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Wilson's disease: A Comprehensive Review of Genetics, Pathophysiology, Clinical Symptoms, Diagnostic Techniques and Current Treatment

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Abstract

Introduction: Wilson's disease (WD) is a genetic disease, inherited in an autosomal recessive manner, caused by a mutation in the ATP7B gene, which results in impaired excretion of copper in the bile. This causes the accumulation of copper in various tissues and organs, leading to their damage. The range and severity of symptoms are wide, so diagnosis is difficult and requires a high index of suspicion. The most common clinical symptoms are hepatic and neuropsychiatric symptoms. Diagnosis is based primarily on clinical suspicion, typical symptoms and reduced serum ceruloplasmin concentration. Treatment includes pharmacological therapies, and in some cases liver transplantation is necessary. Wilson's disease, if left untreated, inevitably leads to serious disability and death.

Purpose of the work: This study aims to review and characterize the clinical and pathophysiological aspects of Wilson's disease.

Materials and methods: A comprehensive analysis of research papers available on PubMed, Google Scholar, Web of Science, Embase and Scopus was undertaken using the searchterms encompassing the following keywords: Wilson's disease, Copper metabolism, Copper toxicity, ATP7B, Ceruloplasmin, Gene Mutation

Results: Wilson's disease is a rare genetic disorder that can lead to severe disability and even death. For this reason, rapid diagnosis and appropriately selected and individualized treatment play a key role. Wilson's disease remains a major diagnostic challenge, but new techniques for its diagnosis, such as genotype analysis, mainly through sequencing, as well as newborn screening, may significantly improve patient prognosis in the future.

Keywords: Wilson's disease, Copper metabolism, Copper toxicity, ATP7B, Ceruloplasmin, Gene Mutation

Introduction

Wilson's disease, also known as hepatolenticular degeneration, is a rare, autosomal recessive disorder characterized by a disorder of copper metabolism. It is caused by multiple mutations in the ATP7B gene, located on chromosome 13. As a result of the mutation, there is a lack or reduced function of the ATP7B transporter important for the excretion of copper in the bile and incorporation of copper into ceruloplasmin. Affected patients accumulate excessive amounts of copper in tissues and organs, mainly the liver and brain, leading to their damage. The disease affects from one in 30,000 to one in 100,000 people and was first described as a syndrome by Kinnier Wilson in 1912. It mainly affects children, adolescents and young adults. The youngest patient reported to have liver cirrhosis due to Wilson's disease was 3 years old, while the oldest group of patients were diagnosed in their eighth decade of life. Clinical manifestations are variable - from asymptomatic to severe neuropsychiatric and hepatic disorders, which can lead to chronic liver disease and even liver failure. Due to the multitude of identified mutations, genetic testing is of little practical use, and diagnosis relies primarily on clinical findings and judicious use of a battery of laboratory and other diagnostic tests. Lifelong drug therapy with chelating agents and zinc salts and liver transplantation can prevent the organ damage and eventual death that are inevitable if left untreated [1,2,3,4,5].

Epidemiology

According to the definition proposed by the European Commission on Public Health, Wilson's disease is defined as a rare disease. The WHO estimates the global incidence of Wilson's disease to be 1/10,000 to 1/30,000. Currently, most sources describe the worldwide incidence of Wilson's disease as 1 in 30,000, although this has changed over the years. In Western countries, Sternlieb and Scheinberg were the first to estimate the incidence of the disease at 5/1,000,000 in 1968. Between 1949 and 1977, Bachman et al. studied WD in Leipzig, Germany, and calculated the incidence of WD to be 29/1,000,000 births. In 1981, Saito reported the incidence of WD to be 33/1,000,000 births. Such estimates are highly dependent on correct diagnosis, and WD may not always have been correctly identified, so the incidence is likely to have been underestimated. With the advent of more accurate diagnostic techniques, more recent studies have shown a higher incidence. The highest reported incidence is six in 90 births on the island of Crete in Greece, where the founder effect was significant. While the most common mutation in Europe and North America is p.H1069Q, the most common mutation in Asia is p.R778L. The incidence is higher in China than in the West. Wilson's disease is one of the most common inherited liver disorders in East Asian populations. Because Kayser-Fleischer rings may be absent, patients may be asymptomatic but have other typical biochemical abnormalities, together with the limitations of diagnostic tests and varying clinical experience of physicians, the true incidence of Wilson's disease may be underestimated [6,7].

Genetics

Wilson's disease is caused by a mutation in the ATP7B gene located on the short arm of chromosome 13, consisting of 20 introns and 21 exons. More than 500 mutations of this causative gene have been identified to date, although different sources report the number of mutations, ranging from 300 to 700. Most of them are missense mutations, but there are also small deletions or insertions, nonsense mutations, and splice junction mutations. Although WD is an autosomal recessive disease, a significant proportion of affected individuals are actually compound heterozygotes, having inherited different mutations from each parent. The most common mutation in the USA and northern Europe, H1069Q, is associated in most cases with a later onset of symptoms and a less severe disorder of copper metabolism. It is a point mutation in exon 14, causing a histidine to glutamic acid substitution in the N domain of ATP7B. In turn, nonsense and frameshift mutations may correlate with earlier onset of symptoms and more severe copper metabolism disorders. Other common mutations are shown in Fig.1. The multitude of mutations contributes to a wide variability in clinical manifestations and age of onset, even among homozygous twins with the same genetic mutation, suggesting that additional factors are also at play [3,4]. The hotspot mutations of the ATP7B gene in the European population are located in exons 8–18, whereas mutations in exons 2–5, which are associated with some severe phenotypes, occur in the Indian population [8].

	Exon	Variants	Protein Amino Acid Change	Allele Frequency
Europe	14	H1069Q	His1069Gln	17–78%
	8	2299insC	Pro767Pro-fs	3–11%
	8	M769V	Met769Val	6–8%
	15	3400delC	Frameshift	3–7%
Asia	8	R778L	Arg778Leu	13–49%
	13	P992L	Pro992Leu	6–16%
	13	2871delC	Frameshift	16–20%
	2	C271X	Cys271Stop	19–24%

Fig. 1. The most common ATP7B gene mutations among Europeans and Asians

Pathophysiology

Copper is one of the essential elements for cell function, but its free form is extremely toxic and can cause permanent damage. To prevent this, the human body has developed special systems that bind the copper molecule and transport it to its destination and eliminate its excess in the bile. Copper homeostasis in the liver is maintained by a network of proteins, which include transmembrane copper transporters (CTR1 and ATP7B), cytosolic copper carriers (chaperones), copper storage proteins (metallothioneins) and copper-requiring enzymes. Some liver enzymes use copper for their activity: ceruloplasmin (CP) ferroxidase, an abundant copper-binding protein secreted by hepatocytes into the blood, cytochrome c oxidase, superoxide dismutase 1, factor VIII and other less abundant proteins. ATP7B and

ceruloplasmin are involved in the copper transport process. The ATP7B protein is normally located in the trans-Golgi network in hepatocytes, where it mediates the incorporation of 6 copper molecules into apoceruloplasmin, creating ceruloplasmin. When there is excess copper in the body, this protein is redistributed to cytoplasmic vesicles, where it participates in the transport of excess copper to the bile canaliculus for subsequent excretion in bile. In Wilson's disease, the ATP7B protein is abnormal, which is why the concentration of ceruloplasmin is reduced and copper gradually accumulates in hepatocytes. At some point, the storage capacity of the liver is exceeded, and free copper leaks out of the liver. There is increased excretion of copper in the urine, but this process is unable to compensate for the defect in biliary excretion, hence the excess copper is deposited in tissues and organs, damaging them. Unbound cytoplasmic copper accumulates and binds to metallothionein, the synthesis of which is induced by copper. When metallothionein is no longer able to bind more copper, its excess is also deposited in lysosomes, where amorphous copper complexes accumulate, inducing cell damage by free radicals. Toxic Cu1+ damages the lysosomal membrane, cell damage occurs and Cu1+ is released into the bloodstream, causing blood hemolysis. Reduced ceruloplasmin concentration is also characteristic of Wilson's disease, but it is not common and is not diagnostic for this disease [2,3,9,10].

Clinical manifestations of Wilson’s disease

Hepatic manifestations:

Liver disease is often the first clinical sign of Wilson’s Disease (WD), appearing in 40–60% of cases, though symptoms and severity can vary widely. Liver involvement in WD ranges from subtle, asymptomatic changes to acute hepatitis-like illness, autoimmune-like hepatitis, cirrhosis, and acute liver failure. Factors like age and gender influence these manifestations, with females more prone to acute liver failure and adults more likely to develop cirrhosis [11]. In children and young adults, WD often first presents as mild-to-moderate fatty liver, detected via imaging or biopsy, with abnormal liver function. Untreated, WD can progress to chronic liver disease, portal hypertension, and coagulopathy. Acute liver failure, the most severe form, is more common in young females and may include Coombs-negative hemolytic anemia, severe coagulopathy, and renal failure and significantly increased serum and urinary copper levels are common in about 5% of Wilson's Disease (WD) patients, most of whom are in their second decade of life. Depressed serum alkaline phosphatase levels are common, and a ratio of alkaline phosphatase (IU/L) to bilirubin (mg/dL) of less than two may help diagnose Wilsonian fulminant hepatitis [2]. Routine assessments, including ultrasound, CT, and MRI, help monitor liver condition, while MELD and Child-Pugh scores assess disease severity. Screening for portal hypertension and hepatobiliary malignancies is essential in cirrhotic patients. Non-adherence to lifelong therapy can lead to rapid disease progression and liver failure, highlighting the importance of ongoing compliance monitoring [12].

Neurological manifestations:

The initial neurological symptoms of Wilson’s Disease (WD) can be subtle, including mild tremors, speech, and writing difficulties. These typically emerge in the mid-teens or twenties, often mistaken for behavioral issues linked to puberty, though later onset (between 45 and 70 years) is also possible. The hallmark of neurological WD is a progressive extrapyramidal disorder, with common symptoms such as dysarthria, dysphagia, apraxia, and tremor-rigidity syndrome. Early motor impairment is often evident in handwriting difficulties. There's a significant link between putaminal dopaminergic innervation and fine motor skills, and analyzing automated handwriting movements could be valuable for monitoring therapy and

assessing striatal dopaminergic innervation [13]. WD patients often experience a high incidence of cognitive impairment and gait disorders. The speed and size of their steps can serve as indicators of cognitive decline. Cognitive impairment plays a significant role in contributing to gait disorders in these patients, and different cognitive and motor dual-tasks can influence gait parameters. The combined effect of cognitive impairment and brain lesions is likely the primary neural mechanism behind gait abnormalities in WD patients [14]. Neurological symptoms of Wilson's Disease can also include choreiform movements, partial parkinsonism or akinetic rigid syndrome, gait disturbances, dysarthria, pseudobulbar palsy, rigid dystonia, seizures, migraine headaches, and insomnia [2].

Ophthalmic symptoms:

Kayser-Fleischer (KF) rings are a key indicator of Wilson's Disease (WD), caused by copper deposition in the cornea. KF rings are present in about 85%–100% of patients with neurological or psychiatric symptoms, 33%–86% of those with hepatic symptoms, and 0%–59% of asymptomatic individuals, according to various studies. Although KF rings are not exclusive to WD and can appear in other liver diseases like primary biliary cirrhosis, cryptogenic cirrhosis, chronic hepatitis, and neonatal hepatitis, their presence in these conditions is rare and usually indicates secondary copper accumulation. These corneal pigmentation rings are indistinguishable from KF rings during a slit-lamp examination, and it's possible that some cases of WD were missed in the past where genetic testing was not performed [6]. Sunflower cataracts, which are brilliantly multicolored, are visible only through slit-lamp examination and do not affect vision. Other less common ocular findings in Wilson's Disease include night blindness, exotropic strabismus, optic neuritis, and optic disc pallor [2].

Psychiatric manifestations:

Epidemiological studies suggest that up to 30% of WD patients initially present with psychiatric symptoms. The first signs may appear in childhood, often manifesting as a decline in academic performance, inappropriate behavior, or impulsiveness. These symptoms are frequently nonspecific, making diagnosis challenging and leading to potential misdiagnoses, such as isolated obsessive-compulsive disorder or anorexia nervosa. As the disease progresses, more typical psychiatric conditions, including behavioral and personality changes, anxiety, depression, manic and hypomanic syndromes, cognitive impairments, sleep disturbances, and sexual dysfunctions, often emerge. Additionally, some patients develop substance abuse issues, which can further complicate their clinical presentation and delay WD diagnosis. Treating psychiatric disturbances associated with WD, whether secondary to the disease or comorbid, generally involves standard WD management along with addressing psychiatric symptoms. Treatment plans must consider the challenges posed by liver impairment due to WD, particularly regarding pharmacotherapy [15].

Other symptoms:

Pathological changes in bone and periarticular structures in WD patients have been linked to various conditions, including osteomalacia, osteoporosis, spontaneous fractures, adult rickets, osteoarthritis, osteochondritis dissecans, chondrocalcinosis, subchondral cyst formation, and azure lunulae (bluish discoloration) of the fingernails. The most commonly affected areas are the knee joints and spine. Myocardial copper accumulation can lead to cardiomyopathy and arrhythmias, though these are clinically rare. Other uncommon extrahepatic manifestations

include hypoparathyroidism, infertility, recurrent miscarriages, and renal abnormalities such as aminoaciduria and nephrocalcinosis [2].

Diagnostics

Since Wilson's initial description of the disease, advancements in diagnostic methods have made it possible to diagnose Wilson's Disease (WD) before neurological symptoms appear. Key diagnostic tools include recognizing Kayser-Fleischer (KF) rings, identifying low serum ceruloplasmin levels, detecting liver disease through biochemical tests, imaging, and liver biopsy to measure copper levels. A recent advancement is the use of genotype analysis, particularly by identifying ATP7B mutations through whole-exome/genome sequencing. The diagnostic approach starts with investigating family history, conducting physical exams for liver or neurological symptoms, and performing biochemical tests for liver disease. Specific copper metabolism tests follow, including serum ceruloplasmin, serum copper, 24-hour urinary copper excretion, and liver biopsy. Ophthalmologic exams to detect KF rings using slit lamp or advanced corneal imaging are also important. Genetic testing for ATP7B mutations may be utilized when there is a high suspicion of WD or for family screening [16].

Serum ceruloplasmin

Ceruloplasmin is a 132-kDa protein primarily produced in the liver and functions as an acute phase reactant. It is the main copper-carrying protein in the blood, with most of it being secreted as holoceruloplasmin (containing six copper atoms per molecule) and a smaller portion as apoceruloplasmin (lacking copper). Serum ceruloplasmin levels are often measured to investigate unexplained liver disease. Normal levels vary with age, being very low in early infancy, peaking in early childhood (300-500 mg/L), and then decreasing to adult levels. A serum ceruloplasmin level below 200 mg/L (<20 mg/dL) is indicative of WD, especially when accompanied by Kayser-Fleischer (KF) rings. However, ceruloplasmin levels can vary, and some patients with low levels may not have WD. Levels below normal can also occur in WD carriers. Low ceruloplasmin levels can also be seen in conditions with significant protein loss (e.g., renal or enteric issues), severe end-stage liver disease, neurological disorders, copper deficiency, and Menkes disease [17].

Serum copper

Copper is a trace element essential for enzyme function, and serum is the preferred sample for assessing copper status. Plasma is less accurate due to lower copper concentrations. Copper levels are measured using inductively-coupled plasma mass spectrometry (ICP-MS) or atomic absorption spectrometry, with ICP-MS being more common. In normal conditions, serum copper levels correspond with ceruloplasmin levels, but in Wilson's Disease (WD), copper can be low or normal despite the presence of excess free copper. Elevated copper can occur due to conditions like acute liver failure or pregnancy, while low levels might indicate WD, Menkes disease, or copper deficiency. Total serum copper is not recommended for diagnosing WD due to its low negative predictive value; normal levels do not rule out WD, but very low levels are indicative of it. For confirmation, measuring serum ceruloplasmin is advised. The normal range for serum copper is 1.1–2.5 μmol/dL, with levels below 0.8 μmol/dL suggesting severe deficiency or WD. High levels may indicate acute liver failure or contamination [18].

Urinary copper

Wilson's Disease (WD) patients almost always have elevated 24-hour urinary copper excretion (>100 µg/day or >1.0 µmol/day). However, the reliability of this test is limited due to various factors. Accurate 24-hour urine collection is challenging, especially in young patients. Issues like incomplete or excessive collection can skew results. Additionally, the intra-individual variation of daily urinary creatinine is around 11%, complicating the assessment. Measuring urinary creatinine alongside copper can help gauge the completeness of urine collection. Martins da Costa et al. found that a 24-hour urinary copper excretion of more than 25 µmol/day after a penicillamine challenge was highly effective for diagnosing WD in children with liver disease. This method had a sensitivity of 88.2% and a specificity of 98.2%. The protocol involved baseline and post-penicillamine collections in copper-free bottles [6].

Liver diagnosis

The imaging techniques are frequently used in WD patients to assess liver involvement. Common findings include fatty infiltration, contour irregularities, and atrophy of the right lobe, which are indicative of non-specific hepatic injury. Specific imaging signs can be observed: peri-hepatic fat layer in Ultrasound (US), hyperdense nodules and a honeycomb appearance, observed in 92% and 58% of WD patients, respectively in Computed tomography (CT) and hypointense nodules on T2-weighted images, surface nodularity of the liver, and widening of the gallbladder fossa in Magnetic resonance imaging (MRI). Recent MRI sequences can estimate liver fat content and detect early WD, especially when histology shows significant hepatic steatosis in MRI. FibroScan® is increasingly used to measure liver stiffness, which helps in assessing fibrosis. A threshold value of 6.6 kPa differentiates between mild and moderate fibrosis, while values over 8.4 kPa indicate severe fibrosis., but further research is needed to validate these findings and assess the role of FibroScan® in managing WD. US remains the primary non-invasive method for annual monitoring of WD patients. For those with detected cirrhosis, biannual US checks are recommended to screen for hepatocellular carcinoma [19]. A liver biopsy to measure hepatic copper concentration is essential when clinical signs and noninvasive tests are inconclusive or when there is suspicion of additional liver conditions. A hepatic copper content greater than 250 µg (4 µmol)/g dry weight is considered strong evidence for Wilson's Disease (WD). A large study found that a concentration of 209 µg (3.3 µmol)/g dry weight had the highest diagnostic accuracy for WD, with a sensitivity of 99.4% and specificity of 96.1%. However, results can be affected by sampling errors, and elevated copper levels may also occur in cholestatic liver disorders [15].

Neurological imaging

To identify neurological abnormalities in Wilson's Disease (WD), a thorough clinical evaluation by a skilled neurologist is crucial. Brain MRI is an effective tool for assessing central nervous system changes. Research shows that cerebral lesions are present in 60% of patients with neurological symptoms and 19% of asymptomatic patients with WD. MRI typically reveals focal lesions as hypointense spots, commonly located in the lenticular nuclei, ventral or lateral thalamic nuclei, subcortical white matter, lamina tecti, and caudate nuclei. Hemisphere or brainstem atrophy is found in 68% of symptomatic patients but only 6% of asymptomatic ones. A distinctive but rare MRI finding is the "giant panda face" sign [13].

Genetic analysis

Mutational analysis is a crucial diagnostic tool for identifying Wilson's Disease (WD). Despite its importance, direct molecular-genetic diagnosis can be time-consuming due to the presence of over 700 potential mutations and the complexity of compound heterozygosity in many patients. Nevertheless, advancements in sequencing technology are making the process faster and more affordable, and it is expected to become a routine diagnostic test in the future [15].

Screening

First-degree relatives of newly diagnosed Wilson's Disease (WD) patients should undergo screening for the disease. If the specific ATP7B mutations are identified in the affected individual, genetic testing can be used as the primary screening method for relatives. If genetic testing is not available, clinical and biochemical assessments should be conducted. These assessments include a brief history focusing on jaundice, liver disease, and neurological or psychiatric symptoms, as well as physical examinations. Laboratory tests should measure serum copper, ceruloplasmin, liver function (including aminotransferases, albumin, and both conjugated and unconjugated bilirubin), and basal 24-hour urinary copper excretion. A slit lamp examination should be performed to check for Kayser-Fleischer (KF) rings. If a relative is found to have an ATP7B genotype indicative of WD, further clinical evaluation is necessary to assess organ damage and other clinical features [16].

Treatment

Pharmacological Therapy for Wilson Disease

For the first fifty years after the discovery of Wilson's disease, there was no effective treatment for this progressive and fatal condition. The aim of pharmacotherapy in Wilson's disease is to prevent excessive copper accumulation in the body or to reverse its toxic effects. This is achieved by reducing copper absorption, stimulating the synthesis of endogenous cellular proteins such as metallothionein (which binds copper in a non-toxic form within cells), promoting copper excretion through urine or bile, or by combining these methods [5]. The approach to treatment depends on whether the patient has visible clinical symptoms, laboratory or histological signs of aggressive liver or nervous system damage, or whether the disease has been detected before symptom onset. This distinction helps in selecting the appropriate therapy and drug dosages, though no studies have systematically explored this approach. Pharmacological agents that remove copper (chelators) include D-penicillamine, trientine, BAL, and tetrathiomolybdate. For patients with symptoms or active disease, chelators are recommended, although some reports suggest that zinc therapy alone may be sufficient. Worldwide, the greatest clinical experience in treating this disease is still with D-penicillamine, though trientine is increasingly considered a first-line option. Combination therapy, in which zinc is administered alongside a chelator (but at different times), has a theoretical basis in both blocking copper absorption and promoting its removal from the body. There are also reports of the effectiveness of using chelators and zinc simultaneously as initial therapy, but further studies are needed to determine whether this approach is more effective than chelator therapy alone [20,21].

After stabilizing disease symptoms or biochemical abnormalities, typically within 2-6 months of starting treatment, maintenance doses of chelators or zinc can be administered. Asymptomatic patients may receive maintenance doses from the outset. Noncompliance with lifelong therapy can result in symptom relapse and liver failure, which, in severe cases, may necessitate a liver transplant to save the patient's life. Treatment monitoring involves both ensuring adherence to therapeutic recommendations and assessing potential side effects [5,21].

D-penicillamine: D-penicillamine treats Wilson's disease primarily by promoting urinary copper excretion and may also induce metallothionein. The usual maintenance dose is 750–1500 mg/day in divided doses, while children receive 20 mg/kg/day. It should be taken 1 hour before meals to improve absorption, and pyridoxine supplementation is needed due to potential interference with its action. Treatment effectiveness is monitored by measuring urinary copper excretion, with a decrease to ≤1.6 μmol/24 h after discontinuation indicating effective treatment. D-penicillamine is rapidly absorbed, but food reduces its absorption by about 50%. It is mainly excreted through the kidneys, with a variable half-life. Improvement in liver function is usually observed within the first 2–6 months, but neurological symptoms may worsen initially in some patients. Side effects are common, with severe reactions occurring in about 30% of patients, including bone marrow toxicity, nephrotoxicity, and dermatological issues [5].

Trientine: Trientine (triethylene tetramine dihydrochloride) is an alternative chelator to penicillamine for treating Wilson's disease. It lacks sulfhydryl groups and forms a stable complex with copper through its four nitrogen atoms. Trientine is poorly absorbed and metabolized in the gastrointestinal tract, with only 1% of the administered dose appearing in the urine. It promotes copper excretion via the kidneys but may be a weaker chelator compared to penicillamine. Trientine is effective for patients intolerant to penicillamine and has fewer side effects, including no reported hypersensitivity reactions. Typical dosages are 750-1500 mg/day, and it should be taken 1 hour before or 2 hours after meals. Monitoring treatment involves measuring 24-hour urinary copper excretion, with values of 200-500 μg/day indicating adequate therapy. Low or high urinary copper levels can signal nonadherence or overtreatment, respectively [5].

Ammonium tetrathiomolybdate: Ammonium tetrathiomolybdate (TM) is a potent decoppering agent that prevents copper absorption in the intestine and reduces copper availability in the circulation. At low doses, TM removes copper from metallothionein, while at higher doses, it forms an insoluble copper complex that deposits in the liver. Although TM is not commercially available and has limited clinical experience, it has shown strong control of free copper levels in clinical trials. TM controlled free copper better than trientine in one study, with fewer neurological worsening cases. Potential adverse effects of TM include bone marrow depression, hepatotoxicity, and neurological dysfunction due to excessive copper removal [5,20].

Zinc: Zinc preparations, such as zinc gluconate, zinc sulfate, and zinc acetate, help treat Wilson's disease by interfering with gastrointestinal copper absorption, though their effects are relatively slow. Research shows that zinc sulfate or zinc gluconate significantly increases urinary copper excretion in Wilson's disease patients. Zinc has proven effective, especially in early or maintenance stages, with fewer side effects compared to penicillamine. It is recommended for early symptoms, pregnant patients, and maintenance therapy. Zinc acetate and zinc gluconate are preferred over zinc sulfate due to less gastrointestinal irritation. Dosage varies: adults take 150 mg/day in 3 doses, children under 50 kg take 75 mg/day in 3 doses, and exact dosing for children under 5 is unclear. Zinc should be taken 2 hours before

meals to optimize absorption and should be spaced from penicillamine by more than 2 hours [22].

Liver Transplantation

Liver transplantation is an effective treatment for individuals with liver diseases. Transplanting a healthy liver into a patient with Wilson's disease essentially restores normal copper excretion and liver function. However, liver transplantation is a complex procedure that requires lifelong immunosuppressive therapy and is typically reserved for patients with acute liver failure or advanced cirrhosis [23].

Other Treatments

Adhering to a low-copper diet is a sensible lifestyle change to help reduce the overall copper load on the body. Patients should aim to limit copper intake to less than 1 mg per day by avoiding high-copper foods (such as shellfish and liver) and consuming other copper-rich foods (such as chocolate, nuts, dried fruits, beans, and mushrooms) in moderation. Water may contain high levels of copper if it comes from copper pipes; most water filters do not remove copper, but running water through the faucet to flush the pipes significantly reduces its level. Purified or distilled water contains almost no copper. Cooking with copper pots should also be avoided. Although there is limited direct evidence on the effectiveness of a low-copper diet in treating Wilson's disease, reducing copper intake within reasonable limits is justified [23,24,25].

Conclusions

In the more than 100 years since Wilson's disease was first described, our knowledge of its genetics and pathophysiology has expanded considerably. According to recent studies, the incidence of WD is higher than previously estimated. The diagnosis can be made based on typical hepatic and neurological symptoms, decreased serum ceruloplasmin levels, the presence of Kayser-Fleischer rings, and abnormal laboratory tests. Many patients suffer from liver failure, are disabled, and even die because of the lack of appropriate diagnosis and treatment specific to the disease. Patients should be given an individual treatment plan, and gene therapy and cell therapy are new treatment avenues that could be used in the future. In summary, early diagnosis of Wilson's disease is key to improving the prognosis, and newborn screening can help in this regard.

Disclosure:
Authors' contribution:
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