Acute Psychosis and Movement Disorders as First Presentations of Wilson's Disease

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Wilson's disease is a rare (1:30,000) autosomal recessive disorder of copper metabolism that is caused by mutations in the *adenosine triphosphatase copper transporting beta* (*ATP7B*) gene, located on chromosome 13. This gene encodes for copper-transporting adenosine triphosphatase (ATPase) [1-3]. Without proper treatment, Wilson's disease is progressive and fatal. In 40–50% of patients, hepatic dysfunction is the initial manifestation [2,3]. For 40–60% of individuals; however, diverse neuropsychiatric signs are the initial clinical manifestation. Psychiatric manifestations include depression, personality changes, behavioral problems, and psychosis [1-3]. A considerable number of patients are initially treated with psychiatric medications before Wilson's disease is diagnosed. Other organs can be involved, leading to diverse manifestations such as Kayser–Fleischer rings, renal tubular acidosis, premature osteoporosis, arthritis, cardiomyopathy, pancreatitis, hypoparathyroidism, and infertility [2,3]. The primary treatment is based on copper chelating agents. Although non-definitive, efficient treatments ameliorate the disease's progression and achieve a partial or total reversibility of symptoms. Liver transplantation, restricted to patients with liver failure, is the most effective treatment currently available [2].

*The last two authors contributed equally to this study

PATIENT DESCRIPTION

An 18 year old female patient was admitted to the adolescent psychiatric department for reassessment and treatment of a protracted psychosis accompanied by an unusual motor disorder. She had been presenting with paranoid delusions, irritability, and sleeping problems since the age of 16. Prior to that, she exhibited no psychiatric or neurological signs, and she had been a good student. The family history was negative for psychiatric or neurological disorders. The patient was first treated with a low dose of an antipsychotic agent (2 mg risperidone per day). Her mental status improved and the delusions disappeared.

She resumed her successful studies. One year later, following cessation of anti-psychotic treatment, the patient immediately fell into a psychotic state, with identical signs and symptoms of paranoid delusions and irritability. Risperidone renewal was prescribed, and the psychiatric manifestations rapidly vanished. However, uncontrolled motoric symptoms appeared, first in the facial area and then throughout her body, including her limbs and trunk. These symptoms were diagnosed as tardive dyskinesia. Electroencephalography, a brain computed tomography scan, and a magnetic resonance brain imaging were unremarkable. Risperidone was changed to olanzapine 5 mg per day, resulting in a reduction of involuntary movements. Following a year of mental stability, including the successful completion of high school, olanzapine doses were reduced. The motor symptoms persisted without any improvement, paranoid delusions relapsed, and rapid mood changes emerged. Olanzapine re-dosing to 5 mg per day failed to achieve clinical improvement. At this point, medical treatment was discontinued and the patient was admitted to a child and adolescent psychiatric department.

At admission, the patient had uncontrolled choreiformic movements involving her face, trunk, and hands. She presented with profound irritation, labile mood swings, associative thinking, and paranoid delusions. The combination of psychiatric symptoms with unusual motor symptoms raised suspicion of a non-psychiatric source for her illness. Apart from the uncontrolled movements, physical and neurological exams revealed no significant pathological findings. The patient underwent a routine workup, including complete blood count, blood electrolytes, kidney and liver function tests, and thyroid function tests. The tests showed mild normocytic anemia (hemoglobin 11 gram%, mean corpuscular volume approximately 86 femtoliter), a mild lactic dehydrogenase elevation (600 units per liter; the upper normal limit being 480 units per liter), elevated chloride (109

mmol/L), and low serum uric acid values of 197 mmol/L (normal ranges 202–416 mcmol/L). These results suggested hemolysis and renal tubular acidosis, which supported a diagnosis of Wilson's disease. Low serum ceruloplasmin levels of 11.5 mg% (the normal range is > 17 mg%) and a mild increase of urine copper excretion of 66 µg per volume over 24 hours (the normal range is < 50 µg per volume for 24 hours). This level rose to 460 µg per volume for 24 hours in a penicillamine exposure test and was compatible with a diagnosis of Wilson's disease. Positive antinuclear antibodies were observed, but with normal immunoglobulins. Otherwise, no significant abnormal results were recorded from tests, including liver enzymes, haptoglobin, and international normalized ratio. Abdominal ultrasound also supported the diagnosis of Wilson's disease as it showed mild splenomegaly (13 centimeters) and nodular pattern of liver parenchyma.

Since no Kayser–Fleisher rings were seen by a consulting ophthalmologist, a liver biopsy was performed. A high liver tissue copper concentration of 265 µg/g dry weight of tissue was shown, which is diagnostic for Wilson's disease (the normal range is < 50 µg/g dry weight of tissue), with almost normal liver histology. Therefore, the patient was diagnosed with Wilson's disease. At this stage, clozapine treatment (an antipsychotic agent with minor motor side effects) significantly improved both psychiatric and motor symptoms. In parallel, penicillamine and a vitamin B supplement were initiated and then changed to trientine dihydrochloride, due to thrombocytopenia. Both neurological and psychiatric symptoms resolved. After 3 years without any symptoms, the clozapine treatment was gradually stopped.

Some months later, at the age of 22 years, the patient presented a transitory psychotic episode, most likely as a result of irreversible brain damage due to copper accumulation. Clozapine treatment was re-initiated. Five years later she is completely stable and free of psychiatric and neurologic symptoms, and is studying at university.

COMMENT

When an adolescent or young adult experiences the onset of psychiatric symptoms accompanied by significant neurological signs and miscellaneous motor symptoms, clinicians should suspect an identifiable organic origin.

Wilson`s disease is one of the rather rare but important hereditary metabolic disorders that can give rise to psychiatric manifestations. Other such disorders include urea cycle abnormalities, remethylation disorders, acute intermittent porphyria, Niemann–Pick disease, homocystinuria, cerebrotendinous xanthomatosis, lysosomal storage diseases, X-linked adrenoleukodystrophy, and creatine deficiency syndrome [4].

Wilson's disease causes copper accumulation in the basal ganglia. Antipsychotic agents generate motor side effects by influencing dopaminergic neurons in the basal ganglia. Thus, the possibility arises that copper accumulation in Wilson's disease makes the basal ganglia more vulnerable to the undesirable motor side effects of antipsychotic agents. It therefore seems appropriate to have a high level of suspicion for Wilson's disease in this situation. Since long-term copper accumulation caused by Wilson's disease can lead to irreversible damage to end organs, missing or delaying a diagnosis impacts morbidity and even mortality. Jukić and colleagues [5] described a comparable case in which a 26 year old woman presented with acute psychosis as a first manifestation of Wilson's disease. A few days after the initiation of haloperidol, she developed abnormal involuntary limb movements, which were first considered, as in the case we describe, as a side effect of the antipsychotic agent. The delayed diagnosis of Wilson's disease in this case left her with chronic damage.

Our patient was diagnosed at a stage of early hepatic manifestation of Wilson's disease, but with advanced brain involvement that presented as neuropsychiatric features. The relatively early diagnosis and treatment saved her from severe progression and even achieved almost full remission. Although copper chelators are available, optimal chelation is usually not achieved, and Wilson's cases may progress even with therapy, albeit more slowly. Adherence to chelators is a challenge but was the correct course in our case. Future novel therapies are being studied, mainly for neuropsychiatric manifestations, as the classical ones are not completely optimal.

Our case description illustrates the need for increased awareness of the neuropsychiatric manifestations of Wilson's disease, especially atypical ones. We must be alert to patients presenting with psychiatric symptoms and signs who demonstrate unusual sensitivity to the motor side effects of antipsychotic agents. Although typical hepatic copper content in our case was diagnostic for Wilson's disease, the non-specific features of anemia and electrolytes were also suggestive of the diagnosis. Thus, these signs should be recognized within the psychiatric community as simple biomarkers for the disease. While Kaiser–Fleischer Rings are considered to be a mandatory diagnostic sign of central nervous system involvement in Wilson's disease, absence of these rings does not rule out the diagnosis. In fact, in about 2% of patients with neuropsychiatric manifestations of the disease, this marker may be absent, as in the described case. The percentage is much higher for patients who only demonstrate liver manifestation [3].

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