,87 mg/dL, but otherliver function tests were within normal limits. Renal and thyroid function were normal, as were folate and vitamin B12 levels. Serum ceruloplasmin level was slightly decreased (0.14 g/L), serum-copper was within the normal range (62 mcg/dL) and 24-hour urinary copper excretion was elevated (832 mcg). Brain magnetic resonance imaging (MRI) was normal.

Regarding previous history, early psychomotor development was globally normal. He was first referred for psychiatric evaluation at the age of 8 because of inattention, overactivity, irritability, short attention span and forgetfulness, for which he was diagnosed with attention-deficit/hyperactivity disorder and treated with methylphenidate, with good clinical response. Learning difficulties were reported since early school years, and there was a previous cognitive evaluation, which reported a medium-inferior IQ. Fluctuating depressive symptoms were reported since the 8th grade, and there was a family history of bipolar disorder. The patient was diagnosed with a brief psychotic disorder and antipsychotic (risperidone 2 mg/day and olanzapine 5 mg/day) and mood stabilizer (valproic acid 800 mg/day) therapy was initiated. He was discharged after 20 days of inpatient treatment, having achieved remission of psychotic symptoms. Given the abnormalities in ceruloplasmin and urinary copper levels, the patient was referred to a metabolic disorders consultation, for further investigation.

Genetic testing of the *ATP7B* gene revealed two heterozygous variants,; one classified as pathogenic and the other as a variant of uncertain significance. Ophthalmology evaluation revealed no Kayser-Fleischer rings. A liver biopsy was also performed, but the results were inconclusive, although hepatic copper concentration was reported as mildly elevated. Following this investigation, the patient was assigned a Ferenci Score of 5, based on the presence of psychiatric symptoms, low ceruloplasmin levels, elevated urinary copper excretion, mildly increased hepatic copper concentration, and the identification of one pathogenic *ATP7B* variant together with one variant of uncertain significance. He was subsequently referred to neurology and genetics appointments.

Neurological evaluation revealed mild psychomotor retardation, postural tremor of the upper limbs, and mild appendicular bradykinesia.

Despite these clinical findings, genetic testing of both parents demonstrated that both variants were inherited from the same parent, and therefore the diagnosis was not confirmed. At the beginning of outpatient psychiatric follow-up, the patient presented with significant extrapyramidal symptoms (EPS), including hypomimia, bradykinesia, appendicular tremor and axial rigidity. These symptoms improved globally after an initial reduction in antipsychotic dosage and a subsequent switch to aripiprazol. Nevertheless, the patient persisted with mild EPS, namely hypomimia, bradykinesia and appendicular tremor,which his parents did not distinguish from his premorbid state.

One year after discharge, the patient had no recurrence of psychotic symptoms, being currently treated with aripiprazol 15 mg/day, suggesting a favorable response to antipsychotic treatment. During follow-up, as the doses of antipsychotic and mood stabilizer were reduced, the irritability described premorbidly became apparent, with low tolerance to frustration and slight emotional dysregulation, for which the treatment with valproic acid was maintained.

DISCUSSION

This patient presented with unspecified copper metabolism abnormalities that appared to impair adequate

copper homeostasis. Although WD was ultimately excluded, we discuss the hypothesis of copper metabolism alterations having played a role in the onset and maintenance of the psychiatric symptoms.

It is noteworthy that heterozygous carriers of ATP7B variants may exhibit reduced serum ceruloplasmin concentrations, borderline normal urinary copper, elevated urinary copper excretion following D-penicillamine challenge testing, and/or moderate elevation of hepatic copper concentration. Such findings could account for the reported biochemical abnormalities observed in this patient, even in the absence of a WD diagnosis.[5]

Copper is essential for normal central nervous system functioning, as it modulates brain synaptic transmission through its effects on N-methyl-D-aspartate receptors, gamma-aminobutyric acid-A receptors, voltage-gated calcium channels and glial apoptosis, all of which have been associated with a wide range of psychiatric disorders.[6]

Other mechanisms that might explain psychiatric features in WD, and which may therefore be relevant to case of this patient, include direct copper toxicity, neurotransmitter imbalances, oxidative stress, mitochondrial dysfunction, cuproptosis, ferroptosis, mitophagy, neurotrophic factor deficiencies and *ATP7B* mutations.[6]

Given this considerations, and despite the potential risks associated with treatment, we hypothesize that this patient may benefit from de-coppering therapy with chelators or zinc, as well as dietary copper restriction, which constitute the current standard treatments for WD.[3] We also question the optimal strategy for long-term monitoring. If the patient had WD, serum copper levels, liver function and neurological status would require regular assessment.[3] At present, the medical follow-up plan of the patient consists of maintaining gastroenterology appointments and re-evaluating liver function and copper levels, without a specific monitoring schedule.

Being a carrier of a pathogenic variant in heterozygosity, preconception genetic counseling is recommended. Although the clinical significance of the copper metabolism alterations in this patient remains uncertain, he has shown a favorable response to treatment with antipsychotics and mood stabilizers and has remained clinically stable throughout follow-up. However, relapse rates after a first psychotic episode are substantial, and increase further if antipsychotic treatment is discontinued.[8] Futures research in the field of secondary psychosis may help clarify the relationship between copper metabolism disturbances and psychiatric symptoms and hopefully allow for better treatment outcomes.

On a brief note regarding the psychopharmacological management, a mood stabilizer was added to the baseline treatment with second-generation antipsychotics because of the family history of bipolar disorder, previous history of depressive symptoms and complaints of near-total insomnia prior to admission, leading us to consider the hypothesizes of a bipolar psychosis.

This case highlights the diagnostic and prognostic complexity in an adolescent with a first psychotic episode and unspecified abnormalities of copper metabolism, and underscores the importance of thoroughly investigating underlying causes in new-onset psychosis.

AUTHORSHIP

Sofia Lemos – Conceptualization; Data Curation; Investigation; Methodology; Writing -original draft

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M. Magarida Venâncio - Supervision; Writing - review & editing

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