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Medication-Induced Hepatitis caused by Antipsychotic Drugs as a Revelation of Wilson's disease

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Abstract **Review Article**

Wilson's disease is an autosomal recessive genetic disorder that results from a mutation in the gene for a heavy metal transporter. This leads to a decrease or absence of copper transport in the bile and its accumulation in organs, particularly the brain. Affected patients have hepatic, neurological or psychiatric forms, and the diagnosis is based on clinical, biological, radiological and presumptive phenotypic arguments, as well as on associated molecular anomalies. Wilson's disease can result in behavioral disorders, depression, and psychosis: schizophrenia or manic depression. The diagnosis can be made if there is a combination of low ceruloplasmin, high cupremia, high cupruria, and a Kayser-Fleisher ring. In case of hemolysis, the cupremia may be elevated. On MRI, signal abnormalities of the basal ganglia, white matter and trunk are indicative of Wilson's disease. Genetic study is performed in case of family history. We present a clinical case of drug-induced hepatitis under antipsychotic drugs in the context of schizophrenia which was revealing of wilson's disease. Although rare, the onset of Wilson's disease can take the form of a late-onset adult psychosis, and is important to address in psychiatry. Is this a comorbidity of schizophrenia and wilson's disease, or is the psychiatric picture merely a consequence of neurological involvement with the disease?

Keywords: genetic disorder, Wilson's disease, depression, antipsychotic drugs.

INTRODUCTION

Wilson's disease is an autosomal recessive genetic disorder that results from a mutation in the gene for a heavy metal transporter. This leads to a decrease or absence of copper transport in bile and its accumulation in organs, particularly the brain [1]. Affected patients have hepatic, neurological, cardiac, renal or psychiatric forms, and the diagnosis is based on clinical, biological, radiological, and presumptive phenotypic arguments, as well as on associated molecular abnormalities. The psychiatric manifestations of Wilson's disease can be behavioral disorders, depression, schizophrenia or bipolar disorder. We present a clinical case of suspected drug-induced hepatitis under antipsychotic drugs in the setting of schizophrenia which was revealing of Wilson's disease. Although rare, the onset of Wilson's disease can take the form of a late-onset adult psychosis, and is important to address in psychiatry.

CLINICAL VIGNETTE

Mr. H. aged 34 years, has as history a problematic use of tobacco and alcohol weaned in 2016, hospitalization at a psychiatric service, discharged with a diagnosis of an acute psychotic episode put on Olanzapine 10mg, discharged well improved, with an evolution that was marked by a cessation of treatment a week later under the pretext that he is no longer sick and an absence of socio-professional reintegration.

In June 2020, he came accompanied by his family to the Arrazi Salé University Hospital and was admitted for a behavioral disorder consisting of heteroaggression with death threats, verbalization of delusions and insomnia, all of which had been evolving for a few months, in whom the psychiatric evaluation found a delusional syndrome of persecution towards his entourage with an intuitive and interpretative mechanism, insomnia, disturbed judgment and negative insight. A complete organic workup was prescribed, and a treatment with psychotropic drugs was initiated (olanzapine 10mg/day and chlorpromazine 300mg/day).

The clinical evolution was marked by the resolution of the psychiatric symptoms after one month, the patient distanced himself from his delirium, criticized his acts and recovered his sleep.

At the end of this month, Mr. H. presented a jaundice with intense pruritus, dark urine and discolored stools.

A drug-induced hepatitis under psychotropic drugs was suspected. A complete workup was performed after discontinuation of the treatment, which revealed normocytic normochromic anemia and a disturbed liver workup with cholestasis (elevation of Pal, GGT, Bilirubin) and cytolysis (elevation of ASAT and ALAT). The ultrasound was unremarkable. As the symptoms did not regress, a transfer to the medical ward was necessary.

The clinical examination revealed an icteric patient with scratchy lesions. The paraclinical exploration showed anemia, a disturbed liver check-up, an ultrasound without particularity, negative HVA HVB HVC CMV EBV HSV HIV serologies. The liver biopsy and its anatomopathological analysis revealed established hepatic cirrhosis. The cupremia and cupruria were measured secondarily and were above physiological values (cupremia at 40.5 µmol/l and cupruria at 1µmol/l), the ceruloplasmin level was 0.55g/l. Wilson's disease was suspected. Slit-lamp ophthalmologic examination was requested which objectified the presence of Kayser flesher's ring and a brain MRI was requested but did not objectify any abnormality.

The diagnosis of Wilson's disease was confirmed.

DISCUSSION

Wilson's disease can be revealed in some subjects by isolated psychiatric manifestations, which can be made of behavioral disorders, a dementia syndrome, a schizophrenic syndrome or a manic-depressive syndrome [2]. In Mr H., the first manifestations of Wilson's disease were psychiatric, and were; in front of the bizarre behavior, the delusional syndrome, the impaired judgment and insight, the persistence of the disorders beyond 6 months and the poor socio- professional reintegration; in favor of a schizophrenia, so the patient was hospitalized in psychiatry for an adequate management.

1- Genetics

Wilson's disease, also known as hepatolenticular degeneration, is an autosomal recessive disorder due to pathogenic mutations in ATP7B. ATP7B is the only gene known to cause Wilson's disease and encodes a transmembrane copper transport ATPase of the same name. Although biochemical tests and clinical criteria can contribute to early diagnosis and treatment, the current gold standard for diagnosis of Wilson disease is direct sequencing of ATP7B or molecular testing for known familial mutations. Genotype-phenotype correlations have been extensively studied, but the direct causes remain unclear. Modifying genes may affect penetrance and phenotypes, but a large-scale study for clinical validation is warranted [3].

Decreased biliary excretion of copper and reduced incorporation of copper into apoceruloplasmin caused by defunctionalization of ATP7B protein lead to accumulation of copper in many tissues and organs, including the liver, brain, and cornea, ultimately resulting in liver disease and extrapyramidal symptoms [4].

2- Clinical Manifestations

Clinically, the main manifestations of Wilson's disease are psychiatric, neurological, hepatic, ophthalmological and hematological.

PSYCHIATRIC	**NEUROLOGIC**
- Mood disorders - Anxiety - Psychotic symptoms - Sleep disorders - Other: obsessive-compulsive disorder, catatonia, irritability, impaired judgment, disinhibition, personality change.	- Parkinson's syndrome - A choreo-athetosis syndrome - In children: academic difficulties, a lack of concentration, speech and writing disorders.
HEPATIC	**OPHTHALMOLOGIC AND HEMATOLOGIC**
- Acute liver failure (asthenia, progressively increasing jaundice, which may be associated with fever, abdominal pain, arthralgias, and even amenorrhea. Cirrhosis occurs at a very early stage of the disease)	- Kayser-Fleischer ring - Hyperhemolysis with significant increase in cupruria

3- Diagnosis

Until 1952, the diagnosis was evoked on clinical symptomatology alone. The association of a low ceruloplasmin (less than 200 ml/l) and a Kayser-Fleischer ring is sufficient to make the diagnosis. However, the absence of a decrease in plasma ceruloplasmin does not exclude the diagnosis. Conversely, a decrease in ceruloplasmin may exist outside of Wilson's disease (nephrotic syndrome, malabsorption syndrome, severe liver failure).

When there is a strong suspicion of Wilson's disease and in the absence of a low ceruloplasmin-

Kayser-Fleischer ring association, liver biopsy with copper quantification may be indicated.

The Kayser-Fleischer ring is almost constant in patients with neuropsychiatric manifestations, but some neuropsychiatric forms do not have a ring. Bilateral, sometimes visible to the naked eye, it is generally only visible with a slit lamp. It is particularly difficult to see in brown eyes, as well as in early forms [5], the experience of the ophthalmologist may influence its detection. Often described as present in all patients with neurological involvement, its absence in the presence of neurological manifestations has sometimes been observed. On the other hand, it may be absent in hepatic forms. Therefore, Wilson's disease cannot be excluded in the absence of a Kayser-Fleischer ring.

The contribution of genetics in screening is important. Prior to genetic discoveries, screening was based on clinical examination, slit lamp examination, serum ceruloplasmin measurement, cupremia, cupruria, liver biopsy and MRI. The study of the gene and its transcript in different families revealed the existence of numerous disease-specific mutations. The isolation of DNA polymorphism markers has led to the identification of disease-specific haplotypes. Family investigation consists of non-invasive genetic screening of the family of an affected individual. The diagnosis is most often indirect, based on a haplotype identity between the known patient and his relatives. Heterozygous or homozygous members of the same family are determined [6]. Genetic diagnosis is thus made by a genetic linkage method.

MRI is the examination of choice because it allows the detection and anatomical localization of paramagnetic deposits. Focal lesions, represented by hyposignals in T1 and hyper signals in T2, are present in 60% of neurological forms, in 19% of presymptomatic forms, and sometimes for hepatic forms. These focal lesions, most often multiple and symmetrical, affect the lenticular nuclei in 37% of cases (putamen 30%, pallidum 27%), the ventral or lateral thalamus in 5% of cases, the white matter 5% and the caudate nucleus2%. Furthermore, T2 signal attenuation is most often seen bilaterally and symmetrically in the putamen, pallidum, and less often in the basal ganglia and substantia nigra. Images of increased T2 signal are also found in the external capsules, the posterior arms of the internal capsules, in the trunk and in the midbrain. In other cases, MRI shows white matter lesions, revealed by asymmetric and mostly multiple (67%) subcortical T2 hyper signals. These white matter lesions are present in 67% of patients with the hepatic form and 27% with the neurological form. They are found in half of the cases in the frontal lobes, in 21% of the cases in the temporal lobes, in 14% of the cases in the occipital lobes and in 7% of the cases in the parietal lobes or the semi-oval centers. These abnormalities are rarely seen in the cortical gray matter [7].

4- Treatment

When left untreated, the course of Wilson's disease is always fatal.

Treatment is based on copper chelators, zinc salts (acetates and sulfates) and liver transplantation.

Copper Chelators

D-penicillamine acts by chelating copper accumulated in the tissues to be eliminated in the urine. It is prescribed at a dose of 1.5-2 g/day in several doses; it is a life-long treatment. It prevents the development of liver damage if prescribed early in the disease [8].

Triethylene tetramine dihydroccchloride or Trientine is another chelator that can be used at a dose of 0.5-1 g/day. It works by blocking intestinal absorption of copper.

Zinc salts (acetates and sulfates)

Zinc is not a copper chelator, but it competes negatively with copper and has a slow and weak influence on the copper balance. Zinc blocks the absorption of copper in the intestine because the induced metalothioenin has more affinity for copper than for zinc. In addition, it increases the fecal elimination of copper during cell desquamation.

Liver Transplantation

Its effectiveness is more marked in hepatic forms than in neurological forms, where it is discussed.

Treatment of Psychiatric Symptoms in Wilson's disease

One approach to the treatment of psychiatric symptoms in Wilson's disease is to expect that the primary treatment (i.e., copper chelator) will improve psychiatric symptoms by treating the primary disease process, with no additional intervention required.

Up to one-third of patients with psychiatric symptoms will improve with chelation therapy alone [8].

Liver transplantation has not always improved neuropsychiatric symptoms, as improvement has only been observed in a minority of patients.

A second approach is to treat psychiatric symptoms with specific interventions, including biological approaches and psychotherapy.

The use of lithium (Loganathan *et al.*, 2008; Tatay *et al.*, 2010; Rybakowski *et al.*, 2013), divalproex (Shah and Vankar, 2003; Aravind *et al.*, 2009), serotonin reuptake inhibitors (Smit *et al.*, 2004; Kumawat *et al.*, 2007b), tryptic antidepressants (Buckley *et al.*, 1990; Benhamla *et al.*, 2007), methylphenidate (Silva *et al.*, 2011), benzodiazepines (Muller, 1999; Shah and Vankar, 2003; Zimbrean and

Schilsky, 2015), haloperidol (Chung *et al.*, 1986), risperidone (Shah and Vankar, 2003), quetiapine (Kulaksizoglu and Polat, 2003), and clozapine (Krim and Barroso, 2001) with good therapeutic results have been described in patients with TD.

Another effective treatment for mood symptoms in patients with WD is electroconvulsive therapy (Negro and Louza Neto). (Negro and Louza Neto, 1995; Shah and Kumar, 1997; Rodrigues *et al.*, 2004; Avasthi *et al.*, 2010; Vaishnav *et al.*, 2013). Cognitive behavioral therapy (Kumawat *et al.*, 2007a) and interpersonal therapy (Keller *et al.*, 1999) have been used independently or in combination with other interventions with good results.

Precautions when Prescribing Psychotropic Medications to Patients with Wilson's disease

Avoid medications with a potential hepatotoxic effect (e.g., valproic acid, duloxetine).

Whenever possible, preference should be given to drugs with minimal hepatic metabolism (e.g., lithium, gabapentin).

When prescribing neuroleptics, preference should be given to the following drugs those with a reduced risk of extrapyramidal side effects (e.g., quetiapine) at the minimum effective dose.

Unless there is evidence of an independent psychiatric condition distinct from Wilson's disease or recurrence of psychiatric symptoms, consideration should be given to tapering off psychotropic medications once remission of symptoms is complete

Consider monitoring cognitive status when treating patients with Wilson disease with psychotropic agents that may impact cognition (e.g., benzodiazepines, lithium).

CONCLUSION

Psychiatric manifestations are an important part of the clinical presentation of WM. They can occur at any time during the course of the disease, including in the absence of liver or neurological involvement, leading to delays or misdiagnosis of Wilson's disease.

Research into the psychiatric aspects of Wilson's disease can be developed in several directions. First, there is a need for a more systematic assessment of psychiatric problems in Wilson's disease using validated psychiatric diagnostic instruments. Second, there is a need for more information about the course of these symptoms over the course of the disease and their consequences.

Third, understanding the correlations between the psychiatric symptoms of WD with biological markers, such as copper levels, ceruloplasmin, genetic mutations, and neuroimaging findings, could provide useful information about the mechanisms of psychiatric disease.

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