# WILSON DISEASE – SHORT REVIEW OF STANDARDS AND UPDATES IN TREATMENT AND REHABILITATION

## DEFINITION AND PREVALENCE

Wilson disease is an autosomal recessive disorder, caused by mutations in the ATP7B gene, which is a membrane-bound copper-transporting ATPase. Clinical manifestations, caused by the toxicity of copper are primarily on the liver and the brain. The prevalence of Wilson disease is about 1 in 40 000 and the carrier prevalence of the ATP7B mutation is approximately 1%.

## CAUSES

ATP7B protein deficiency violates the excretion of copper, leading to a positive copper balance, accumulation in liver and toxicity due to free radicals aggregation. Because of the low serum ceruloplasmin levels, which usually connects more than 90% of the serum copper, during disease progression the concentration of non-ceruloplasmin copper (free copper) is increased. It is then accumulated in other parts of the body such as the brain, causing neurological and psychiatric manifestations.

## CLINICS

Wilson disease may present with hepatitis, cirrhosis or hepatic decompensation, beginning usually in adolescence but can occur later, too. Hepatic decompensation is accompanied by increased serum bilirubin, decreased serum albumin and coagulation factors, ascites, peripheral edema and hepatic encephalopathy. In case of severe liver failure, hemolytic anemia may occur because of the large amounts of copper, entered the bloodstream. An association between hemolysis and liver disease makes the diagnosis of Wilson disease very probable. Neurological symptoms usually manifest at the age of 20, although they may also occur in the age of 50. The three main manifestations are: dystonia, discoordination and tremors. Disturbances often occur in the speech and swallowing. In some patients the clinical picture resembles that of Parkinson's disease. It can be observed also memory loss, migraine-like headache and seizures. Mental changes are also described – loss of emotional control, depression, hypoactivity or lack of sexual inhibition. In women, spontaneous abortion and amenorrhea can be observed. There are also cholelithiasis and nephrolithiasis, osteoarthritis (especially of the knee joints), microscopic haematuria and increased urine excretion of phosphorus, amino acids, glucose and urate.

## ESTABLISHED THERAPY

Initially, the treatment of the disease has been conducted using *penicillamine*, but now its place is limited because of its toxicity and the worsening of neurological symptoms. *Trientine* is less toxic chelator and has replaced the use of *penicillamine*, as it is often cited as the drug of first choice because of fewer side effects. Still as an experimental medicine is discussed the application of *tetrathiomolybdate* (TM). It has been approved in the USA and Canada and it is recommended for patients with neurological form of the disease due to the rapid effect in managing the toxic manifestations.

Usually the choice of treatment regimen is determined by the clinical manifestation, for which there are developed schemes and they are updated as needed:

1. *Initial therapy of neurological or psychiatric symptoms*

*Cuprimine* is proved to be inadequate because the worsening neurological symptoms. *Zinc* acts too slowly and while clearing the toxicity of the copper, it may already have caused significant damage. That is why TM was developed in order to obtain rapid and reliable results without significant side effects. Another possibility is the application of *trientine*, emphasizing its significantly less toxicity than the one of *cuprimine*.

2. *Initial therapy in hepatic manifestation*

Proposed combination of first choice is *trientine* and *zinc* for 5-6 months and then continue only with *zinc*. In case of severe damage to the liver, the transplantation remains as a single option.

3. *Supporting therapy*

In achieving a negative balance of copper, *zinc* therapy is recommended.

4. *Asymptomatic patients*

Treatment with *zinc* is recommended.

5. *Pregnant women*

Treatment with *zinc* is recommended again, because it is not teratogenic.

6. *Therapy of children*

The first choice is *zinc*, dosed according to the body weight.

7. *Additional therapy*

- *Diet*

To avoid copper-rich foods like liver and mussels. Nutritional supplements and vitamins with mineral composition containing iron should not be accepted. It is well to monitor the content of copper in the water, especially that which is used for cooking. Adding antioxidants to the dietary regime is recommended, especially vitamin E.

- *Physical therapy*

It is little said on the importance of this part of medicine for patients with Wilson disease, but it is absolutely necessary especially for those who manifest neurological symptoms. Articulation problems, pains from osteoporosis and limb deformations are preventable with timely intervention with adequate physical procedures. Dystonia affects the quality of life of patients and lead to contractures of articulations, which can also be avoided by intervention of a specialist. Disturbances of speech are no less stressful for patients and their families, so proper speech exercises and consultation would help reducing and overcoming this deficit.

When stabilizing the situation and restoring the balance of copper in the body, it is important to evaluate the functional deficit of the patient and according to the intellectual ability to target appropriate labor vocational rehabilitation in order to have a profession and achieve economic independence and social psychological comfort and integration.

**REFERENCES**


1. Roberts E, Schilsky M. Diagnosis and Treatment of Wilson Disease:An Update. HEPATOLOGY, June 2008,
2. Garcia-Villarreal L, Daniels S, Shaw SH, Cotton D, Galvin M, Geskes J, et al. High prevalence of the very rare Wilson disease gene mutation Leu708Pro in the island of Gran Canaria (Canary Islands, Spain): a genetic and clinical study. HEPATOLOGY 2000;32:1329-1336
3. Gaffney D, Fell GS, O'Reilly DS. ACP Best Practice No 163. Wilson's disease: acute and presymptomatic laboratory diagnosis and monitoring. J Clin Pathol 2000;53:807-812.
4. Shiono Y, Wakusawa S, Hayashi H, Takikawa T, Yano M, Okada T, et al. Iron accumulation in the liver of male patients with Wilson disease. Am J Gastroenterol 2001;96:3147-3151.
5. Sen S, Felldin M, Steiner C, Larsson B, Gillett GT, Olausson M, et al. Albumin dialysis and Molecular Adsorbents Recirculating System (MARS) for acute Wilson's disease. Liver Transpl 2002;8:962-967.


***To get further information on Wilson disease, as well as on the opportunities for medical rehabilitation and patients' training, please contact Medical Centre "RareDis".***


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