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Wilson's disease - clinical picture, factors influencing disease progression, treatment methods

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Abstract

Wilson's disease, also known as hepatolenticular degeneration, is a rare genetic metabolic disorder that leads to excessive accumulation of copper in the body, particularly in the liver and brain. This results in the gradual damage of these organs and leads to a variety of clinical symptoms. The symptoms of Wilson's disease can be diverse, leading to a broad spectrum of clinical manifestations including fatigue, jaundice, hand tremors, mood disorders, difficulty walking, speech disturbances, as well as neurological and psychiatric issues. The treatment of Wilson's disease typically involves the oral administration of copper-chelating agents, which help the body to eliminate the excess copper. In some cases, symptomatic treatment related to liver or brain damage may also be necessary. The diagnosis of Wilson's disease is based on laboratory tests, imaging studies (such as MRI or CT scans), and the assessment of clinical symptoms. Due to the variety of symptoms, patients are often misdiagnosed, and untreated Wilson's disease inevitably leads to death. Genetic testing can also be useful in confirming the diagnosis. Although Wilson's disease is a chronic condition, with appropriate treatment and monitoring, its symptoms can be effectively managed, and further damage to the liver and brain can be prevented. Regular monitoring of copper levels in the blood, as well as liver and brain function, is crucial for the effective management of Wilson's disease.

Aim of the study

The article discusses the diverse clinical symptoms that can occur in Wilson's disease and outlines the factors influencing the development of the disease, which are available to physicians for diagnosis and appropriate treatment.

Material and methods:

A systematic review of scientific and medical literature was conducted using the PubMed and Google Scholar databases. The review highlights ongoing research and future perspectives in Wilson disease therapy.

Keywords: Wilson's disease, Kayser-Fleischer ring, ceruloplasmin, copper metabolism

Disclosure:

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Introduction

Wilson's disease is a very rare genetic disorder inherited in an autosomal recessive manner. The first cases of this disease were described by Dr. Samuel Alexander Kinnier Wilson in 1912, but the earliest mentions of the disease appeared in the literature at the end of the 19th century, when Westphal described two young patients with a progressive neurological disease different from multiple sclerosis, which he called pseudosclerosis. In his pathological studies, Wilson revealed areas of softening within the basal ganglia of the brain and cirrhosis of the liver. Initially, the disease was called progressive lenticular degeneration.(1,2)

Pathogenesis

The pathogenesis of this disorder involves a mutation in the ATP7B gene. This gene encodes a P-type ATPase responsible for copper transport. As a result of mutations in this gene, there is a restriction in the secretion of copper from liver cells into bile and a reduction in the synthesis of ceruloplasmin. The excess copper is released into the circulation and accumulates in other tissues, particularly in the brain and liver, leading to the impairment of copper incorporation into apoceruloplasmin in hepatocytes and disruption of copper excretion via bile through the intestines. Consequently, this causes copper to accumulate in various organs.(4,5) Accumulation of copper in organs leads to impaired function and the appearance of various symptoms, including liver failure, neurological and psychiatric disorders, and copper accumulation in the cornea (Kayser-Fleischer ring).(1,3) The estimated prevalence of the disease in the population is about 1 in 30,000, although there are populations where an increased frequency of the disease is observed, such as in China and other Asian countries.

There is also a higher incidence of the disease in isolated populations, such as the Canary Islands (1 in 2,600) and Sardinia (1 in 7,000).(5,6,7)

Stages of the disease

It is currently understood that the pathological process leading to the symptoms of Wilson's disease begins with the accumulation of copper in hepatocytes, caused by structural changes in the membrane of the P-type ATPase enzyme. This enzyme is responsible for the active transport of copper and is involved in the processes of incorporating copper into ceruloplasmin and subsequently excreting it into bile (stage I). When the capacity of liver cells to sequester copper is exceeded, there is a massive release of copper ions into the intercellular space, leading to hepatocyte breakdown (stage II). Once the amount of free copper ions in the blood exceeds a critical threshold, they can freely circulate in the bloodstream, often bound to albumins as "free copper," allowing them to cross the blood-brain barrier and access the brain and other organs (stage III). In the initial phase of stage I, the disease may be asymptomatic. The first symptoms often appear in stage II, manifesting as liver failure, acute hemolytic anemia, or blood coagulation disorders. In some cases, stage II can be fatal, but more commonly, spontaneous improvement occurs. In stage III, there may initially be an asymptomatic period, but over time, symptoms related to liver damage, neurological issues, or both may appear. (3,8)

Clinical picture

Symptoms of Wilson's disease can appear at any age, but the disease typically begins between the ages of 5 and 35, with a peak occurrence between the ages of 20 and 30. Only about 3% of patients experience symptoms later in life. The youngest diagnosed patient was 2 years old, while the oldest patients were diagnosed in their eighth decade of life. (9,10,11)

The main symptoms of Wilson's disease are classified into four categories: hepatic, neurological, psychiatric, and ophthalmic. The clinical presentation of hepatic symptoms in patients with Wilson's disease is also highly varied.

A. We identify the following forms of hepatic symptoms:

1. Clinically asymptomatic liver damage with only biochemical abnormalities (changes only in liver enzyme levels).
2. Acute hepatitis (approximately 25% of cases).
3. Fulminant liver failure (6-12% of all such cases are attributed to Wilson's disease).
4. Chronic hepatitis with cirrhosis (compensated or decompensated) - the most common hepatic form of Wilson's disease, occurring in 95% of cases of patients with the neurological form. (12,13)

B. Neurological symptoms - in turn, constitute the initial symptoms in approximately 40-60% of cases, most commonly appearing between the ages of 20 and 30. Among the most frequently occurring neurological symptoms are: speech articulation difficulties (dysarthria). Dystonia of the tongue, throat, and larynx leads to swallowing difficulties and drooling. The late phase of dystonia often leads to contractures.

Also present are symptoms resembling parkinsonism, tremors when maintaining posture, swallowing difficulties (dysphagia), gait disturbances, involuntary movements (such as tics, chorea), symptoms of autonomic nervous system dysfunction (26-30%), headaches, while pyramidal symptoms are very rarely observed. A characteristic facial appearance in individuals affected by Wilson's disease, known as "Wilson's face," is also described, resulting from dystonia of the facial and jaw muscles. Cerebellar symptoms occur in approximately 25% of patients.(12,13,14).

C. Psychiatric symptoms - their frequency varies widely in the literature (from 20-65%). In the case of Wilson's disease, various psychiatric disorders can be observed, including personality disorders, mood disorders, depression, mania, and antisocial behavior. The most serious psychiatric disorders are mood disorders. These disorders can influence risky behaviors and lead the patient to commit suicide. Patients also struggle with memory impairments.(15,16)

D. Ocular symptoms - Kayser-Fleischer ring (K-F ring) is considered pathognomonic for Wilson's disease. These are copper deposits in the Descemet membrane of the cornea, which appear in most patients with the neurological form of the disease and in a significant

proportion of patients with the hepatic form. Diagnosis is made based on examination with a slit lamp. The K-F ring fades during treatment, but its correct recognition is important because a similar symptom may be present in cholestasis; however, proper ophthalmic examination allows for its differentiation. Other ocular changes observed in Wilson's disease include the so-called sunflower cataract, characterized by the deposition of copper in the lens in the form of a central disc with radially extending fibers, which, however, does not interfere with vision.(13,17).

Other symptoms- resulting from copper deposition in tissues and its metabolism can affect many other organs and make the correct diagnosis of the disease difficult. Wilson's disease can affect any organ or system.

Changes in bones and joints may increase the risk of osteoporosis, fractures, or pain with movement. Skin changes, such as hyperpigmentation, discoloration, and rashes, may also occur due to the disease. The kidneys can be affected by the disease, damaging the renal tubules and disrupting the filtration process, leading to the accumulation of excess calcium and phosphorus in the body. Another important organ affected by Wilson's disease is the heart, where rhythm disturbances and acquired heart defects may occur. In women, improperly metabolized copper may cause menstrual irregularities, while in both sexes, it can affect fertility.(18,19,20,21,22)

Factors influencing disease progression include

Genetic Mutations

A mutation in the ATP7B gene, located on chromosome 13 (13q14.3-q21.1) and consisting of 21 exons, is responsible for Wilson's disease (WD). Currently, over 500 mutations in this gene have been identified that can lead to the development of WD. As a result, there are practically no commercial tests available for routine exclusion of all mutations, although whole-gene sequencing is possible. Genetic testing is of paramount importance in preliminary diagnosis, but in the future, enhanced gene therapy may become an alternative treatment method for this disease. (23,24)

2. Gender Influence

The influence of gender on the clinical presentation has been demonstrated in both neurodegenerative diseases (such as Parkinson's disease, Alzheimer's disease, Lewy body dementia) and liver diseases (e.g., fatty liver disease, liver fibrosis due to chronic inflammation). Therefore, in Wilson's disease (WD), which causes damage to both the liver and the brain, such differences should also be observed. Gender differences in the course of WD are primarily attributed to the effects of estrogen and differences in iron metabolism. It has been observed that women are more likely to develop liver-related symptoms of WD, while men tend to exhibit neuropsychiatric symptoms. The impact of gender on the clinical presentation and course of WD. Perhaps in the future, consideration of factors causing these differences (e.g., estrogen) and the use of iron-chelating drugs (such as deferoxamine) will be taken into account in supportive therapy for WD. (25)

3. Inflammatory Factors

In Wilson's disease (WD), the genetic defect causes copper to initially accumulate in the liver, leading to hepatocyte damage and liver inflammation, which can be asymptomatic. This inflammation is often diagnosed as nonspecific, and key diagnostic factors include copper content in liver biopsy, copper metabolism, and genetic testing. As the disease progresses, copper deposits in other organs and tissues, exerting a toxic effect on cells. This leads to cytotoxic edema, gliosis in the brain, and intensified inflammatory state in the liver. The inflammatory process appears to be secondary to copper deposition in tissues but may become a target for future supportive therapies for WD. Currently, there are no studies investigating the impact of anti-inflammatory drugs on WD. (26)

4. Iron Metabolism

The concentration of iron bound to ferritin in the brain naturally increases with age and in the course of neurodegenerative diseases. Gender-related differences have been observed, as iron levels are higher in men, and they are more prone to neurodegenerative diseases. Based on this, the hypothesis has been proposed that iron accumulation in the brain is a risk factor for the development of these diseases, by increasing oxidative stress, free radical production, and interactions with amyloid β and other proteins involved in the pathogenesis of

neurodegenerative diseases. In Wilson's disease (WD), there is theoretical justification for iron metabolism disorders. In patients with WD, the concentration of ceruloplasmin, a copper transport protein, is usually reduced. Ceruloplasmin also participates in iron transport, so its dysfunction should lead to iron metabolism disorders. Demonstrating the role of iron overload in the etiology of WD could have significant therapeutic implications because confirming such disorders could lead to treatment modifications, such as the use of iron chelation therapy (e.g., deferoxamine). (27,28)

5.Oxidative Stress

Considering the toxic effect of copper accumulation in various tissues in the course of Wilson's disease (WD) and analyzing the cellular mechanisms of damage in the etiopathogenesis of WD, a theory proposing the significant role of oxidative stress in the damage to copper-overloaded hepatocyte mitochondria has been suggested. This leads to damage to the respiratory chain, increased production of free radicals (caused by changes in the oxidation state of Cu^{2+}), and enhanced lipid peroxidation of cell membranes. Currently, oxidative stress is considered in the context of iron metabolism disorders, which may also affect the course of WD. Studies show that patients with WD have reduced antioxidant capacities, which are significant for the exacerbation of neurological symptoms, and decreased levels of antioxidants such as vitamin E. These observations may form the basis for new supportive therapies that could utilize antioxidants. (29,30)

Treatment methods

1.Drug treatment

D-Penicillamine

D-Penicillamine is administered in doses of 1.0–1.5 g per day, divided into three doses; the maintenance dose is 1 g per day. It is recommended to take the medication approximately 0.5 hours before or after meals. In Poland, the Cuprenil preparation is used, available in tablets of 250 mg. Pyridoxine supplementation (vitamin B6) is necessary during treatment. The medication is introduced very cautiously, with the dose increased every 3 days by approximately 0.5 tablets (equivalent to 0.25 g), to avoid exacerbating neurological symptoms

associated with rapid release of copper into the blood. However, numerous adverse effects (such as allergies, leukopenia, thrombocytopenia, nausea, vomiting, myasthenic syndrome, kidney damage, etc.) may limit the use of D-penicillamine. It is worth noting that leukopenia and thrombocytopenia are common symptoms of Wilson's disease even before starting therapy. (31)

Zinc Salts

These medications work slower than D-penicillamine. In Poland, the zinc sulfate preparation is available (Zincteral – tablets of 200 mg, containing 126 mg of zinc sulfate). The medication is taken in three divided doses per day according to the following schedule: one tablet in the morning, two tablets at lunchtime, and one tablet in the evening, always approximately 0.5 hours before eating. It is important not to take it with milk. Treatment can start with the full dose, but the reduction in copper absorption from the gastrointestinal tract becomes apparent only after two weeks. Zinc salts are considered to cause fewer side effects (mainly nausea, vomiting, and gastric mucosal inflammation), so they are recommended for patients with the preclinical form of the disease, as well as for children, women of childbearing age, and pregnant women. (31)

Trientine (TN, Trientine Dihydrochloride)

In cases of intolerance to the aforementioned medications, patients can be given trientine dihydrochloride (trientine—Syprine). One of the main challenges in the pharmacotherapy of Wilson's disease (WD) is ensuring proper medication adherence by patients. Traditional medications used in WD therapy must be taken three times a day, between meals, which affects adherence to recommendations. To improve patient convenience, the use of a chelating agent—trientine (TN)—once daily has been proposed. The TN form as dichloride hydrochloride, used since the 1970s, is unstable at room temperature and requires refrigeration storage (2-8 degrees Celsius). This makes it difficult to take the medication correctly, especially in relation to work or travel, and requires taking it 3-4 times a day. The modified form of the drug—trientine tetrahydrochloride—is thermally stable and can be taken less frequently.

Trientine is routinely used in the treatment of WD as an oral copper-chelating agent, but like other drugs used in WD therapy, it does not penetrate the blood-brain barrier (BBB). Theoretically, drugs that can penetrate the BBB should more effectively remove excess copper from the central nervous system (CNS), which could lead to more effective treatment of neurological symptoms of WD. Research on such drugs is in the early stages, and experimental studies on WD models have not yet been conducted to assess copper removal from the CNS. The concept of a BBB-penetrating drug is very promising but requires further research to confirm the effectiveness and safety of such a preparation, currently in animal models. Unfortunately, this drug is not registered in Poland, and therapy with it is very expensive. (32, 33)

2. Gene Therapy

Gene therapy, which may lead to the correction of copper metabolism in the body through the transfer of the correct ATP7B gene, represents a promising therapeutic strategy for Wilson's disease (WD). In asymptomatic patients, gene therapy may prevent the onset of disease symptoms. Meanwhile, in patients with WD symptoms, it may lead to the restoration of normal copper metabolism in the body, elimination of copper deposits in tissues, and consequently, the resolution of disease symptoms. Currently, gene therapies for WD are at the stage of animal studies.(34,35)

3. Cell Therapies

An innovative method of treating Wilson's disease (WD), investigated in animal models, is the transplantation of healthy hepatocytes. Whole liver transplantation results in complete normalization of copper metabolism, but studies so far have shown that it is not necessary to transplant the entire organ to restore normal copper metabolism. Even the presence of only 40% healthy liver cells is sufficient to achieve proper copper metabolism parameters in the body. However, further research and observations are necessary. Currently, there are no studies underway on hepatocyte transplantation in patients with WD. (34,35,36)

Prevention

Due to the hereditary nature of Wilson's disease, it is essential to conduct comprehensive diagnostics in the siblings of patients. It is also recommended to screen the children of patients, although the risk of developing the disease in them is significantly lower than in

siblings. Early detection of Wilson's disease at the preclinical stage and initiation of appropriate treatment practically eliminates the risk of developing clinical symptoms of the disease.

Summary

Wilson's disease poses unique diagnostic and therapeutic challenges due to its diverse clinical presentation and the factors influencing it. Symptoms of the disease can affect various organs such as the liver, brain, eyes, heart, and joints, making diagnosis based on a comprehensive analysis of symptoms, laboratory, and imaging findings. Genetic factors play a crucial role in the pathogenesis of the disease, with mutations in the ATP7B gene being the primary risk factor. Additionally, gender influence and changes in copper and iron metabolism have a significant impact on the course of the disease and its symptoms. Various methods are used in the treatment of Wilson's disease, including pharmacotherapy, chelation therapy, as well as gene and cell therapy. D-penicillamine, zinc salts, and trientine are the most commonly used drugs, each with its advantages and limitations. Gene and cell therapy represent promising directions in therapy development, although they are currently in the experimental research phase. Given the hereditary nature of Wilson's disease, prevention plays a significant role, including the diagnosis of patients' siblings and monitoring potential carriers of genetic mutations. Early diagnosis and effective treatment help reduce the risk of complications and improve the quality of life for patients affected by this rare metabolic disorder.

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As a review paper, our work does not present new data or analyses. Therefore, there are no specific datasets or data availability to report. The information and findings presented in this review are based on previously published studies, which can be accessed through their respective sources as cited in the reference section.

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Conflict of Interest Statement

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