LIVER TRANSPLANTATION FOR WILSON DISEASE: REVIEW AND A CASE REPORT OF AN UNEXPECTED NEUROLOGICAL COMPLICATION

Daniela Anghel[1,2], Ana Campeanu[2], Irinel Popescu[1,3], Emil Matei[3], Bogdan Dorobantu[1,3], Dana Tomescu[1,4], Laura Popa[4], Ioana Lupescu[1,5], Radu Tanasescu[1,6]

[1]University of Medicine and Pharmacy "Carol Davila", Bucharest
[2]Department of Neurology, Fundeni Clinical Institute, Bucharest
[3]Department of General Surgery and Liver Transplantation, Fundeni Clinical Institute, Bucharest
[4]Center of Anesthesiology and Intensive Care, Fundeni Clinical Institute, Bucharest
[5]Department of Radiology, Medical Imaging and Nuclear Medicine, Fundeni Clinical Institute, Bucharest
[6]Department of Neurology, Colentina Hospital, Bucharest

ABSTRACT

Wilson's disease is a rare autosomal recessive inherited disorder of copper metabolism, which results in copper accumulation in several tissues, especially with liver injury and failure. Orthotopic liver transplantation (OLT) can be lifesaving for patients with hepatic complications of Wilson's disease- fulminant liver failure or unresponsivness to medical therapy in chronic liver disease, with or without neurological manifestations. We report the case of a 19-year-old woman receiving a liver transplant for acute liver failure caused by Wilson's disease, who developed headache as the only symptom of a serious neurological complication after transplantation. The clinical course and neuroimaging demonstrating aneurismal subarachnoid hemorrhage are presented. The neurological complications and the difficulties of medical management in an immunosuppressed patient are discussed. Headache in a recently transplanted patient for acute liver failure may be a sign of a serious cerebral complication, subarachnoid hemorrhage. Early recognition and proper management may prevent life-threatening neurologic complications but chronic immunosuppression may impede a favourable outcome.

Key words: Wilson's disease, acute liver failure, liver transplantation, subarachnoid hemorrhage

INTRODUCTION

Wilson's disease (WD) is a genetic metabolic disorder, characterized by excessive absorption of copper from the small intestine and decreased excretion of copperinto bile. The autosomal recessive genetic defect, localized to chromosome arm 13q, affects the copper-transporting adenosine triphosphatase (ATPase) gene (*ATP7B*), which encodes a protein that helps transporting copper from intracellular chaperone proteins into the secretory pathway, both for excretion into bile and for incorporation into apo-ceruloplasmin. Although some ATP7B mutations occur spontaneously, most are inherited as an autosomal recessive trait. There are numerous gene mutations that can impair the protein's function, leading to copper accumulation mainly in the liver, but also in the brain, cornea and kidney.

DIAGNOSIS

Patients with WD usually present with liver disease during the first decade of life or with neuropsychiatric illness during the third decade, but the disease may present at any age (1). Acute hepatic

Author for correspondence:
Daniela Anghel, Department of Neurology, Fundeni Clinical Institute, 258 Fundeni Av, Bucharest
e-mail: anghellc@yahoo.com

failure may be the first presentation of WD and autoimmune hepatitis in previously asymptomatic patients, so the determination of the etiology is critical as treatment and prognosis differ between these two entities (2). The diagnosis is confirmed by measurement of serum ceruloplasmin, urinary copper excretion, and hepatic copper content in byopsied tissue, as well as the detection of corneal Kayser-Fleischer ring, which is present in 95% of patients with neurologic symptoms and over half of those without neurologic symptoms (3).

Neurologic disease may manifest as motor abnormalities with Parkinsonian picture (dystonia, hypertonia and rigidity), choreic picture or pseudosclerotic picture (with tremors and dysarthria).

Magnetic resonance imaging (MRI) and computerized tomography (CT) of the brain may detect increased density on CT or hyperintensity on T2 MRI in the basal ganglia. Additional abnormal findings can be found as hyperintensities in tectal-plate and central pons (central pontine myelinolysis-like). A characteristic finding in WD is the ''face of the giant panda'' sign, but this is found only in a minority of patients. Generalized brain atrophy or simultaneous involvement of basal ganglia, thalamus, and brainstem may be present (4).

Genetic testing is an important element of early WD diagnosis at least in some categories of patients: when clinical findings are not sufficient to support a definite WD diagnosis, for familial screening, for differential diagnosis of fulminant hepatitis (5). The most common mutation in Caucasians is H1069Q mutation (6).

Scoring system

In 2001 at the 8th International Conference on WD and Menkes disease a scoring system for the diagnosis of WD was discussed. A combination of clinical and biochemical tests with a score ranging from 0 to 4 for each test were developed (7). This scoring system is presented in Table 1.

The patients with a total score of at least 4 are considered to have Wilson disease.

The patients with a total score of two to three are considered to need more investigations.

The diagnosis of Wilson disease is improbable for scores between zero and one.

It has been difficult to find a simple genetic screening test for the disease, since over 500 different mutations have been identified. Thus only the H1069Q (exon 14) analysis is considered for scoring.

Acute liver failure caused by WD occurs either in patients with previously unknown disease-predominantly in young females (1), or in patients who were previously treated but stopped their medication. The diagnosis of WD in acute liver failure is difficult, because many of the copper metabolism parameters, including serum and urinary copper and reduced serum ceruloplasmin, are believed to be less reliable and specific (5). Suspicion for acute liver failure in WD should be particularly high in patients with combination of an alkaline phosphatase elevation/total bilirubin elevation ratio < 4 and an AST/ALT ratio > 2.2 (8).

TABLE 1. *Scoring system developed at the 8th International Meeting on Wilson's disease, Leipzig 2001*

Liver copper (in absence of cholestasis)		**Serum ceruloplasmin**	
Normal (< 50μ/g)	-1	Normal (> 0,2 g/l)	0
< 5xUNL (50-250 μ/g)	1	0.1-0.2 g/l	1
> 5xUNL (250 μ/g)	2	< 0.1 g/l	2
Rhodanine stain (in absence of quantitative liver copper determination)		**Coomb's negative haemolytic anemia**	
absent	0	present	1
present	1	absent	0
Mutation analysis		**Clinical symptoms and signs**	
2 chromosomes mutations	4	**KF rings**	
1 chromosome mutation	1	present	2
no mutation detected	0	absent	0
Urinary copper Neurological signs (in absence of acute hepatitis) (or typical abnormalities at MRI)			
normal (< 0.9 μmol/day or < 100 mg/day)	0	severe	2
1-2 x UNL	1	mild	1
> 2 x UNL	2	absent	0
normal but > 5 x UNL after D-penicillamine	2		

UNL: upper normal limit; KF: Kayser-Fleischer

TREATMENT

Diet. Foods with very high concentrations of copper (shellfish, nuts, chocolate, mushrooms, and organ meats) generally should be avoided. Well water or water supplied through copper pipes should be checked for copper content. Copper containers or cookware shouldbe avoided.

Medical therapy is based on copper chelators or blockers of intestinal absorbtion. These drugs are presented in Table 2.

For routine monitoring, serum copper and ceruloplasmin, liver biochemistries and international normalized ratio, complete blood count, urinary copper (especially for those on chelation therapy) and physical examination should be performed regularly, at least twice annually (5). The benefit of treatment is monitored by measuring 24-hour urinary copper excretion while on treatment. Values of urine copper excretion below 200 μg/day may indicate either nonadherence to therapy or overtreatment and excess copper removal.After adequate treatment with a chelator, stable patients may be continued on a lower dosage of the chelator or shifted to treatment with zinc salts. Patients who stop treatment risk developing acute hepatic failure.

Liver Transplantation. Because the biochemical defect resides mainly in the liver, orthotopic liver transplantation (OLT) can be used for complete reversal of the metabolic abnormality (9). Liver transplantation is life-saving but not without risk for patients with wilsonian fulminant hepatitis or chronic severe hepatic insufficiency unresponsive to medical therapy. Survival is satisfactory (ranges from 79-87%) and appears to be better for patients having a transplant for chronic advanced liver disease than for those with acute liver failure. Associated neurological or psychiatric symptoms due to WD may improve after liver transplantation (10), but patients with isolated long standing neurological impairment from WD are unlikely to recover after OLT, so this condition is considered by some authors to be a contraindication for OLT (11).

Cadaveric donor or living donor transplant can be performed. Successful live donor transplant is possible when the donor is a family member heterozygous for WD.

Gene therapy and hepatocyte transplantation may represent the future option for treating WD (12).

WD is a treatable disorder and early diagnosis is essential; the goal of therapy is to reduce copper accumulation by enhancing its urinary excretion (with chelating agents) and by decreasing its intestinal absorption (with zinc salts), liver transplantation being sometimes necessary.

CASE REPORT

We report the case of a 19-year-old female who underwent urgent liver transplant after she was reffered to our hospital for fulminant hepatic failure, secondary to WD.

The patient was diagnosed with WD two weeks before admission, on the basis of clinical signs of icterus and hepatomegaly and specific laboratory findings (low serum ceruloplasmin, high urine copper, no other causes of acute liver failure, such as viral, toxic or autoimmune hepatitis). She had no neuro-

TABLE 2. *Drugs used for treatment of WD*

Drug	Action	Neurological effects	Side effects	Doses
D-Penicillamine	General chelator, increases cupruria	Deterioration in a minority of patients at the beginning	Fever, rash, proteinuria, lupus-like reaction Aplastic anemia Leukopenia Thrombocytopenia Nephrotic syndrome Hepatotoxicity	Maximum dose 20 mg/kg/day; reduce by 25% when clinically stable Reduce dose for surgery and during pregnancy
Trientine	General chelator, increases cupruria	Deterioration in a minority of patients at the beginning	Gastritis Aplastic anemia Sideroblastic anemia	Maximum dose 20 mg/kg/day; reduce by 25% when clinically stable Reduce dose for surgery and during pregnancy
Zinc	Blocks intestinal absorption of copper	May cause initial deterioration	Gastritis, pancreatitis Zinc accumulation Possible disimmunity	Usual dose in adults: 50 mg elemental Zn three times daily;
Tetrathiomolybdate	Chelator, blocks copper absorption	Almost no neurologic deterioration during initial treatment	Anemia, neutropenia Hepatotoxicity	Experimental in the United States and Canada

logical symptoms, no Kayser Fleischer rings and, because of her unstable medical condition, requiring urgent transplantation, cerebral MRI or CT were not considered necessary.

At the time of the diagnosis of WD she had a moderate form of liver failure, so she was started on treatment with D-penicilamine and zinc, but soon her liver function deteriorated and complicated with renal and respiratory failure. Subsequently, she underwent a liver transplantation from a cadaveric organ donor.

At the time of transplantation, her MELD (Model for end stage liver disease) score was 26 and the liver profile at the time of liver transplantation revealed increased AST – 649 mg/dL, ALT–310 mg/dL, ALP–195 mg/dL, total bilirubin – 19.6 mg/dL, direct bilirubin – 13.8 mg/dL, INR – 3.4, normal serum creatinine – 0.6 mg/dL, low serum albumin – 2.5 mg/dL. She was started immediately on immunosuppressive theraphy with daclizumab, followed by tacrolimus and steroids.

In the forth day after transplantation she experienced an episode of acute liver rejection, resolved with steroids. For the next three days she complained of headache and was treated with non-sedating analgesics (injectable acetaminophen). Because of persisting severe pain, a neurological examination was requested and revealed meningism in absence of fever, anisocoria with right mydriasis, left Babinski sign with the rest of the exam being normal. Brain CT completed with angioCT and MRI with angioMRI showed subarachnoid hemorrhage (SAH) in the right sylvian fissure and suprasellar cistern (Fig. 1), caused by a spontaneous rupture of an aneurysm located at the bifurcation of right internal carotid artery (Fig. 2). The brain MRI also revealed moderate vasospasm in the right middle cerebral artery (Fig. 3), early hydrocephalus and no characteristic signs of WD, as the patient didn't have neurologic involvement due to WD (Fig. 4 and 5).

The Hunt and Hess clinical severity scale was grade 2 (moderate to severe headache, nuchal rigidity, no neurologic deficit except cranial nerve palsy) on a scale of 5.The Fisher Grade, which classifies the appearance of SAH on CT scan and estimates the risk of vasospasm, was 3 on a scale of 4 (SAH more than 1 mm thick), but with the highest risk of vasospasm.

The patient was started on oral nimodipine 60mg every 4 hours (even if it cannot significantly reduce

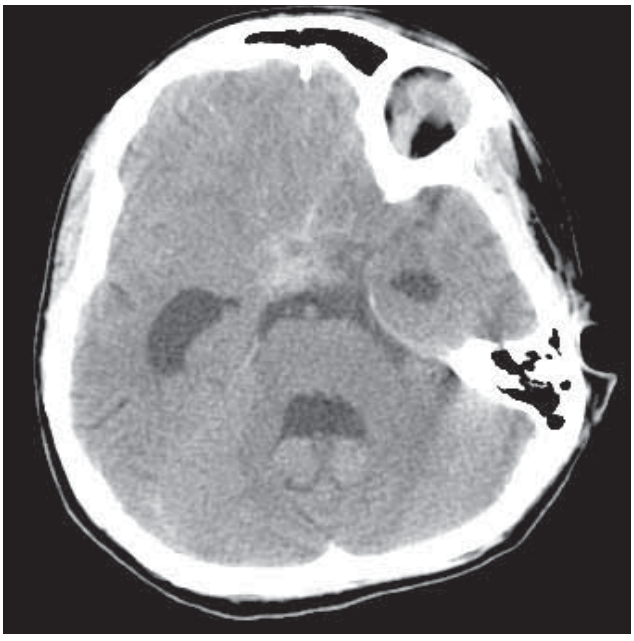

FIGURE 1. *Cerebral CT. Hyperdensity in the right sylvian fissure and suprasellar cistern*

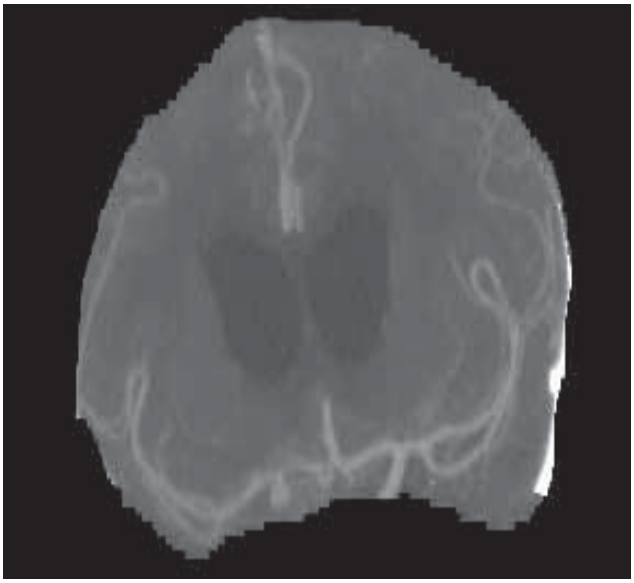

FIGURE 2. *Cerebral CT angiography. Aneurysm at the bifurcation of right internal carotid artery*

the amount of angiographic vasospasm) and was transferred to a neurosurgery unit for aneurysm clipping and drainage of hydrocephalus through a ventriculoatrial shunt. Unfortunately, the vasospasm consequences couldn't be avoided and the patient became hemiplegic, because of an infarct in the teritory of right middle cerebral artery. Her evolution was initially good, but she experienced an episode of shunt obstruction due to infection, managed with antibiotics and replacement of the shunt. Four weeks later she was admitted again in the posttransplant intensive care unit of our hospital,

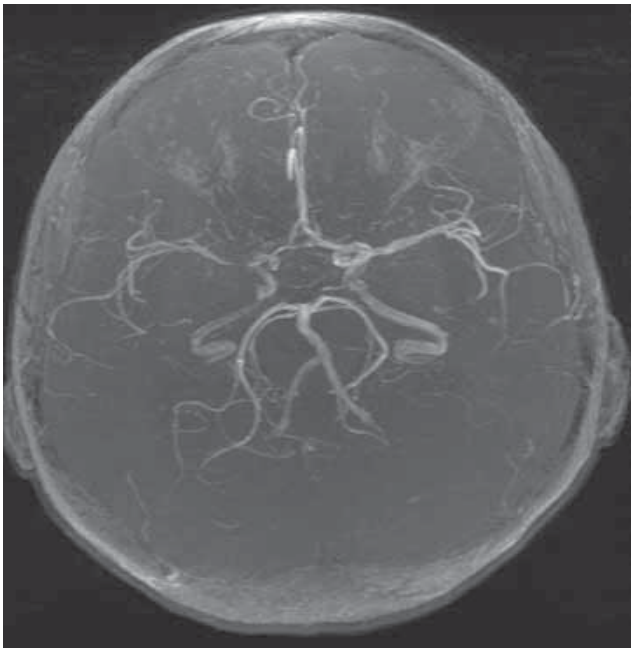

FIGURE 3. *Cerebral MRI angiography. Vasospasm in the right middle cerebral artery*

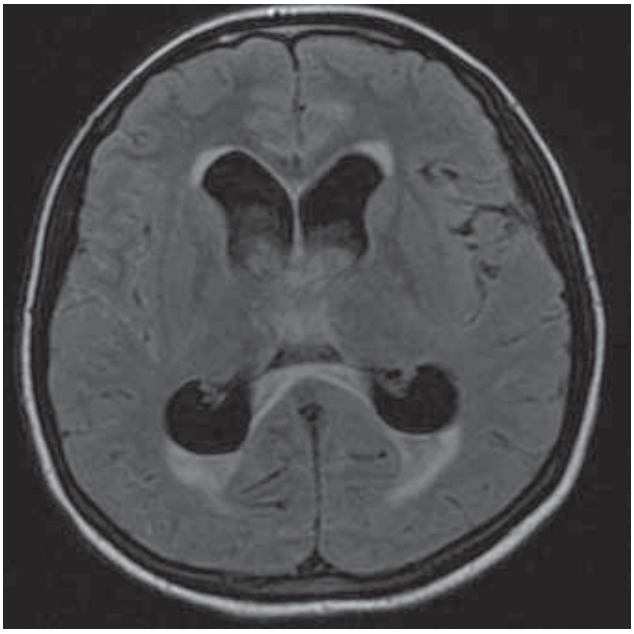

FIGURE 4. *Axial FLAIR. Symmetrical hydrocephalus and no characteristic signs of WD*

for further management of the liver graft, of the immunosuppression and of neurological impairment. Despite a very good function of the transplanted liver, the patient evolution was complicated by neuropsychic deterioration due to chronic hydrocephalus and infarction in the right middle cerebral artery teritory, frequent infections due to immunosuppressed condition and, finally, death due to intractable sepsis.

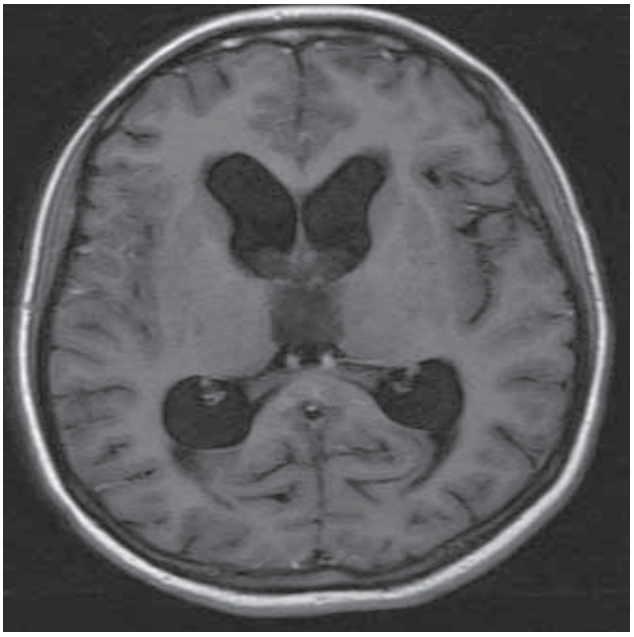

FIGURE 5. *Axial T1. Symmetrical hydrocephalus and no characteristic signs of WD*

DISCUSSION

Our patient was an established case of WD with primary liver involvement, who needed rapid liver transplantation for the management of unresponssive liver failure.

Aneurysmal SAH was an incidental association with WD, but coagulopathy, the burden of a difficult surgical intervention, such as liver transplantation, and early rejection of the graft treated with steroids were probably the precipitating factors.

Cerebral aneurysm is caused by a congenital anomaly or an acquired disease, in patients with preexisting familial history, hypertension, smoking, alcohol drinking, atherosclerosis or cerebral trauma. Congenital aneurysms are sometimes associated with polycystic kidney disease, some connective tissue diseases (fibromuscular dysplasia, Ehlers-Danlos disease, Marfan's syndrome, neurofibromatosis 1) and high-flow states (vascular malformations, fistulae). None of these causes were present in our patient.As the majority of intracranial aneurysms, the patient's aneurysm was asymptomatic until liver surgery.

Aneurysms typically form in the bifurcations of the large vessels from the circle of Willis. The location of the aneurysm causing anisocoria is usually at the junction of the internal carotid artery and posterior communicating artery. The aneurysm compresses the superior part of the third cranial nerve, where the pupil fibers are located. On the

other hand, our patient's anisocoria would have been caused by leaking of blood from aneurysm, which might have compressed the nerve.

Complications of SAH are:

- aneursymal rebleeding;
- acute hydrocephalus (ventricular enlargement within 72 hours);
- chronic hydrocephalus (appears after 10 or more days and is characterized by incontinence, gait instability, and cognitive deterioration);
- cerebral vasospasm (occurs within 4-14 days following hemorrhage); severe headache, change in mental status or appearance or exacerbation of a focal deficit are the main signs (13). In our patient, vasospasm caused ischemic brain injury and limited the possibility of coiling, as the endovascular treatment of aneurysm.
- seizures increase the risk of aneurysm rebleeding and neurologic deterioration;
- cerebral hyponatremia induces hypoosmolality, which can lead to cerebral edema;
- fever increases cerebral metabolic rate, releases excitatory neurotransmitters and breaks down the blood brain barrier.

After the aneurysm was ''secured'' from rebleeding, the focus of medical management of the patient shifted to identifying, monitoring, and preventing the neurologic complications of SAH.

Systolic blood pressure was kept between 90 and 140 mmHg; oral nimodipine was indicated to reduce the poor outcome related to aneurysmal SAH. Early vasospasm, defined as arterial narrowing seen on diagnostic angiography within the first 48 hours of aneurysmal rupture is predictive of cerebral infarction and neurological worsening as well as unfavorable outcome at 3 months (14). Symptomatic cerebral vasospasm was treated with volume expansion (hypervolemia), induction of hypertension and hemodilution (triple-H therapy), but cerebral angioplasty and/or selective intraarterial vasodilator therapy was not possible in this patient. Acute hydrocephalus needs temporary or permanent CSF drainage; because the patient suffered recent abdominal surgery, a ventriculo-atrial shunt was chosen instead of a ventriculo-peritoneal one, to decompress the ventricles.

Neurologic deterioration occurred in the next few months, caused by complications of SAH and by systemic infections in a chronic immunosuppressed patient, a severe sepsis being the cause of death.

CONCLUSION

The patient represents a case of acute liver failure as a modality of onset in Wilson's disease, which was complicated during liver transplantation by rupture of a previously asymptomatic cerebral aneurysm. Subsequent SAH had a progressively worse evolution. As it is cited in the literature, the liver transplantation for acute wilsonian liver failure successfully overcomes the imminent death, but our patient had associated conditions (such as pre-existing coagulopathy, early liver rejection treated with steroids, immunosuppression) that may have delayed an early diagnosis and worsened the prognosis of aneurysmal SAH.

To our knowledge, the association of aneurysmal subarachnoid hemorrhage with post-transplantation state for Wilson's disease has not been previously described.

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