DOI:10.4274/Tnd.60566

Wilson's Disease

Wilson Hastalığı

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Summary

Wilson's disease is a autosomal recessive disorder of copper metabolism. Clinical phenotypes include hepatic, haemolytic, neurologic and psychiatric diseases. Wilson's disease is caused by mutations in the ATP7B gene. ATP7B encodes a hepatic copper-transporting protein, which is important for copper excretion into bile. Neurological symptoms in Wilson's disease include variable combinations of dysathria, ataxia, parkinsonism, dystonia and tremor. Wilson's disease is lethal if untreated. This review discusses the epidemiology, genetics, clinical features, etiopathophysiology, diagnostic tests, and treatment of Wilson's disease. *(Turkish Journal of Neurology 2013; 19:122-127)*

Key Words: Wilson's disease, liver, neurological symptoms, Kayser-Fleischer rings

Özet

Wilson hastalığı bakır metabolizmasının otozomal resesif geçişli bir hastalığıdır. Klinik fenotipler hepatik, hemolitik, nörolojik ve psikiyatrik hastalıkları içerir. Wilson hastalığına ATP7B genindeki mutasyonlar neden olur. ATP7B hepatik bakır taşıyıcı proteini kodlar ve bakırın safraya atılımında önemli rol oynar. Wilson hastalığındaki nörolojik semptomlar dizartri, ataksi, parkinsonizim, distoni ve tremorun değişik kombinasyonlarını içerir. Wilson hastalığı eğer tedavi edilmezse öldürücüdür. Bu gözden geçirmede Wilson hastalığının epidemiyolojisi, genetiği, klinik özellikleri, etyopatofizyolojisi, tanısal testleri ve tedavisi tartışılacaktır. *(Türk Nöroloji Dergisi 2013; 19:122-127)*

Anahtar Kelimeler: Wilson hastalığı, karaciğer, nörolojik semptomlar, Kayser-Fleischer halkası

Introduction

Wilson's disease (WD) is a condition that is inherited in an autosomal recessive pattern and that develops due to the copper mechanism dysfunction. Numerous organs, primarily the liver and the brain, may be affected by excess copper deposits in the affected people. Wilson's disease can be fatal in the absence of proper treatment.

Wilson's disease is first described by the American neurologist Samuel Alexander Kinnier Wilson in 1912 (1). In his thesis work completed in The National Hospital at Queen Square, Wilson described this disease in detail and named it as progressive lenticular degeneration. Kayser mentioned the pigmented corneal rings 10 years before Wilson described the disease. It is commonly assumed that Kaiser made this description on a patient who had WD. The excess copper deposition in the liver and the brain of the WD patients was discovered in 1929 and 1930, and the serum ceruloplasmin was found to be reduced in these patients in the year 1952 (2). After the initial suggestion in 1921 by Hall that the disease might have a genetic etiology, this hypothesis was later confirmed by Bearn in 1960 (3). In 1993, the ATP7B gene associated with the disease was cloned (4).

Wilson's disease had remained a progressive and fatal disease until the year 1951. Cumings proposed the use of British anti-Lewisite (BAL) or Dimercaprol, which were already used in arsenic poisoning, as chelation treatment in WD patients. In 1951, Cumings, Denny-Brown and Porter reported the benefit of intramuscular Dimercaprol in the treatment of WD (2). The first chelating agent was intramuscular Dimercaprol. As an alternative for this agent, which was known to have numerous side effects, John Walshe's report on the positive clinical effects of Penicillamine had proved to be revolutionary for the treatment of this disease (5). In

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Received/Geliş Tarihi: 30.05.2013 **Accepted/Kabul Tarihi:** 02.07.2013

1969, Walshe started using Trientine in cases that are resistant to or intolerant of Penicillamine. These two medicines remain to be the primary chelating treatments to this day. Schouwink and Hoogenrand proposed the use of zinc in the early 1960's (2). Walshe reported that ammonium tetrathiomolybdate could also be used for treatment (2). Ammonium tetrathiomolybdate is a chelating agent commonly used by veterinarians for copper poisoning. Its application in humans with neurological WD is still being investigated.

Epidemiology and Risk Factors

The prevalence of the disease changes between one in 5000th or 30.000th people (6). The ratio of WD mutation carriers in the population is about 1/90 (7). It should be noted, however, that the countries with higher rate of consanguineous marriage would yield higher ratios. It has been reported that certain genetic risk factors may have an impact on the WD phenotype and the disease progression but this report has not yet been confirmed.

Genetics

ATP7B gene present on the long arm of chromosome 13 (13q14–q21) has 21 exons and encodes a 1465 amino acid-long transmembrane ATPase (ATP7B) (7). Mutations on this gene cause WD. ATPase is a copper-binding enzyme. The dysfunction of the ATP7B that is expressed in hepatocytes causes copper deposits in the liver and subsequently WD. So far, there have been over 650 mutations reported. Sixty percent of these mutations are classified as missense mutations. The genotypic manifestations of ATP7B are complex and are expressed as compound heterozygotes in most patients. The types of mutations vary by population. The most common ATP7B mutation seen in European patients is the histidine to glutamate substitution at position 1069 (H1069Q). This mutation accounts for the 30-60% of the mutations in the Caucasian population. The most common mutatioin in southeast Asia is R778L. Both types of these populations were seen in Indian population. The phenotype of the disease may change depending on the properties of these mutations. For instance, H1069Q mutation is characterized by the late onset of the disease and rapid neurological involvement.

Clinical Profile

The symptoms of the disease often begin at the 2nd and 3rd decades. In large case series, the onset of the neurological findings corresponds to ages between 15 and 21. While they are remarkably rare, WD onsets at very young (2 years) and very old ages (70 years) were also reported.

The dysfunctions in the organs where the freely circulating copper in the serum settle on constitute the symptoms and signs of WD (Table 1). All cases necessarily include the involvement of liver. This involvement may vary between a mild increase in serum transaminases, and acute fulminant or chronic hepatitis. The patients with fulminant hepatitis may experience nausea, vomiting, weight loss and bleeding. Anemia and the deficiency of coagulation factors, which are the signs of chronic liver failure may present as initial signs. Cirrhosis develops in the advanced stages of the disease. Even though it is rare, hepatocellular carcinoma in the presence of chronic cirrhosis and inflammation may be seen in WD. Wilson's disease should always be included in the workup for the patients with chronic liver dysfunction that is not attributable to other causes.

Neurological involvement is present in the 40-50% of the cases as the initial sign (2). Since such symptoms may not be distinctly pronounced in the beginning, all cases with suspected WD should go under neurological examination. After the detection of liver disease symptoms in the patient, the emergence of neurological involvement symptoms is generally between 2 to 5 years. There have been reports on the neurological involvement without liver symptoms in some older patients. Dysarthria, tremor, dystonia, and parkinsonism are the most commonly seen clinical profiles. Dystonia may be of focal or generalized type. In some patients, the dystonic involvement of the facial muscles causes a smirking look (risus sardonicus). Similarly, the involvement of tongue and pharyngeal muscles may cause speech impediments and swallowing problems. Due to the laryngeal muscle involvement, the patient may seem like whispering and the intelligibility of the speech drops. Parkinsonism and/or dystonia in the extremities and axial muscles affects gait negatively. Among movement disorders, chorea, tics and myoclonus are less commonly seen. Cerebellar system findings like ataxia are seen in 25% of the patients. These cerebellar findings may cause or contribute to impairment in gait or speech. Rarely, epileptic seizures can also be a part of the clinical profile. The seizures may develop also as a result of the removal of excess copper from the body. Behavioral problems and mental state changes start almost at the same time as somatic neurological findings. Cognitive and behavioral symptoms may be mild or severely problematic (8). The decline in academic performance

Table 1. Clinical signs of Wilson's disease

Hepatic
- Increase in permanent liver enzymes
- Chronic hepatitis
- Cirrhosis (decompensated or compensated)
- Fulminant hepatic damage (+/- hemolytic anemia)

Neurological
- Dysarthria-anarthria
- Dysphagia
- Tremor (commonly "flapping")
- Dystonia
- Cognitive impairment
- Parkinsonism (rigidity, bradykinesia, postural changes)
- Chorea
- Gait disorders
- Pseudobulbar paralysis
- Episodes
- Sleep disorders

Ophthalmic
- Kayser-Fleischer ring
- Sunflower cataract

Psychiatric
- Depression
- Anxiety
- Personality changes
- Psychosis

Other systems (rare)
- Kidney failure, aminoaciduria and kidney stone
- Amenorrhoea, ovary dysfunction, infertility, abortus
- Cardiomyopathy, arhythmias
- Anemia, thrombocytopenia

may be the first cognitive warning sign for the patient's relatives. The most severely affected areas are executive functions, memory (due to working memory impairment rather than a primary memory involvement), and visuo-spatial functions (9). The severity of mental state involvement is determined by the spread of the existing lesions. Psychiatric symptoms exist in 30-50% of the patients. The most common ones among such symptoms are anxiety, mood disorders and psychotic symptoms.

A brown-greenish ring forms in the peripheral cornea due to free serum copper settling on the Descemet's membrane on cornea's inner surface. This pathognomic finding for the disease is called Kayser-Fleischer ring (KFR). Kayser-Fleischer ring, even though sometimes being visible to the naked eye, is often not detectable with the classical eye examination and requires the use of slit-lamp examination. Kayser-Fleischer ring is first seen in the upper pole of the cornea. Even though it is traditionally believed that KFR is necessarily present at the onset of the neurological findings, it may not be present 5% of the time in a WD patient with neurological involvement (10). Kayser-Fleischer ring may rarely be present in chronic liver patients, especially those with prolonged cholestasis and cryptogenic cirrhosis as well. Kayser-Fleischer ring fades to normal following medical treatment or liver transplant. The persistence or recurrence of this ring is indicative of poor treatment compliance. Another eye-related symptom, "sunflower cataract" is bright colored and can only be seen in slit-lamp examination (11). The rate of occurrence is lower than KFR. Sunflower cataract does not cause visual problems and it is responsive to the treatment.

Urinary, cardiac, endocrine and musculo-skeletal systems can also be involved in WD. Therefore, laboratory and clinical findings related to these systems may also be present (10). Among skeletal abnormalities are osteomalacia, osteoporosis, spontaneous fractures, osteoarthritis, osteochondritis dissecans, chondrocalcinosis, subchondral cyst formation and azure lunula on the fingernails. Knee joints and spine are the most commonly affected regions on the skeletal system. Myocardial copper accumulation may cause cardiomyopathy and arrhythmia. But this condition is exteremely rare. Among other rare clinical findings are hypoparathyroidism, infertility, recurrent pregnancy loss and kidney failures can be considered.

Diagnostic Methods

Laboratory tests should be made when the clinical evidence indicates WD. As mentioned above, the detection of KFR strengthens the diagnosis. Serum aminotransferase activity is generally elevated except for the really early stages of the disease. However, aminotransferase activity is increased minimally and does not reflect the severity of the liver disease in most patients. In a typical case, serum ceruloplasmin level is low (less than 0.2 g/L, Normal: 0.2-0.5 g/L), serum copper level is high. Serum copper level decreases due to low ceruloplasmin. However, there are WD cases where both of these parameters are within the normal range. Normal ceruloplasmin levels may be seen in 10% of the WD patients (12). Therefore, test results within the normal ranges of these parameters do not rule out WD diagnosis. Low ceruloplasmin levels may also be seen in hypoproteinemia, Menkes disease, chronic liver disease, nephrotic syndrome and aceruloplasminemia (13). In addition, low ceruloplasmin level can be seen in 1% of the healthy population and 10-20% of the heterozygous WD carriers.

In almost all patients, 24-hour urine copper excretion is increased and this serves as a more reliable indicator compared to serum copper and ceruloplasmin levels (14). The concentration of the urine copper is more than 100 µg in 24 hours in WD patients. In healthy individuals, copper excretion normally exceeds 70 µg/24h. The reference amount for the normal value of 24 hour copper excretion can vary between laboratories. In most labs, results greater than 40-50 µg/24^h are considered abnormal. During the collection of samples, disposable polyethylene containers should be preferred. The patient should be on a copper-deficient diet. It could sometimes be difficult to interpret the 24^h copper excretion amount because this value can be increased in other liver diseases, especially in the case of obvious liver damage. Primary biliary cirrhosis, primary sclerosing cholangitis, Alengille syndrome and autoimmune hepatitis are among the chronic liver diseases where high levels of urine copper excretion are observed. People who are heterozygous for WD may have above normal 24-hour urine copper levels. These levels, however, are generally between 50 µg/24^h and 100 µg/24^h. Facilitating urine copper excretion by Penicillamine administration is especially a helpful method in the cases of uncertainty. This method is only standardized in a pediatric population (15). In application, 500 mg Penicillamine is administered first, and then urine samples are collected at 12 hours and 24 hours. If the copper excretion is above 1600 µg/24^h, the patient is determined to have pediatric WD. The predictive value of this test in adult and heterozygous carriers is still unknown.

Among the laboratory test for WD, liver biopsy is the most reliable one. A mild increase in copper content in the dry liver tissue is largely indicative of WD (16). The analysis requires the acquisition of sufficient amount of liver tissue in the biopsy. Normally, the copper content in the dry tissue is less than 55 µg/g. A copper concentration greater than 250 µg/g indicates a possible presence of WD. There are, however, some issues with this test. Readings within those ranges still do not rule out the presence of WD. Liver copper levels may still appear to be normal in cases with liver fibrosis if sufficient amount of tissue was not acquired. In addition, prolonged cholestasis may also yield elevated copper levels in the liver tissue. Therefore the increase in the copper levels should be evaluated together with the histological, clinical and biochemical data.

Neuroimaging may be a valuable diagnostic tool in WD patients. Cranial magnetic resonance imaging (MRI) provides more useful information compared to computerized tomography. Signal intensity changes in putamen, globus pallidus, caudate nucleus, thalamus, mesencephalon, pons and cerebellum and necrosis are the most important signs (Figure 1). Cortical atrophy and white matter changes may also be seen in WD. The signal changes are of hyperintense type in T2-weighted and hypointense type in T1-weighted images (Figure 1). In some WD cases, T2-weighted images may show the characteristic "face of the giant panda" sign in the tegmentum of pons. Cranial MR changes may also be present in patients without any neurological complaints.

Lastly, the detection of ATP7B mutations can be a useful tool for the conclusive diagnosis (7). An exhaustive scan for all possible mutations associated with WD is prohibitively difficult and expensive. Since there is a large number of mutations, ruling out a diagnosis on the basis of only a few mutations may lead to irreversible errors. Molecular analysis should only be used for diagnostically challenging cases or as a research tool.

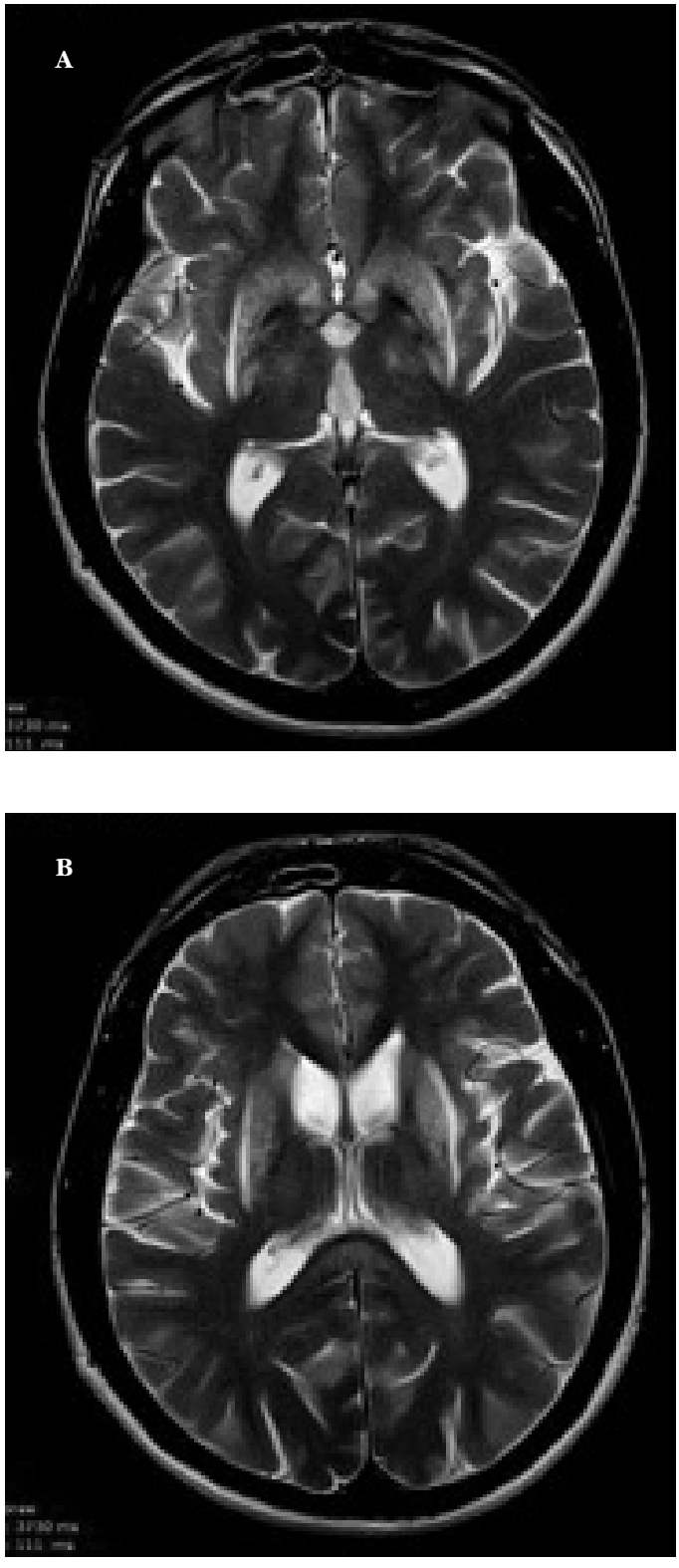

Figure 1 a-b: Signal changes on caudate nucleus and putamen seen in the T2 weighted cranial MRI of a Wilson's disease patient.

Family Screening

Since WD is an autosomal recessive disease, patient's family should also be examined. The probability of a sibling developing WD is 25%. Liver function tests, serum copper level, ceruloplasmin concentration and 24 hour urine copper analyses must be made also on the first-degree relatives. When compared to the general population, the nieces and nephews of the patient (1/600) as well as the cousins (1/800) are under an increased risk for WD. It is beneficial to conduct the serum copper level, ceruloplasmin concentration and 24 hour urine copper analyses on these individuals. The interpretation of serum ceruloplasmin and 24 hour urine copper levels in individuals heterozygous for WD may be difficult. Detection of the asymptomatic family members can allow for more rapid application of the treatment methods.

Etiopathogenesis

Copper is an element of fundamental importance for cellular functions. The daily required amount for copper is 1-2 mg. Presence of free copper inside the cell may lead severe toxicity and irreversible damage. The copper that is absorbed in the intestine is stored in metallothionein in non-toxic form. Nutritional copper is used in numerous enzymatic processes and the excess copper is excreted from the liver through the bilial system. The mechanism for the excretion of excess copper is damaged in WD (18). ATP7B protein and ceruloplasmin is related to copper transportation. In normal conditions, ATP7B protein exists in the trans-Golgi network in hepatocytes and mediates the incorporation of 6 copper molecules inside apoceruloplasmin for the formation of ceruloplasmin. When there is excess copper, ATP7B is redistributed to the cytoplasmic vessicles and removes copper through biliary ways. In individuals with WD, the defective ATP7B protein caused by ATP7B gene mutation cannot perform these tasks. Consequently, the ceruloplasmin amount decreases. Copper progressively accumulates on hepatocytes. When there is a copper overflow from the liver, the urine copper level increases dramatically. After one point, however, the excretion defect cannot be compensated for. The increased level of serum copper settles on tissues and gives rise to the clinical symptoms.

Neuropathology

The most frequently affected brain structures in WD patients are putamen, globus pallidus, caudate nucleus, thalamus, subthalamic nucleus, brainstem and frontal cortex (19). Cortical atrophy is seen in most of the patients and the ventricles enlarge. Macroscopically, putamen and caudate nucleus show changes in color. In the advanced stages, cavitation in putamen and frontal lobes or cysts can be observed. The spongy degeneration in the cerebral cortex and the subcortical white matter is most pronounced in the frontal lobe.

Microscopically, neuron loss, pigment and lipid-containing macrophages and gliosis is seen in the brains of WD patients. Opalski cells are among the differential pathological properties (20). These cells are characterized by large and mildly abnormal nuclei. Opalski cells are thought to be originated from degenerated astrocytes.

Diagnosis

All cases of neurological involvement progressing with movement disorders in the childhood and adolescence should be evaluated for WD. If there are atypical extrapyramidal clinical

symptoms in the older ages, WD should again be included in the differential diagnosis list. The diagnosis is made after an agreement of clinical, neuroradiological and laboratory findings is reached. Early detection of the disease is crucial in preventing morbidity and mortality.

Treatment

The primary goal in the treatment of WD is the removal of excess copper and/or reducing its absorption (21). A copper-deficient dietary approach may prove to be beneficial for WD patients but it should not be considered as being the sole treatment approach. Foods with high copper content, such as chocolate, hazelnuts, walnuts, mushrooms and shellfish should be removed from patient's diet.

Zinc is used to reduce the copper absorption in the intestines. Its effect on copper is mostly indirect. Zinc operates by increasing metallothion synthesis which facilitates copper binding to the intestinal epithelial cells and then excretion with stool. The daily dose for zinc for adults is 150 mg. The most important advantage of the zinc treatment is the lack of known side effects. Ten percent of the patients experience gastric discomfort and nausea. This side effect is alleviated by replacing zinc sulphate with zinc acetate. Gastric symptoms generally subside within days or weeks. Zinc is especially useful for treatment of the asymptomatic or presymptomatic individuals or during maintenance period following the onset of chelators.

Penicillamine and Trientin are the two most commonly used chelating drugs in WD. Penicillamine binds to the copper floating in the serum or settled in the organs, forming the Penicillamine-copper complex which is then excreted with urine. Penicillamine also isolates intracellular free copper. The starting dose is 750-100 mg per day. Since the bioavailability of the drug can be decreased because of certain food items, it is recommended that Penicillamine is taken before meals. A starting from a smaller dose like 250-500 mg at the beginning and slowly building up to a full dose over the next few weeks may decrease side effects. Regular monitoring of blood count and urine protein carries importance in the early prevention of potential side effects. The rate of side effects is 10-20% and the may require the termination of that particular drug treatment. Among the side effects that can be observed in the first week are rashes, lymphadenopathy, neutropenia, thrombocytopenia and proteinuria. Penicillamine use should be stopped if these side effects are seen and alternative methods should be considered. Other potential side effects that may present later are nephrotoxicity (lupus-like syndrome) and bone marrow suppression (thrombocytopenia and aplasia). Skin complications may be seen in extended uses of Penicillamine. These include progeriatric changes (for doses over than 1000 mg per day), elastosis perforans serpiginosa and aphthous stomatitis. Since Penicillamine can also affect pyridoxine metabolism, this vitamin should also be given (50 mg/week) to kids, pregnant woment, or WD patients with malnutirion or other diseases. Depending on the amount of urinary copper excretion, the dose of Penicillamine can be increased to as high as 1-2 gr/day. Neurological problems can be exacerbated in 20-50% of the patients after the start of the treatment. Moreover, these neurological problems may no longer be treatable. The exact reason for this neurological decline is not known but it is hypothesized that the dissolved copper is transported to the central nervous system with blood and re-settle there. For this reason, the patient should be informed about the possibility of this problem and preferrably asked to spend the next few weeks in the hospital.

Trientin has become the primary choice for treatment due to the fewer number of side effects compared to Penicillamine. The starting dose 1200-1800 mg/day is divided into two or three smaller doses. The maintenance dose is 900-1200 mg. Trientin should not be taken with meals. Side effects include pancytopenia, hypersensitivity reaction, sideroblastic anemia and hepatic siderosis. Complete depletion of copper deposits through the use of Penicillamine and Trientin treatment may lead to seizures. The neurological decline after Trientin was reported to be milder than Penicillamine but this possibility should still be taken into consideration. Neurological decline can also be seen in patients who are taking zinc treatment, albeit more rarely.

A relatively novel method of treatment, Ammonium tetrathiomolybdate, competes with the absorbtion of copper and facilitates its excretion. Anemia and leukopenia may be seen as side effects. A double-blind, randomized study comparing Trientin and Ammonium tetrathiomolybdate showed that the latter drug may yield a better outcome for patients with neurological signs (23).

The effects of the chelating treatments start at 6 to 8 weeks and a visible improvement in the neurological symptoms can be observed at 6 to 12 months clinically. After achieving a clinical improvement or stability, the chelator dose is reduced and the zinc treatment is started. The best practices in treatment are still a matter of debate and there is not a universally accepted approach. Vigilant monitoring of the patients and their compatibility with the drug treatment is of detrimental importance. Achieving normal ranges in the laboratory test results under chelator treatment regimes approximately takes 1 year. The goal is to keep the free copper level under 25 mg/day during the protective phase.

If WD has already caused fulminant hepatitis and is unresponsive to medical treatment, liver transplant may be a treatment option (24). However, the patients at the advanced stages of the disease with debilitating neurological findings have still have high mortality rates even after the transplantation. Severe neurological damage cannot be reversed after transplantation.

Most patients need symptomatic treatments for neurological symptoms (e.g. for the treatment of dystonia or parkinsonism symptoms). However, treatments with potential extrapyramidal side effects, such as neuroleptics should absolutely be avoided. These types of drugs may cause irreversible declines in the neurological symptoms.

Prognosis

As long as WD is detected early and the proper treatment procedures are followed, the patients have normal life expectancies. Untreated cases of WD will lead to mortality within 2-5 years after the onset of neurological symptoms.

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