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Hepatology Snapshot:

Wilson's disease: Fatal when overlooked, curable when diagnosed

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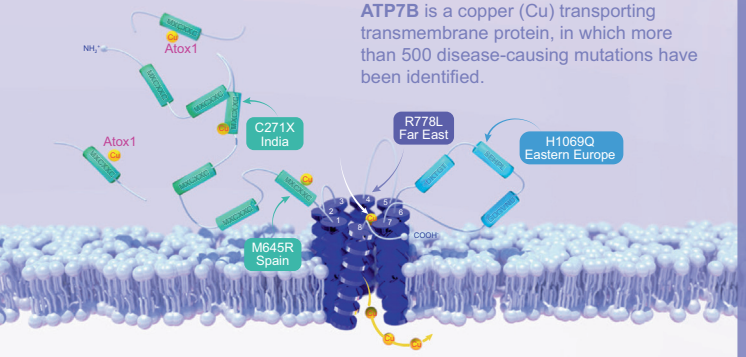
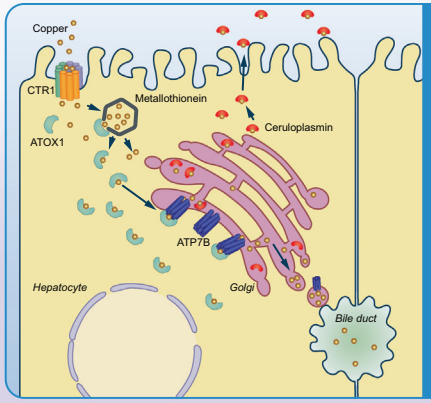
REGIONAL PREDOMINATING MUTATIONS

Wilson's disease (WD) is an autosomal recessive disorder caused by mutations in the *ATP7B* gene coding for the **ATP7B** protein.

ATP7B is a copper (Cu) transporting transmembrane protein, in which more than 500 disease-causing mutations have been identified.



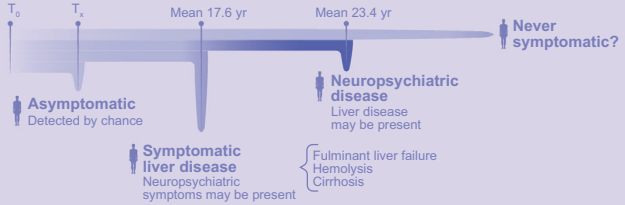


ATP7B mediates excretion of excess Cu into the bile and incorporation of Cu into ceruloplasmin[3]

When **ATP7B** is dysfunctional, ceruloplasmin formation and biliary excretion of Cu stops.

Accumulation of Cu leads to symptomatic disease of the liver and the brain.

NATURAL HISTORY OF WD WITH AGE AT PRESENTATION



CLINICAL SYMPTOMS

LIVER DISEASE

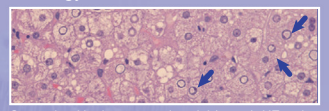
The presentation of hepatic disease may be an asymptomatic increase in aminotransferases, any form of chronic liver disease; acute liver failure or decompensated cirrhosis, hepatitis, steatohepatitis, steatosis or (in ~5% of cases) fulminant liver failure.

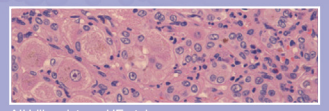
HEMOLYSIS

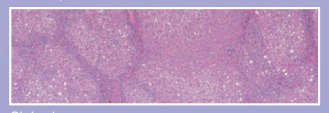
Non autoimmune hemolysis is caused by toxic levels of free Cu. It is always observed in patients presenting with acute liver failure (ALF), but may also be monosymptomatic.

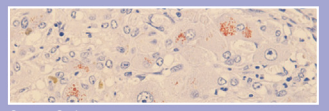
HEPATIC HISTOLOGY*

May resemble any other liver disease; histology can never rule out WD.


Steatosis with glycogenated nuclei (arrow), HE stain

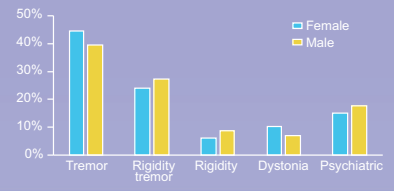

AIH-like picture, HE stain


Cirrhosis


Copper Stain

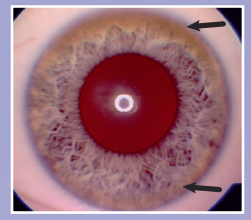
NEUROPSYCHIATRIC DISEASE

Presenting symptoms in 427 patients with neurological phenotype of WD.



KAYSER-FLEISCHER RING

Kayser-Fleischer rings are Cu deposits that form in Descemet's membrane of the cornea. They appear as brown or golden rings, seen in 90% of neurological and 40% of hepatological WD presentations. They disappear during treatment.

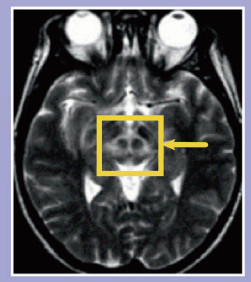


RARE MANIFESTATIONS

- **Kidney:** Hypercalciuria, nephrolithiasis, renal tubular acidosis, aminoaciduria hypophosphatemia
- **Skeletal:** Osteoarthritis, steoporosis condrocalcinosis
- **Heart:** Arrhytmias, cardiomyopathy
- **Other:** Sunflower cataracts, blue lunulae, lipomas

THE PANDA SIGN**

T2 weighted MRI may show Cu deposits in the basal ganglia, in some cases as the "face of the giant panda sign".



DIAGNOSIS

Some findings are often present, but none of them in 100% of WD patients. These include:

- **Low ceruloplasmin in plasma**
  Because most P-Cu is in ceruloplasmin, total P-Cu will also decrease. However, "free" non-ceruloplasmin Cu will be increased.
- Copper content in the liver biopsy >5 times ULN.
- **Elevated 24 h urine Cu.** The kidney excretes Cu from the non-ceruloplasmin bound Cu.
- **Kayser-Fleischer rings**
- **Demonstration of copper induced changes in basal ganglia**

The Leipzig score is useful for interpretation of finds (Table 1)

TREATMENT

Most patients will have normal life expectancy on medical treatment. Without treatment the disease progresses to death. Neurologic symptoms may progress during initial treatment.

- Chelators such as D-penicillamine of trientine bind copper and thereby increase its urinary excretion
- Zinc inhibits the intestinal uptake of copper and induces metallothionein in the liver and the gut epithelium
- **Tetrathiomolybdate (TTM)** is currently being evaluated in clinical trials. It increases biliary Cu excretion.
- **Liver transplantation** is the only life saving treatment in patient's presenting with ALF. It may also be necessary in patients with decompensated cirrhosis.

Keywords: Wilson disease; Liver histology; Copper metabolism.

*Histology images by Dr. Merima Herac; **Reproduced with permission from Jacobs DA, *et al*. The "double panda sign" in Wilson's disease. Neurology 2003; 61 (7): 969. Available at: https://n.neurology.org/content/61/7/969

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Wilson's disease (WD) is an autosomal recessive disorder caused by mutations in the *ATP7B* gene. Copper is an essential micronutrient which is incorporated into a variety of proteins and metalloenzymes (cytochrome C oxydase, superoxide dismutase, dopamine-ß hydroxylase, lysil-oxydase, tyrosinase), as well as being necessary for the proper growth, development, and function of many organs, including the liver, bone, connective tissue, brain, and heart.[1,2]

Hepatic ATP7B protein regulates the whole body content of copper by mediating its excretion into bile or irreversible incorporation into ceruloplasmin.[1–3] Under normal conditions, most of the copper in plasma is contained in ceruloplasmin while "free" or (non-ceruloplasmin-bound) copper in plasma is low.[4] The dysfunction of the ATP7B protein leads to impaired biliary excretion of copper and thereby to copper accumulation in the liver and extrahepatic tissues.[1,2,4] At the same time, plasma ceruloplasmin is typically lower than normal, and "free" copper becomes elevated.

The disease most often presents between 5 and 35 years of age but may become symptomatic at any age (the youngest reported symptomatic patient was 2 and the oldest was 74 years old) or may never become symptomatic.[5] The clinical picture is highly variable with hepatic and neurologic disease the main forms of presentation.[4,5] Patients with hepatic disease typically present with elevated aminotransferases but some present with cirrhosis and around 5% with acute liver failure. In 3–4% a non-autoimmune hemolysis is seen.[4,6] Patients with fulminant WD present with deep jaundice, hemolysis, moderately elevated aminotransferases and low alkaline phosphatases.[4,10] While most children are diagnosed at a pre-cirrhotic state, about half of adult patients have cirrhosis at diagnosis.[6] Patients with hepatic presentation rarely have neurological symptoms.

The typical neurological features include tremor, dysarthria, dystonia; about 90% have Kayser-Fleischer rings;[7] around 60% also have psychiatric symptoms[8] and most have abnormal liver histology.[6] Liver histology is non-specific and may include the whole spectrum of liver pathology. Steatosis is a common finding in non-cirrhotic patients where it may resemble non-alcoholic steatohepatitis.[9] Hepatic presentations are more common in childhood, while neurologic presentations are usually diagnosed later. There is a significant gender effect: Hepatic presentation is more common in females and neurologic presentation in males[5] and 2/3 of the acute fulminant patients are women.[5] More than 800 different *ATP7B* mutations have been identified but the different phenotypic presentation of WD cannot be related to specific mutations.[5]

The diagnosis may be straightforward in the presence of typical neurological symptoms and Kayser-Fleischer rings, but diagnosis is often missed for several years. No single test is specific or sensitive on its own.[4] Most often a range of tests including measurements related to copper metabolism (serum copper, ceruloplasmin, urinary copper excretion, hepatic copper content) and molecular genetic testing are needed to diagnose or exclude WD.[4] The Leipzig Score is useful for this purpose (see Table 1).[4] First degree relatives have to be evaluated, and to do this, genetic testing is particularly valuable.

Life-long treatment with copper-chelators (D-penicillamine, triethylenetetramine, tetrathiomolybdate) or zinc is needed.[4] In the absence of randomized studies the recommendation that a copper chelator should be the initial treatment[4] is based on experience rather than evidence. For most patients with acute fulminant WD and some with decompensated cirrhosis, liver transplantation is the only way to save their lives. Liver transplantation for neurologic WD has limited success and is not recommended. For children with acute Wilsonian liver failure the "revised Wilson's Index" helps to select patients for emergency liver transplantation. It assigns a score from 0 to 4 to actual values of serum bilirubin, international normalized ratio, aspartate aminotransferase, white cell count, and albumin. A score of >11 has a sensitivity and specificity of 93% and 97%, respectively, for mortality prediction.[10]

All other patients can achieve normal life expectancy on medical treatment.[4]

Table 1. Diagnostic tests for Wilson's disease.

	Abnormal	Leipzig Score					Caveat
		−1	0	1	2	4	
Clinical symptoms							
Kayser-Fleischer rings	Present		Absent		Present		Requires slit lamp examination Absent in up to 50% with hepatic WD and 10% with neurological WD May be seen in severe cholestasis
Neuropsychiatric symptoms*			Absent		Present		Psychiatric symptoms are uncharacteristic
Laboratory findings							
Plasma ceruloplasmin (mg/dl)	<20		>20	10–19.9	<10		Normal in up to 50% in hepatic WD Increased by estrogens Low in malabsorption
24 h Urine-Cu (µmol/24 h)	>1.6 >0.64 in children				>1.6		Increased in cholestasis and hepatocellular necrosis. Not useful in anuric.
Hepatic copper (µg/d dry weight)	>250	<50		51 –250	>250		Lower than 250 µg/g in 20% of WD Elevated in cholestasis
ATP7B mutations** (N)			None	1		2	2 mutated alleles are not found in all of patients

WD, Wilson's disease.
*Typical MRI findings in absence of clear symptoms also score 2.
**Disease causing, must be determined in newly discovered cases.

Conflict of interest

Peter Ferenci declares advisory roles for Univar, Alexion, Vivet Therapeutics and an unrestricted research grant from Gilead. Peter Ott declares no conflict of interest.

Please refer to the accompanying ICMJE disclosure forms for further details.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2019.02.002.

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