

Resolved Psychosis after Liver Transplantation in a Patient with Wilson's Disease

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Abstract: A psychiatric involvement is frequently present in Wilson's disease. Psychiatric symptoms are sometimes the first and only manifestation of Wilson's disease. More often a psychiatric involvement is present beside a neurologic or hepatic disease.

We describe the case of a 18 years-old male patient who shows a clinic and laboratoristic pattern of cirrhosis and an history of subchronic hallucinatory psychosis, behavioral symptoms and mood disturbances with depressed mood. He hadn't familiar history of liver or psychiatric disease. Laboratory and imaging tests confirmed the diagnosis of Wilson's disease with psychiatric involvement. After liver transplantation copper metabolism and liver function normalised and we noticed no recurrency of the psychiatric illness. Very few cases of psychiatric improvement after orthotopic liver transplantation (OLT) has been described until now.

Keywords: Copper metabolism, genetic liver disease, OLT, psychosis, psychiatric illness, Wilson's disease.

INTRODUCTION

Wilson's disease (WD), or hepatolenticular degeneration [1], is an autosomal recessive disorder caused by the mutation of the ATPase7B gene [2]. The role of the ATPase7B is the ATP-dependent escretion of copper into the biliary system [3]. The effect of copper accumulation in the liver leads to acute liver failure, chronic hepatitis or liver cirrhosis [4], while the overload of copper can generate both neurological and psychiatric involvement [5].

Accumulation of copper in the cytoplasm of hepatocytes results in cellular necrosis and leakage of copper into the plasma. The excess copper then collects in extrahepatic tissues, including the basal ganglia and the limbus of the cornea. ATP7B transports copper into the secretory pathway of the cell for incorporation into the cuproenzymes and excretion from the cell. An increase in the intracellular copper level causes ATP7B to move to a cytoplasmic vesicular compartment. As the copper is concentrated into vesicles for excretion from the cell, the cytosolic copper concentration decreases, and ATP7B returns to the trans-Golgi network. The movement of ATP7B appears to involve amino acid sequences in its carboxyl terminus. The copper concentration is higher in brains of people with Wilson disease than in other people or animals with diseases of copper overload. Wilson himself referred to a "mental change", whose "importance should not be underestimate" [1]. From 30% to 100% of symptomatic patients with WD suffer from psychiatric symptoms. From 10% to 20% of patients present

psychiatric disorders from 1 to 5 years before the diagnosis of WD and one third of this patients receive psychiatric treatment, including hospitalization [6]. The most frequent psychiatric symptoms in WD are personality changes such as irritability and low threshold to anger, depression sometimes leading to suicidal ideation and attempts, deteriorating academic and work performance that is present in almost all neurologically affected patients [7]. Anxiety, behavioral abnormalities, cognitive impairment have also been described [8]. Psychiatric symptoms in WD usually showed a limited response to neuroleptic medication or other psychiatric drugs [9]. In other cases psychiatric symptoms improved after penicillamine treatment [5, 10, 11]. The improvement was noticed after 1 or 2 years of treatment [5]. Few cases of psychiatric WD who underwent OLT have been described: in one case behavioural and personality disorders were completely unaffected after transplantation [20]. We describe the case of a 18-year-old patient with complete normalization of copper and ceruloplasmine levels and efficacy of OLT on psychiatric abnormalities.

MATERIALS AND METHODOLOGY

A 18-year-old boy was referred to Our Institute in February, 1992. Few months before he suffered from severe asthenia, fever (38-39° C), vomiting, diarrhea and pain referred to right hypochondrium. Examination showed gynaecomastia, pitting oedema and hepatosplenomegaly.

During hospitalization he had hallucination and phomene. No neurological deficit was noted.

Laboratory investigations showed platelets 45.000/mm³, aspartate aminotransferase (AST) 106 IU/L, alanine aminotransferase (ALT) 107 IU/L, γ -glutamyl-tranferase (GGT) 131 IU/L, International Normalised Ratio 1.4, PChE

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2165 U/l. Hepatitis virus serology, TORCH, Monotest, Widal-Wright, Weil-Felix, Tine test, alpha-antitrypsin assay and autoimmunity tests were negative. Serum ceruloplasmin level was 16 mg/dl, serum copper concentration 45 mcg/dl, urinary copper concentration/24 h after 600 mg of D-penicillamine [12] 303 mcg/24h.

Ultrasound scanning showed a cirrhotic liver with diffusely disomogeneous ultrasonographic structure, splenomegaly with omogeneous ultrasound structure.

EGDS revealed oesophageal varices (F3).

Liver biopsy detected architectural abnormalities with chronic hepatitis with high grading and bridging fibrosis; the staging was III-IV sec. Desmet [13]. Liver copper content was 255 mcg/g dry weight.

The values of the copper balance and liver biopsy were diagnostic of Wilson's disease.

A psychiatric consultation was arranged and was found a Psychotic Disorder Due To Wilson's Disease (American Psychiatric Association. DSM IV TR ed. APA Washington DC 1994). The clinical picture presented auditory, somatic and formed visual allucinations (as "zoopsias") and persecutory delusions. Insomnia, asthenia, anorexia, depressed mood and social isolation were associated.

In order to evaluate the involvement of the CNS the patient underwent slit lamp examination, that was negative for the presence of Kayser-Fleisher's ring. Magnetic resonance imaging (MRI) brain scan was normal. The clinical picture, results of laboratory examination and liver copper content however suggested Wilson's disease.

The patient reached endstage liver disease and required a transplant; therefore d-penicillamine treatment was not attempted.

RESULTS

The patient underwent OLT in July 1993 ("S. Giovanni Battista" Hospital, Torino) and after operation we observed a sudden improvement of liver function and copper excretion. Laboratory investigations demonstrated platelets 284.000/mm³, aspartate aminotransferase (AST) 27 U.I./l, alanine aminotransferase (ALT) 21 U.I./l, International Normalised Ratio 1.3 INR, PChE 8660 U/l. Serum ceruloplasmin level rised to 39 mg/dl, serum copper concentration 89.47 mcg/dl, basal urinary copper (17.4 µg/24 h); only urinary copper concentration/24 h after challenge of D-penicillamine was still high (360 mcg/24h) Moreover the transplant resolved any psychiatric disfunction. We observe this regression until now, twelve years after the transplantation.

After the operation MRI brain scan was still normal and Kayser-Fleisher's ring was absent again. Evoked potentials (somatosensory, visual and brainstem auditory EPs: SEP, VEP, BAEP) proved normal.

Finally, in february 2009, 99mTc-ECD-SPECT (single photon emission tomography) revealed an abnormal distribution of the drug in the brain, with deficient perfusion of left temporal lobe and normal perfusion in the basal ganglia.

DISCUSSION

Wilson's disease is a genetic disorder due to the mutation of the ATPase7B, that represents the sole mechanism of copper excretion. Mutated ATPase7B fails the incorporation of copper in ceruloplasmin that results in the decrease of the holoceruloplasmine synthesis with low ceruloplasmin serum level in affected patients. Progressive copper accumulation in the liver causes an oxidative damage that leads to acute or chronic hepatitis, asymptomatic cirrhosis or acute liver failure [14]. In young adults neuropsychiatric symptoms predominate and are associated, in 90% of cases, with Kayser-Fleisher's ring [15].

Psychiatric symptoms are often the first and unique manifestation of the disease, particularly in adolescents and young-adults; this can bring to futile psychiatric treatments [16] and delay the diagnosis from 1 to 5 years [4].

More frequently psychiatric disease is associated with hepatic and/or neurologic involvement.

The most frequent psychiatric symptom is depression [7]. Depression seems to be correlated with alterations of serotonergic trasmission in the thalamus-hypotalami and mid-brain-pons region, in particular with low density of the pre-synaptic serotonin transporter (SERT) [5]. This alterations could be related also with psychotic symptoms; in fact it is well known that in schizophrenic psychosis there is an alteration of serotonergic transmission [17].

Emotional lability, lack of appropriate emotions, personality changes, increased or reduced sexual interest, cognitive impairment, schizophrenia, nervous anorexia [18] and catatonia [19] have also been described [4].

Our patient suffered from severe liver disease (cirrhosis Child Pugh B7) with severe pschiatric involvement. The patient didn't suffer from neurologic symptoms; neurological examination and MRI brain scan were normal.

The treatment of WD consist of copper-chelating agents such as penicillamine [20]. Zinc sulphate or acetate inhibit intestinal copper absorption and had produced succesfull results in patient with neurologic disease [21]. Zinc sulphate therapy is more indicate than penicillamine therapy because penicillamine can determine a massive dismission of copper into circulation with acute worsening of clinic conditions.

On the other hand it is not yet clear which is the best therapy in patients with psychiatric involvement. In such cases penicillamine or zinc sulphate has been usefull for psychiatric symptoms [22], without any employment of neuroleptic medications [4]. In other cases psychiatric drugs determined a decline of psychiatric situation [23].

In this case the patient didn't assume any medical therapy because he presented the indication for a sudden liver transplantation for decompensated cirrhosis accompanying the psychiatric illness. The sole risolutive therapy for WD is liver transplantation that normalises liver function and correct the metabolic defect of copper excretion [24].

After transplantation we observed the normalisation of liver function, of copper metabolism and of psychiatric symptoms. Only urinary copper concentration/24h after penicillamine challenge was elevated. We suppose high

value of urinary copper excretion indicate a persistent copper overload in extrahepatic tissues. In considering high postoperative urinary copper levels, we suggest not to discontinue medical therapy after OLT.

In the post-operative the patient underwent again brain MRI, ECD-SPECT and evoked potentials (EPs) for neurological evaluation. MRI brain scan and EPs were normal, while the SPECT showed an asymmetric distribution of the drug. Several studies demonstrate that ECD-SPECT is the most sensitive neuroimaging procedure in the monitoring of the disease, also in patients without neurological symptoms. In one study there was a particular frequency (86%) of diffused or focal decrease of ECD uptake [25]. Also in our patient we observed a deficit of perfusion in the left temporal lobe, though MRI and EPs were normal.

In the late postoperative (twelve years after the operation) liver functional values were still normal and no more psychiatric abnormalities were observed.

As an hypothesis, we suppose that our patient didn't have relapses because he underwent liver transplant in an early phase of the psychiatric disease: infact MRI before the transplant showed normal images. Unfortunately in 1994 we didn't dispose of the SPECT. If confirmed in other studies this hypothesis could suggest the importance of early treatment.

Literature offers scarce and discordant data regarding the curative effects of OLT under psychiatric aspects. It has been described both the curative effect of the transplant on neuropsychiatric symptoms [26] and the severe worsening of psychiatric illness [27]. In conclusion from our study emerge some perspectives of resolution also of psychiatric disease accompanied by late-postoperative persistent improvement, especially in case of early treatment.

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