

WILSON DISEASE

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ABSTRACT

Wilson disease (hepatolenticular degeneration) is due to a genetic abnormality inherited in an autosomal recessive manner that leads to impairment of cellular copper transport. The clinical manifestations of Wilson disease are predominantly hepatic, neurologic, and psychiatric, with many patients having a combination of symptoms. Regardless of the clinical manifestations present initially, patients often develop other clinical manifestations as the disease progresses. Behavioral and psychiatric symptoms are more common in patients with neurologic involvement than in patients with hepatic involvement. However, behavioral and psychiatric symptoms due to Wilson disease are often misdiagnosed.

This article presents the case of a 23 year old male, presenting with psychiatric symptoms (depressions, insomnia) which progressed despite psychiatric treatment. After two years he was diagnosed with Wilson disease, confirmed by genetic testing.

Keywords: Wilson disease, psychiatric symptoms, ATP7B gene mutation

INTRODUCTION

Wilson disease (hepatolenticular degeneration) is due to a genetic abnormality inherited in an autosomal recessive manner that leads to impairment of cellular copper transport. It is found worldwide, with a prevalence of approximately one case in 30,000 live births in most populations. Impaired biliary copper excretion leads to accumulation of copper in several organs, most notably the liver, brain, and cornea. Over time, the liver is progressively damaged and eventually becomes cirrhotic. The rate at which this occurs varies between patients. A small percent of patients (approximately 5 percent) develop acute liver failure, most often in the setting of advanced fibrosis of the liver. In addition, patients may develop neurologic complications, which can be severe.

The clinical manifestations of Wilson disease are predominantly hepatic, neurologic, and psychiatric, with many patients having a combination of symptoms (1). Hemolysis is also a common finding

in patients with acute liver failure due to Wilson disease, but sometimes may occur episodically independent of liver failure.

Patients may present with a wide variety of symptoms (especially those with neurologic symptoms) (2). Even within a given family, patients often present with different symptoms (3). There is wide variability in the reported rates of the different clinical manifestations seen at the time of presentation (2,4,5): liver disease: 18 to 84 percent of patients; neurologic symptoms: 18 to 73 percent of patients; psychiatric symptoms: 10 to 100 percent of patients. The wide variability in the estimates may in part be attributable to ascertainment bias based upon the clinical specialty to which the patient was referred (eg, to pediatricians where neurologic presentations are less likely, or to neurologists who are likely to see patients with neurologic symptoms).

Regardless of the clinical manifestations present initially, patients often develop other clinical manifestations as the disease progresses (eg, patients who present with liver disease may subsequently

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develop neurologic or psychiatric symptoms). Conversely, liver failure may develop in those whose neurologic or psychiatric symptoms led to the diagnosis of Wilson disease.

Patients with chronic hepatitis due to Wilson disease are often asymptomatic from their liver disease. Such patients are typically diagnosed through family screening, after being found to have abnormal liver tests, or after presenting with neurologic or psychiatric manifestations of Wilson disease. In addition, Wilson disease often results in hepatic steatosis and may be diagnosed in a patient being evaluated for nonalcoholic fatty liver disease (6). Most of these patients have a low level of serum ceruloplasmin, but only 50 percent have Kayser-Fleischer rings. Almost all have liver copper concentrations of >250 mcg/g dry weight liver, but some have levels as low as 75 mcg, with normal being less than 40 mcg (9). As the disease progresses, patients develop hepatic fibrosis and may present with evidence of compensated or decompensated cirrhosis, such as jaundice, ascites, thrombocytopenia, splenomegaly, palmar erythema, and variceal hemorrhage. In addition, patients may come to attention when abdominal imaging obtained for other reasons reveals evidence of cirrhosis or is suggestive of portal hypertension.

Cirrhosis is present at the time of diagnosis of Wilson disease in approximately 35 to 45 percent of patients overall (9,10), including those presenting with neuropsychiatric symptoms or who are asymptomatic (7,8,9,11). In a series that included 14 patients over the age of 40 years who presented with neurologic symptoms and underwent liver biopsy, significant fibrosis was present in 10 (71 percent; 9 with cirrhosis and 1 with advanced fibrosis) (7). In a series with 34 patients with neurologic Wilson disease, 14 (41 percent) were found to have cirrhosis (9). In a study that included 18 asymptomatic patients detected through screening because of an affected sibling, two (11 percent) had cirrhosis at the time of diagnosis (9).

Behavioral and psychiatric symptoms are more common in patients with neurologic involvement than in patients with hepatic involvement (12,13). However, psychiatric symptoms may precede the recognition of hepatic or neurologic Wilson disease by a significant period of time. The most common behavioral and psychiatric symptoms include de-

pression (reported in 20 to 30 percent of patients with Wilson disease), personality change, incongruous behavior, and irritability (2,12). However, behavioral and psychiatric symptoms due to Wilson disease are often misdiagnosed (eg, they may be attributed to puberty). As a result, it is uncommon for patients to be diagnosed with Wilson disease when the only manifestations are behavioral or psychiatric, and diagnosis may be delayed significantly in these individuals. Behavioral and psychiatric manifestations of Wilson disease include (1,2,12,14-16): depression; declining school performance; personality changes (which may be subtle); irritability; impulsiveness; labile mood; sexual exhibitionism; inappropriate behavior; dysthymia; bipolar affective disorder; psychosis.

Regarding ocular manifestations, Kayser-Fleischer rings are brownish rings that are due to fine, pigmented, granular deposits of copper in Descemet's membrane in the cornea. Kayser-Fleischer rings are thought to reflect copper within the central nervous system, and they dissipate over time with treatment directed towards the removal of copper. Kayser-Fleischer rings are a characteristic feature of Wilson disease and are seen in approximately 98 percent of patients with neurologic manifestations and approximately 50 percent of patients with hepatic manifestations. While often only detected by slit-lamp examination (typically done in a patient already suspected of having Wilson disease), Kayser-Fleischer rings are sometimes visible without a slit-lamp examination when they are sizable, especially in those with lighter colored irises where the contrast between the background color makes it more obvious. However, Kayser-Fleischer rings are rarely the first finding in a patient with Wilson disease. Sunflower cataracts are another ocular manifestation of Wilson disease and occur when copper deposits accumulate in the lens. These, too, are generally seen with a slit-lamp examination.

The neurologic manifestations of Wilson disease are numerous and can mimic other neurologic disorders, especially any type of movement disorder. Disorders that should be considered include essential tremor, young-onset Parkinson disease, and generalized dystonia. Disorders that may rarely mimic Wilson disease include Huntington disease, pantothenate kinase-associated neurodegeneration

(Hallervorden-Spatz disease), idiopathic torsion dystonia, chorea-acanthocytosis, and benign familial chorea. The presence of Kayser-Fleischer rings, seen in approximately 98 percent of patients with neurologic Wilson disease, can help differentiate Wilson disease from these other disorders.

The differential diagnosis for the psychiatric manifestations of Wilson disease includes disorders such as depression, bipolar disorder, schizophrenia, dementia, and drug abuse. As with the neurologic manifestations, the presence of Kayser-Fleischer rings can often help differentiate patients with Wilson disease from these other disorders.

Untreated, Wilson disease is universally fatal (1). Copper accumulation in the liver eventually leads to the development of cirrhosis, and among patients with neurologic Wilson disease, the neurologic disease may progress until the patient becomes severely dystonic, akinetic, and mute. Progression is usually gradual, but sudden deterioration may also occur. The majority of patients will die from liver disease (cirrhosis or acute liver failure), while the remainder die due to complications due to progressive neurologic disease. The prognosis for patients who receive and are adherent to treatment for Wilson disease is excellent, even in some who already have advanced liver disease. In patients without advanced liver disease, life expectancy is normal, though treatment may lead to worsening of neurologic symptoms in a fraction of patients. Among patients requiring liver transplan-

tation, survival following transplantation is excellent.

CASE REPORT

A 23 year-old male patient was admitted to the Psychiatric Clinic of the Emergency County Hospital in Cluj-Napoca in February 2018.

The patient had previously accused lack of appetite and repeated stomach aches in September 2016 for which he visited his GP. Full blood count, liver enzymes, urine analysis, H. Pylori antibodies and stool sample culture test were performed at the time and they only revealed a slight thrombocytopenia (129.000 plts/ μ l).

A few months after, the patient started having trouble concentrating, presented with short term absences and insomnia. An EEG was performed in June 2017 and it revealed pathological irritative waves located in the right occipital lobe, aggravated by the stimulation procedures (hyperventilation and intermittent light stimulation). It was interpreted as an occipital epileptogenic focus and antiepileptic treatment with Carbamazepine 100 mg three times a day for six months was initiated.

However, the patient's condition did not improve, his concentration difficulties and insomnias were getting worse and after a psychiatric consult, in August 2017, the patient was diagnosed with Schizophrenia and antipsychotic treatment with Olanzapine, Phenobarbital and Haloperidol was initiated.

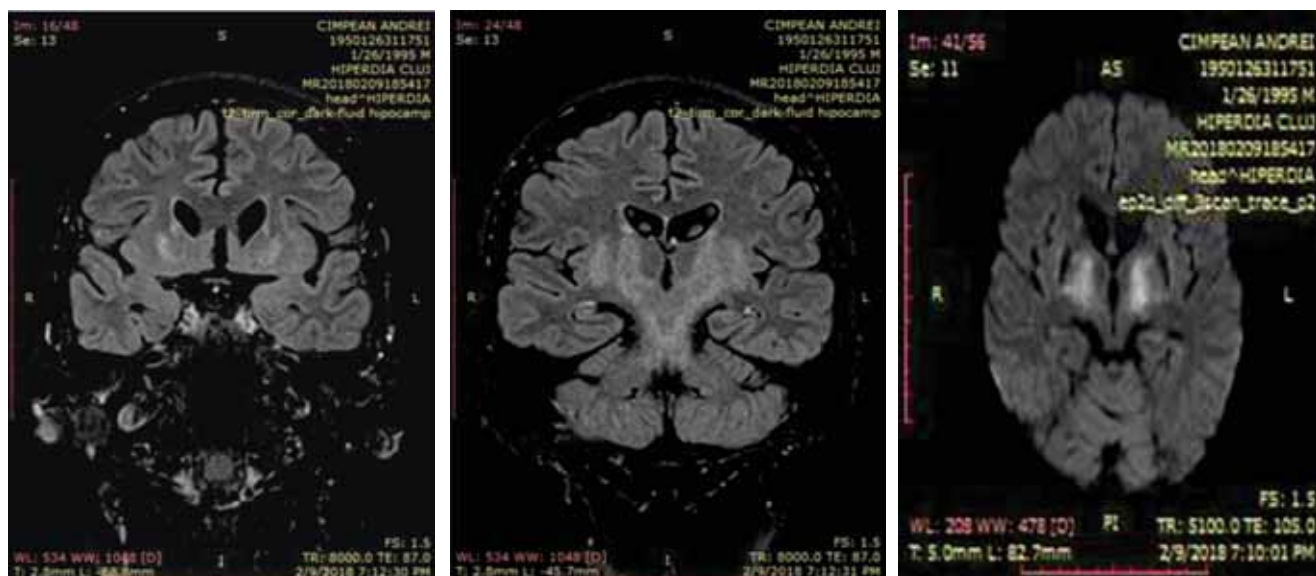


FIGURE 1. Brain MRI showing hyperintense T2 lesions located in the basal ganglia and thalamus

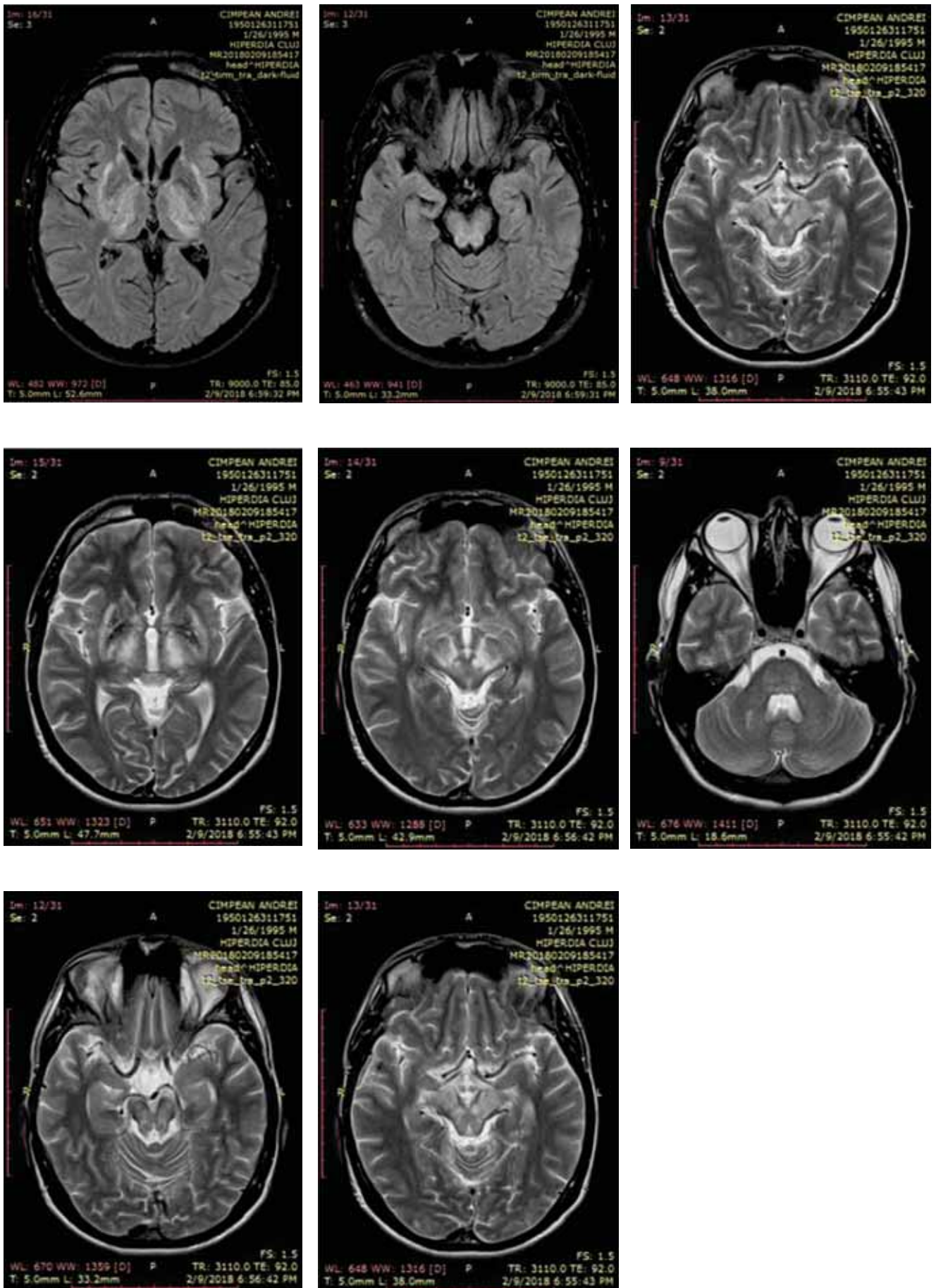


FIGURE 2. Brain MRI showing hyperintense T2 lesions in the basal ganglia, thalamus and brain stem

Despite the treatment, the patient's mental and physical status kept getting worse. His ability to speak and walk were rapidly degrading and he was admitted to the Psychiatric Clinic of the Emergency County Hospital Cluj at the beginning of February 2018.

An EEG was repeated and it revealed pathological waves located in the right frontal lobe with a tendency to become generalized.

For further investigation of the patient's condition, a brain MRI was performed, and it showed bilateral, symmetric hyperintense T2 lesions located in the basal ganglia, thalamus, brain stem (pons and mesencephalon) and cerebellar dentate nuclei raising the suspicion of a metabolic encephalopathy.

The patient was then transferred to the Neurological Clinic of the Emergency County Hospital Cluj for further investigations and treatment.

When he was transferred, the patient presented with altered mental status, partially responsive to stimuli, the inability to keep his mouth shut, excessive drooling, the inability to stand up, walk, speak or eat.

On neurological examination the patient presented with partially impaired consciousness, no

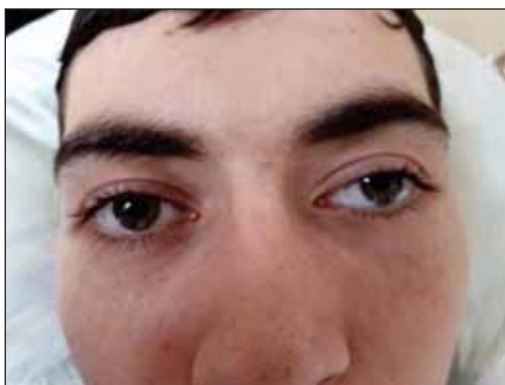


FIGURE 3. Characteristic facies of a Wilson disease patient

meningeal signs, involuntary movement of the left upper limb (myoclonus), dysphagia, severe dysarthria, severe paraparesis, absent knee jerk on the left, reduced knee jerk on the right, ankle and plantar reflexes normal, symmetrical bilateral, cog-wheel present on both upper limbs, rigidity of all four limbs, Babinski sign present on the left, urinary incontinence.

Complete blood work was repeated, and it showed low levels of uric acid (2,41 mg/dl), iron (31µg/dl), ceruloplasmin (6,7 mg/dl), folic acid (3,64 ng/ml), slight leukopenia (3,28 10⁹/l), thrombocytopenia (109 10⁹/l), lymphopenia (0,55 10⁹/l), altered coagulation status (INR=1,22), high levels of creatin kinase (368 IU/l), normal levels of liver enzymes.

Considering the clinical, biological and imaging findings a suspicion of Wilson disease was raised. In order to confirm the diagnosis, blood and urinary copper levels were analysed: low levels of blood copper (53µg/dl) and high levels of urinary copper (240 µg/24h) were found.

An ophthalmological examination with a slit-lamp was performed, and it showed circular, peripheral, dark corneal deposits (Kayser-Fleischer rings) and sunflower cataract on both eyes.

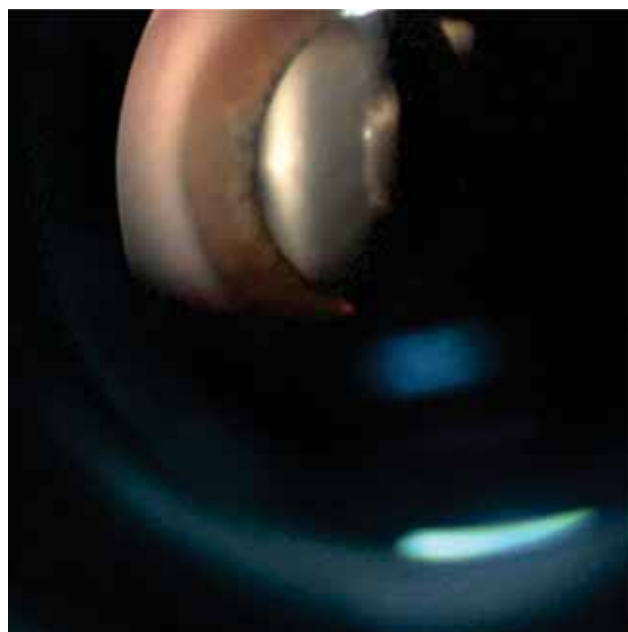


FIGURE 4. Kayser-Fleischer ring

For additional information on the liver disease an abdominal ultrasound was performed, showing a severely altered liver structure and splenomegaly, suggestive of a chronic hepatopathy.



FIGURE 5. Abdominal ultrasound showing a severely altered liver structure

Genetic testing for ATP7B gene mutation for Wilson disease was performed and the patient tested positive.

After these additional investigations the patient was diagnosed with Wilson disease and treatment with D-penicillamine 250 mg (with a starting dose of 250 mg daily and a progressive increase to 1750 mg daily) and zinc acetate 50 mg two times a day, together with a restrictive diet for copper rich foods.

CONCLUSION

It is important to know that Wilson disease can mimic a psychiatric disorder and that you should always check for red flags in the clinical and biological evaluation of a psychiatric patient that can point to a different cause of an altered mental status.

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