



Global Advanced Research Journal of Medicine and Medical Science (ISSN: 2315-5159) Vol. 3(9) pp. 262-266, September 2014  
Available online <http://garj.org/garjmms/index.htm>  
Copyright © 2014 Global Advanced Research Journals

*Full Length Research Paper*

# Hepathopathy in children and young patients – Do you think of Wilson’s Disease (Hepatolenticular Degeneration)?

I. Buraga<sup>1,2\*</sup>, G. Mihailescu<sup>1,2</sup>, R.M. Anton<sup>2</sup> M. Buraga<sup>1</sup> and C. Baetu<sup>2</sup>

<sup>1</sup>University of Medicine and Pharmacy Carol Davila, Bucharest  
<sup>2</sup>Colentina Clinical Hospital, Department of Neurology, Bucharest

Accepted 11 September, 2014

The Hepatolenticular Degeneration (HLD) also known as Wilson’s Disease (WD) is a rare inborn systemic disorder of copper metabolism. It is an autosomal recessive transmitted disorder of copper transport due to mutations in the ATP7B gene located on the long arm (q) of the chromosome 13 (13q 14.3) which encodes a copper-transporting P-type ATPase (ATP7B) residing in the trans-Golgi network of hepatocytes affecting 1 in 30000-100000 people worldwide. (Merle et al., 2007; Roberts and Schilsky, 2008). This gene codes for a membrane-bound, P-type copper-transporting ATPase expressed primarily in the liver (Merle et al., 2007). Patients have to be homozygote who inherited two copies of the disease gene from mother and father. Those who inherit only one copy of the disease gene are heterozygotes – carriers. More than 500 mutations have been reported in different parts of the world, from which 380 have a confirmed role in the pathogenesis of the disease (Wilson disease mutation database). It is estimated, as no genetic screening was performed due to high costs, that 1 in 90-100 individuals is a carrier for WD. The ATP7B gene codes a membrane bound P-type copper transporting ATP-ase expressed primarily in the liver, responsible for the copper transportation from the hepatocytes, were it is stored, into the bile and for its binding to apoceruloplasmin in order to form ceruloplasmin, a 132kDa protein, a ferroxidase which transports 90% of the circulating copper in healthy people.

**Keywords:** Wilson disease, D-penicilamine, copper, Kayser-Fleischer

## INTRODUCTION

There are some theories regarding the etiology of the disease, but the basic underlying cause is not exactly known. It can be a lack of ceruloplasmin produced, or enough ceruloplasmin but of a poor quality, or the incapacity of the liver to metabolize or to excrete copper by the biliary system. In addition other genes related to

copper and oxidative stress, copper-binding prion protein (M129 V or M), apolipoprotein E3 homozygosis, medium factors, ethnicity may influence the age of onset, the course of the disease or the clinical form. Its clinical expression varies and the disease penetrance and modifying factors are not all known.

Due to this dysfunction copper accumulates from birth in high quantities first in the liver, responsible for a presymptomatic period of subclinical hepatitis and afterwards depending on the form of the disease and on copper intake (nutrition), storage of copper may occur in

\*Corresponding Author E-mail: [cris\\_baetu@yahoo.com](mailto:cris_baetu@yahoo.com),  
[buragaioan@yahoo.com](mailto:buragaioan@yahoo.com)

extra hepatic tissues like the Descemet membrane in the cornea (eye), basal ganglia in the brain and kidney. The organ damage is irreversible. The signs and symptoms of the disease may be present in children or teenagers due to the toxic copper accumulation in these organs, especially in the liver, causing an acute or chronic non-viral hepatitis or compensated or decompensated cirrhosis, acute hemolysis, sending the patient to the hepatologist, or due to other specific symptoms, to the neurologist, nephrologist, and for diagnosis to the ophthalmologist.

WD can start with a presymptomatic period during which copper accumulation in the liver causes subclinical hepatitis, and progresses to liver cirrhosis and development of neuropsychiatric symptoms (Merle et al., 2007) and can be diagnosed in a patient between 3-55 years of age (though there were described cases of patients over 70 years of age) (Ala et al., 2005) suffering from a liver disease of unknown etiology, or atypical autoimmune hepatitis or steatohepatitis of unknown etiology (disease where other causes of liver injury were excluded, in particular, serological markers of infection with hepatitis A, B, and C viruses absent and antiorganellar antibodies absent) associated or not with neurologic or psychiatric symptoms (Durand et al., 2001).

Hepatic dysfunction in Wilson's disease may assume several forms. Asymptomatic enlargement of the liver and spleen may occur, sometimes with elevation of liver enzymes. Acute transient hepatitis is the mode of presentation in 25% of those in whom hepatic symptoms herald disease onset. Although this may be mistaken for viral hepatitis by the unwary, the presence of hemolytic anemia in conjunction with the hepatic dysfunction, or elevation of unconjugated (indirect) bilirubin, should alert the clinician to the possibility of Wilson's disease (Brewer, 2001).

### **So, is WD a neurologic or a gastroenterological disease?**

Gow et al. found out that 22 patients out of 30 WD patients studied had liver manifestations (Gow et al., 2000), with a lower rate of Kayser Fleischer ring and low ceruloplasmin blood levels than the neurological forms, but he was not the only one.

The symptoms and signs can be initially not specific: anorexia, weight loss, fatigue, ascites, jaundice, hepatosplenomegaly with mild elevations of ALT and AST, but can evolve to a severe liver failure associating neurological and/or psychiatric signs and symptoms.

Women are more frequent affected by fulminate hepatic failure and can associate Coombs-negative hemolytic anemia and acute renal failure.

The brain copper is stored especially in the basal ganglia, after the hepatic accumulation, so neurological signs and symptoms such as tremor, rigidity, bradykinesia, dystonia, dysarthria, dysphagia, instability,

ataxia can appear later, in the second to the fifth decade. Psychiatric symptoms include agitation, mood disorders, anxiety, depression, psychosis, cognitive impairment.

So, the patients with hepatic problems are diagnosed at younger ages than patients with predominantly neurologic symptoms where there is a delay between onset of symptoms and diagnosis (Merle et al., 2007).

WD is the identified etiology in 5% of acute liver failure (ALF) patients worldwide (Ostapowicz et al., 2002). Prior series demonstrate that virtually all patients with WD presenting with ALF will die rapidly without urgent transplantation. Therefore, establishing the diagnosis quickly and unequivocally is critical for patient management and for family screening as well. Classically, reduced serum ceruloplasmin (Cp) levels have been associated with WD but are believed to be less reliable in the fulminant setting. Additional specific laboratory findings associated with fulminant WD include Coombs' negative hemolytic anemia, low serum uric acid levels, low serum alkaline phosphatase activity and increased aspartate aminotransferase:alanine aminotransferase (AST:ALT) ratios. (Ostapowicz et al., 2002).

The renal function can also be affected conducting to aminoaciduria, nephrolythiasis, hyperpigmentation, hemolysis, osteoporosis, thrombocytopenia, Fanconi syndrome.

WD must be considered at all ages in patients with hepatic disease, neurological and/or psychiatric symptoms even in patients older than 50 years of age, though it starts generally much earlier (cases are reported even in children under 5 years of age with acute liver failure and cirrhosis) (Roberts and Schilsky, 2008).

### **DIAGNOSIS**

The diagnosis of WD is difficult before symptoms onset, and may involve a multidisciplinary team appreciating the clinical signs and symptoms corroborated with the laboratory tests.

Each of the diagnostic tests has its limitations, and only the combination of clinical, biochemical and genetic tests provides a powerful and reliable tool for the diagnosis of Wilson's disease (Merle et al., 2007).

Genetic testing of patients families may be useful even in the absence of symptoms in order to start the specific treatment earlier, but it is expensive and not available in every country.

1. Serum ceruloplasmin level (measured enzymatically, by radioimmunoassay, radial immunodiffusion or nephelometry): can be very low < 50 mg/l and this is a strong evidence of the disease, it can be low (<200mg/l), but can also be normal or high – being of a low quality and so reduced in function, or due to the reduced half-life of apoceruloplasmin, delaying in this case the diagnosis.

Serum ceruloplasmin concentrations are elevated by acute inflammation and in hyperestrogenemia and can be very low physiologically in children younger than 6 months, having a peak in early childhood higher than in adults, and than in adult ranges.

20% of the heterozygotes have decreased levels of serum ceruloplasmin.

Serum ceruloplasmin < 50mg/l should be taken as a strong evidence for WD diagnosis.

Serum ceruloplasmin within the normal range do not exclude the diagnosis.

So it is really difficult to interpret this diagnostic criterion alone. Other associated criteria are needed.

2. Serum copper levels (non-ceruloplasmin bounded) (< 80µg/dl). Can be at low values due to low ceruloplasmin.

Can be at high levels in acute liver failure due to increased release from the liver.

3. 24 hour urinary copper excretion (>100mg/24h or >1,6 µmol/24h). The test should be done in every suspected or diagnosed patient. Findings >40mg/24h or 0.6 µmol/24h suggest to repeat the test.

4. Liver biopsy showing increased levels of copper in the liver (> 250µg/g dry weight) and histological signs of chronic liver damage.

The major problem with hepatic parenchymal copper concentration is that in later stages of Wilson's disease, distribution of copper in the liver is often inhomogeneous (McDonald et al., 1992).

5. The presence of the Kayser Fleischer ring due to deposition of copper in the Descemet membrane – at the ophthalmologic examination with a slit lamp (more frequent in patients with neurologic or psychiatric symptoms). May associate sun flower cataracts due to deposition of copper in the lens.

The Kayser Fleischer ring may be present in patients with chronic cholestasis and in children with neonatal cholestasis. It may be absent in children with WD with the hepatic form, and in some adults but this does not exclude the disease. It can be present in 95% of those with neurological symptoms (Roberts and Schilsky, 2008).

6. D-Penicillamine challenge test in symptomatic children using 500 mg D Penicillamine administered 2 times at 12 hours interval may induce a urinary copper excretion of >1600 µg copper/24 h

Additional tests:

Testing liver function  
Testing kidney function

Brain imaging – MRI showing focal high intensity lesions and atrophy, should be performed in all patients with neurologic symptoms.

Genetic testing for family screening – coding region for ATP7B (especially first degree relatives of WD patients) and for mutation analysis by whole-gene sequencing.

## TREATMENT

As it is a genetic disease, no etiologic treatment exists, and the treatments used will be for the whole life even during pregnancy. The goals of the treatment should be: reducing copper intake, reducing copper absorption, remove excess copper from the body, prevent copper storage, treat associated diseases induced by the copper storage – hepatic insufficiency, renal failure, neurologic and psychiatric symptoms.

Reduce copper intake – copper rich water and food: cocoa, chocolate, liver, mushrooms, nuts, shellfish.

Copper is an essential metal, an important cofactor for many proteins. The average diet provides 2-5mg/day. In WD daily intake should be <1mg/day

### Chelating agents

Used in presymptomatic or asymptomatic patients or as maintenance doses (Brewer et al., 1997).

D Penicillamine – binds copper and forms a stable compound released in urine. It may be necessary to associate Vitamin B6. It should be used as initial treatment. The usual dosage of penicillamine for initial treatment is 250–500 mg four times daily, given on an empty stomach, although some advocate lower dosages (Pfeiffer, 2007).

Early administration of D-penicillamine was associated with survival without transplantation. These results suggest the importance of early diagnosis of this form of Wilson's disease before the onset of encephalopathy, and favour early administration of D-penicillamine which could avoid the need for transplantation in most cases (Durand et al., 2001).

Side effects: Aplastic anemia, pancytopenia, immunocomplex nephritis (nephrotoxicity), systemic lupus erythematosus, myasthenia gravis, worsening of neurological symptoms (that's why it is not the treatment of choice in patients with neurological symptoms), polyneuropathy, optic neuritis, polymyositis.

The side effects are improved by changing the treatments with Zn salts and Trientine (Merle et al., 2007).

Trientine (Syprine) used in presymptomatic patients or those on maintenance therapy or in decompensated neurological and hepatic forms. Usual daily dose is 750 to 2000 mg, divided into three doses.

Chelator, induces cupruria. Fewer adverse events compared to D-Penicillamine and better tolerated as the

induced cupruria is less important. It should be used as initial treatment.

Tetrathiomolybdate recommended in forms with neurological symptoms.

Mechanism of action: chelator for copper and blocking enteral copper absorption.

Copper is absorbed by enterocytes mainly in the duodenum and proximal small intestine and transported in the portal circulation in association with albumin and histidine to the liver. There copper is used for metabolic needs and the excess is excreted into the bile.

#### Maintenance therapy

Zinc salts (acetate, sulfate or gluconate) reduce intestinal absorption of dietary copper via induction of metallothionein formation in intestinal enterocytes. Used in asymptomatic or presymptomatic patients and first line treatment in patients with neurological signs and symptoms (EASL, 2012).

Zinc acetate (Galzin) – blocks enteral copper absorption and eliminates copper in stool

Used for asymptomatic or presymptomatic patients. Dosage: 50 mg of elemental zinc three times daily.

#### Orthotopic treatment

Emergency liver transplantation for severe fulminant liver failure, decompensated end-stage cirrhosis unresponsive to treatment, patients with hepatic encephalopathy a decrease in prothrombin time below 20% of normal (Durand et al., 2001).

Wilson's disease accounts for 6–12% of all patients with acute liver failure who are referred for emergency transplantation (Walshe and Dixon AK, 1986; Eisenbach et al., 2007). Acute liver failure due to Wilson's disease occurs predominantly in young females (female:male ratio 4:1) (Walshe, 1987).

Recent interventions including exchange transfusion, plasmapheresis, molecular adsorbent recirculating system, and albumin dialysis aimed at rapid reduction of serum copper to help break the

cycle of hemolytic anemia, renal complications and perpetuation of liver damage appear promising but to date have not altered the overall outcome of ALF-WD patients (Auth et al., 2005; Kreymann et al., 1999; Rakela et al., 1986). Despite these advances, early diagnosis and listing for transplantation seems the best course in this setting.

The specific treatment can maintain or improve hepatic function, but neurologic and psychiatric signs and symptoms may remain stable or can worsen, and have a poorer outcome (Merle et al., 2007). The latter can get worse even by changing the treatments. The Kayser Fleischer ring and sun flower cataracts can slowly disappear with specific treatment if correctly conducted (Roberts and Schilsky, 2008).

Antioxidants, mainly vitamin E, may have a role as adjunctive treatment. Serum and hepatic vitamin E levels have been found to be low in Wilson's disease. Symptomatic improvement when vitamin E was added to the treatment regimen has been occasionally reported but no rigorous studies have been conducted. One study suggests no correlation of antioxidant deficiency with clinical symptoms (Sinha et al., 2005).

Animal data suggest a role for amitriptyline in impending liver failure due to Wilson's disease, as it reduces the copper-induced apoptosis of liver cells, and thereby increases survival of ATP7B deficient rats (Lang et al., 2007).

#### PROGNOSIS

Untreated Wilson's disease is universally fatal, with most patients dying from liver disease and a minority from complications of progressive neurologic disease. With chelation treatment and liver transplantation, prolonged survival has become the norm (Merle et al., 2007).

#### REFERENCES

- Ala A, Borjigin J, Rochwarger A, Schilsky M (2005). Wilson Disease in Septuagenarian Siblings: Raising the Bar for Diagnosis. *Hepatology*. 41: 668-670.
- Auth MK, Kim HS, Beste M, Bonzel KE, Baumann U, Ballauff A, et al (2005). Removal of metabolites, cytokines and hepatic growth factors by extracorporeal liver support in children. *J. Pediatr. Gastroenterol. Nutr.* 40:54-59.
- Brewer GJ (2001). *Wilson's Disease: A Clinician's Guide to Recognition, Diagnosis, and Management*. Boston: Kluwer Academic Publishers.
- Brewer GJ, Johnson V, Kaplan J (1997). Treatment of Wilson's disease with zinc: XIV. Studies of the effect of zinc on lymphocyte function. *J. Lab. Clin. Med.* 129:649-652
- Durand F, Bernuau J, Giostra E, Mentha G, Shouval D, Degott C, Benhamou JP, Valla D (2001). Wilson's disease with severe hepatic insufficiency: beneficial effects of early administration of D-penicillamine. *Gut*. 48:849-852.
- EASL (2012). *Clinical Practice Guidelines: Wilson's Disease*. *Journal of Hepatology* vol. 56 j 671-685.
- Eisenbach C, Sieg O, Stremmel W, Encke J, Merle U (2007). Diagnostic criteria for acute liver failure due to Wilson disease. *World J. Gastroenterol.* 13:1711-1714.
- Gow PJ, Smallwood RA, Angus PW, Smith AL, Wall AJ, Sewell RB (2000). Diagnosis of Wilson's disease: an experience over three decades. *Gut*. 46:415-419
- Kreymann B, Seige M, Schweigart U, Kopp KF, Classen M (1999). Albumin dialysis: effective removal of copper in a patient with fulminant Wilson disease and successful bridging to liver transplantation: a new possibility for the elimination of protein-bound toxins. *J. Hepatology*. 31:1080-1085.
- Lang PA, Schenck M, Nicolay JP, Becker JU, Kempe DS, Lupescu A, et al (2007). Liver cell death and anemia in Wilson disease involve acid sphingomyelinase and ceramide. *Nature Med.* 13:164-170.
- McDonald JA, Snitch P, Painter D, et al (1992). Striking variability of hepatic copper levels in fulminant hepatic failure. *J. Gastroenterol. Hepatology*. 7:396-8
- Merle U, Schaefer M, Ferenci, P, Stremmel W (2007). Clinical presentation, diagnosis and long-term outcome of Wilson's disease: a cohort study. *Gut*. 56:115-120. doi: 10.1136/gut.2005.087262

- Ostapowicz G, Fontana RJ, Schiodt FV, Larson A, Davern TJ, Han SH, et al (2002). Acute Liver Failure Study Group. Results of a prospective study of acuteliver failure at 17 tertiary care centers in the United States. *Ann. Intern. Med.* 137:947-954.
- Pfeiffer RD (2007). Wilson's Disease. Reprinted with permission from Thieme Medical Publishers (Semin Neurol. (2):123-132) Homepage at [www.thieme.com](http://www.thieme.com)
- Rakela J, Kurtz SB, McCarthy JT, Ludwig J, Ascher NL, Bloomer JR, et al (1986). Fulminant Wilson's disease treated with postdilution hemofiltration and orthotopic liver transplantation. *Gastroenterol.* 90:2004-2007.
- Roberts, EA, Schilsky L (2008). Diagnosis and Treatment of Wilson Disease: An Update. *AASLD Practice Guidelines. Hepatol.* 46 (6): 2089-2011.
- Sinha S, Christopher R, Arunodaya GR, Prashanth LK, Gopinath G, Swamy HS, et al (2005). Is low serum tocopherol in Wilson's disease a significant symptom? *J. Neurol. Sci.* 228:121–123.
- Walshe JM (1987). The liver in Wilson's disease. In: Schiff L, Schiff ER, editors. *Diseases of the Liver.* 6th ed. Philadelphia: Lippincott. pp. 1037–1050
- Walshe JM, Dixon AK (1986). Dangers of non-compliance in Wilson's disease. *Lancet.* 12:845–847.
- Wilson disease mutation database. Available from: <http://www.wilsondisease.med.ualberta.ca/database.asp>.