

# Effect of liver transplantation on brain magnetic resonance imaging pathology in Wilson disease: a case report

## *Wpływ przeszczepu wątroby na zmiany w rezonansie magnetycznym mózgu w chorobie Wilsona – opis przypadku*

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### Abstract

The authors present a case report of a 28-year-old patient with hepatic, but no neurological, signs of Wilson disease, with pathological changes in both the globi pallidi and caudate found with routine brain magnetic resonance imaging (MRI). The patient was recommended for liver transplantation by hepatologists, and during the two years of observation after liver transplantation, MRI brain abnormalities due to Wilson disease completely regressed. On the basis of this case, the authors present an argument for the prognostic significance of brain MRI in Wilson disease as well as current recommendations concerning liver transplantation in Wilson disease.

**Key words:** Wilson disease, liver transplantation, copper metabolism.

### Introduction

Wilson disease (WD) is an inherited, autosomal recessive copper metabolism disturbance characterised by copper accumulation in many organs (liver, brain, cornea and kidneys) with secondary damage to affected tissues [1,2]. The cause of the disease is a mutation in

### Streszczenie

Autorzy przedstawiają przypadek 28-letniego pacjenta z wyłącznie wątrobowymi objawami choroby Wilsona, bez objawów neurologicznych, oraz ze zmianami w obrębie gałek białych i skorup w rezonansie magnetycznym mózgu (RM). Chory został zakwalifikowany przez hepatologów do przeszczepienia wątroby. Po dwóch latach od operacji stwierdzono całkowite ustąpienie zmian patologicznych w obrazie RM. Na przykładzie opisanego przypadku omówiono znaczenie rokownicze badań RM mózgu w chorobie Wilsona oraz aktualne zalecenia dotyczące przeszczepiania wątroby w leczeniu tej choroby.

**Słowa kluczowe:** choroba Wilsona, przeszczepienie wątroby, metabolizm miedzi.

the *ATP7B* gene, which is highly expressed in the liver, kidney and placenta and which encodes transmembrane protein ATPase (*ATP7B*) [3-5]. More than 500 mutations of *ATP7B* have been described in WD so far (<http://www.hgmd.cf.ac.uk>).

There is a wide spectrum of WD symptoms, including hepatic, neurological, psychiatric, and ophthalmolo-

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**Table 1.** Modified King's College Scale – the tool used to qualify Wilson disease patients for liver transplantation ( $\geq 11$  points indicates very high risk of death without liver transplantation – indication for procedure)

Score	0 pts.	1 pts.	2 pts.	3 pts.	4 pts.
Bilirubin [ $\mu\text{mol/L}$ ]	0-100	101-150	151-200	201-300	> 301
AST [IU/L]	0-100	101-150	151-300	301-400	> 401
INR	0-1.29	1.3-1.6	1.7-1.9	2.0-2.4	> 2.5
White blood cell count [ $10^9/\text{L}$ ]	0-6.7	6.8-8.3	8.4-10.3	10.4-15.3	> 15.4
Albumin [g/L]	> 45	34-44	25-33	21-24	< 20

logical symptoms [1,2,6,7]. The most frequent and important neurological symptoms include tremor (intentional, postural, resting and asterixis), dystonia (focal, segmental and risus sardonicus), rigidity, parkinsonian symptoms, drooling and dysarthria (hypokinetic, spastic, cerebellar and dystonic) [1,2,6]. Typical WD brain magnetic resonance imaging (MRI) changes include symmetrical T2-weighted hyperintensity or mixed signal intensity in the putamina (with a hyperintense peripheral putamina rim), globi pallidi, caudate nuclei, thalami and pons [6,8-18]. The midbrain, cerebellum, corticospinal tracts, cortex and subcortical areas are also very often affected. Data on the reversibility of the described MRI pathology through pharmacological treatment have been found; therefore, brain MRI has been proposed as a recovery index [8-20].

Since the establishment of the copper-related aetiology of WD, there have been several drugs and procedures implemented in WD treatment, such as chelating agents (dimercaprol, d-penicillamine and trientine), agents decreasing copper absorption from the digestive tract (zinc salts), compound mechanism drugs tetrathiomolybdate and, in some extreme cases, liver transplantation (LT) [1,2,6,21]; however, the pharmacological treatment of WD is undoubtedly effective [1,2,6].

Liver transplantation is a well-documented life-saving method of WD treatment in extreme cases, such as in patients with acute fulminant liver failure or in patients with chronic liver failure not responding to medical therapy. Usually, LT is recommended for patients without dominance of WD neuropsychiatric signs (apart from encephalopathy) [1,2,6,22,23].

Liver transplantation should be performed only if indicated by hepatic failure data, according to the recommended criteria (Nazer Index, King's College Scale) (Table 1) [23,24]. There are still no recommendations or indications to use this procedure in WD in the case of neuropsychiatric deterioration or a lack of effective

pharmacological therapy on neuropsychiatric presentation [1,2,6,22,23], but this issue is still under discussion [24-28].

During pharmacological therapy for WD, we expect the normalisation of copper metabolism and liver enzymes and the regression of liver and neuropsychiatric symptoms [1,2,6,22].

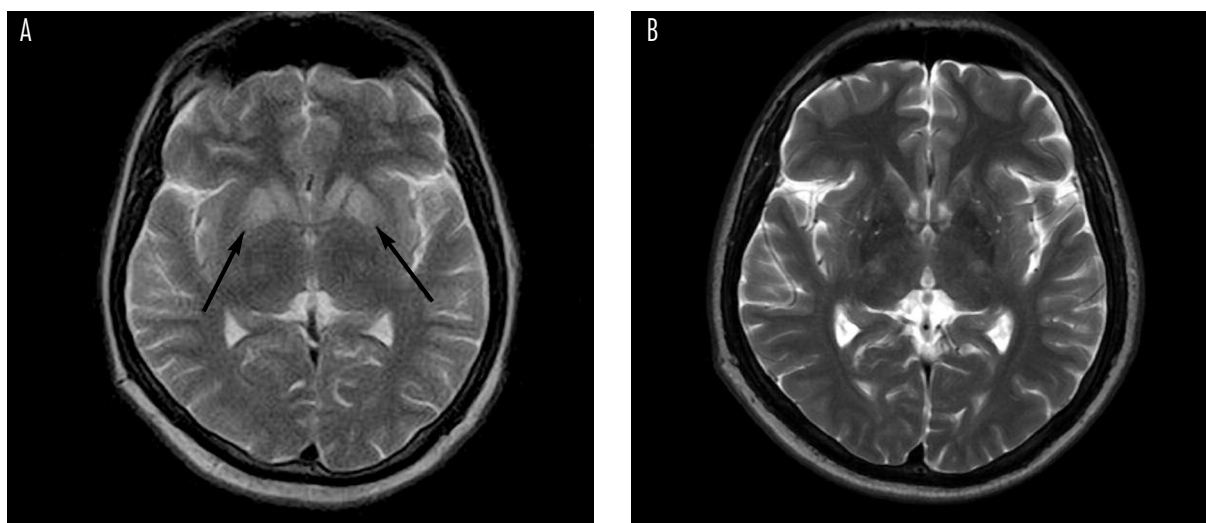
Liver transplantation, as a treatment option for the hepatic form of WD, should also cause a decrease in neuropsychiatric signs, but there are few observations of such a decrease [25,27,29-36], and neurological worsening after LT has even been described [32].

We describe a patient with the hepatic form of WD, without neuropsychiatric signs, with typical brain WD MRI pathology, for whom abnormalities in the MRI reversed 24 months after LT.

## Case report

A 28-year-old patient with liver cirrhosis of unknown aetiology was admitted to our department in May 2008 to exclude or confirm a WD diagnosis. The patient's hepatic symptoms and signs started in January 2008 as abdominal pain and oedema in the legs. The patient was diagnosed in a regional hospital with liver cirrhosis, oesophageal varices, spleen enlargement and suspected WD and was admitted to our department.

A neurological examination on admission did not reveal any pathology, but in an ophthalmologic examination, Kayser-Fleischer rings were detected bilaterally. Assessing copper metabolism, we found a decreased serum ceruloplasmin level (4.9 mg/dL; normal range: 25-45) and increased daily urinary copper excretion (1773  $\mu\text{g}/24$  hours; normal range: 0-50), but the serum copper level was within the normal range (75  $\mu\text{g}/\text{dL}$ ; normal range 70-140). In a genetic examination, we found mutation c.3207C>A (p.H0169Q) in only one allele of *ATP7B* (the whole gene was not sequenced). Other la-



**Fig. 1.** The brain MRI in the presented patient with Wilson disease. T2-weighted sequences at different time points of the disease: A) at the diagnosis of Wilson disease – increased signal intensity in T2 in the caudate and globi pallidi (black arrows); B) two years after liver transplantation (without focal changes – regression of changes shown on previous MRI scan)

laboratory results included slightly elevated liver enzymes [ALAT 52.8 IU/L (normal range: 10-40), ASPAT 85 IU/L (normal range: 10-42), bilirubin 113  $\mu\text{mol/L}$  (normal range 3.4-17.0), GGTP 107.9 IU/L (normal range: 7-64), LDH 247 U/L (normal range: 109-193)], coagulopathy [INR 2.4 (normal range: 0.8-1.2)] and, by ultrasound examination, a cirrhotic liver with hypo- and hyperechogenic changes, fibrosis and free liquid in the peritoneal cavity around the liver. The patient was assessed at 7 points on the King's College scale. In the brain MRI, typical WD changes were found – symmetrical hyperintense changes in T2-weighted sequences in both globi pallidi and the caudate (Fig. 1A). D-penicillamine was introduced in increasing doses up to 1000 mg. After the initiation of chelation therapy, the patient was also referred to hepatologists, who sent him to a transplant surgeon. The patient was qualified for LT, which he underwent in June 2009. The procedure was complicated by hepatic artery thrombosis, resulting in liver retransplantation in July 2009. After the surgical procedures, the patient was followed by the transplant surgeons, and he received only immunosuppression therapy due to LT.

The patient was admitted to our department again two years later in April 2011 according to procedures for control examinations of patients with WD. The neurological examination on admission did not reveal any pathology, and there were no signs of liver failure (the oedema of the legs and abdominal pains had disappeared,

and the liver parameters were in the normal range). His copper metabolism had none of the disturbances typically observed in WD patients: he had a normal level of serum ceruloplasmin (35 mg/dL) and a normal serum copper level (95  $\mu\text{g/dL}$ ). An ophthalmological examination did not reveal any Kayser-Fleischer rings, and in the brain MRI (Fig. 1B) we did not find any of the WD pathology observed in the previous examination.

## Discussion

Pharmacological treatment in the majority of WD cases leads to clinical improvement in both the hepatic and neuropsychiatric forms of the disease. Therapeutic success can be assessed not only with the improvement of clinical symptoms, including improvement of neurological and/or liver function, but also with additional examinations, such as brain MRI and/or liver ultrasound examinations [1,2,6,9-11,22,26,27]. Especially in the predominantly neuropsychiatric form of WD, a brain MRI follow-up, in addition to the clinical examination, is used as a marker of treatment efficacy. There are reports of reversible MRI lesions in WD during correct pharmacological treatment (trientine, d-penicillamine or zinc salts) [6,9-11,16,18-20,26] as well as after LT [27,31,36], but in both cases, brain MRI pathology regression was observed for a very long time after the WD treatment was started or LT was performed.

Interestingly, in some recovered neuropsychiatric WD patients, the MRI brain pathology does not change [6,13]. Overall, the regression of MRI WD symptoms depends mainly on the latency of the disease (the time between the first symptom onset and the start of treatment) and the patient's compliance [1,2,6,9,22].

From neuropathological studies, we know that during copper intoxication in WD, there is initially a loss of neurodendra and neuroglia with local oedema detectable in MRI studies. These changes are reversible with correct and early pharmacological treatment or LT [1,2,6]. However, untreated copper intoxication in WD leads to neuron necrosis and irreversible cystic changes in the brain, as assessed by MRI. Therefore, the period of time during which the disease is untreated may be the major factor affecting brain pathology, as assessed by MRI, reversibility in WD [6,8,9,13]. Further prospective studies with brain MRI at WD diagnosis and during the follow-up period are needed to better understand this issue.

Liver transplantation as a WD treatment option was first used in 1971 [34], and since then there have been several reports concerning the effects of LT in WD [6,22,25,27-36]; however, the indication for LT in WD is still under discussion. Generally, according to the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD), the indications for LT should be limited [1,22]. Irrespective of hepatologists' recommendations, some groups have tried to perform liver transplants in WD patients with severe WD, with predominant neurological form, or patients for whom pharmacological treatment is ineffective, but the results of such case reports are conflicting [21,25,31-36]. These data are not consistent with the neuropathological understanding of WD because when the disease remains untreated for an extended period (as in the case of a delayed diagnosis), the organs are damaged. In particular, damage to the brain in the form of neuron depletion and glial cell proliferation is not reversible, so LT in such patients should not cause neurological improvement [6,30,31].

The presented patient underwent successful LT, although he did not fulfil the King's College criteria for LT (Table 1). Interestingly, although he had no neurological signs before transplantation, in the MRI we observed changes that were characteristic of WD, which regressed after LT. It is worth emphasising that in WD patients, brain MRI examinations could, in addition to diagnosis and treatment monitoring, also help to distinguish hepatic and neurological changes. Typical WD

brain MRI changes are symmetrical T2-weighted hyperintensity or mixed intensity in the putamina and globi pallidi, caudate nuclei, thalami and pons. The midbrain, cerebellum, corticospinal tracts, cortex and subcortical areas are also affected. The T1-weighted signal has generally been found to be reduced in the basal ganglia [1,2,6,8-18]. In some cases, especially hepatic cases, T1-weighted hyperintensity in the globi pallidi has been observed. Such a finding is characteristic of hepatic encephalopathy and metal (iron and/or manganese) deposition in the globi pallidi. Therefore, the density of the globi pallidi could be different in the predominantly neurological or hepatic forms of WD. In our patient, brain MRI before transplantation revealed a hyperintense T2-weighted signal from the globi pallidi – which typically occur in the disease – but there were no T1-weighted hyperintensity changes, which are typical of encephalopathy and iron deposition.

We believe that the lack of T1-weighted hyperintensity in the brain MRI suggests that our patient had only early WD brain MRI pathological changes, without necrosis or cystic changes, which could completely disappear after effective pharmacological treatment. We suggest that the improvement of brain MRI (resolving changes in the globi pallidi and caudate) in our patient was due to the early stage of the disease in the brain, which caused primarily oedema, and not necrosis or glial proliferation.

## Disclosure

The authors report no conflict of interest.

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