Review

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Epidemiology, diagnosis, and treatment of Wilson's disease

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Summary **Wilson's disease (WD) is an autosomal recessive disease caused by a mutation of the *ATP7B* gene, resulting in abnormal copper metabolism. The major clinical features of WD include liver disease, neurological disorders, K-F rings, and osteoporosis. The prevalence of WD in China is higher than that in Western countries. Early diagnosis and lifelong treatment will lead to better outcomes. Drugs such as sodium dimercaptosuccinate (Na-DMPS), Zn, and Gandou Decoction can be used to treat WD. Some studies have shown that the combination of traditional Chinese medicine and Western medicine is the best approach to treating WD. In order to identify better treatments, this article describes the specific clinical symptoms of Wilson's disease, its diagnosis, and treatment options.**

Keywords: Wilson's disease, Kayser-Fleischer rings, D-PCA

1. Introduction

Wilson's disease (WD), also named hepatolenticular degeneration, is an autosomal recessive disorder of copper (Cu) metabolism caused by an *ATP7B* gene mutation (*1*). WD was first identified by Wilson in 1912 (*2*). Cheng reported the first two cases of WD in China (*3*). Research on WD began to surge after the 1950s, and the number of reported cases had gradually caught up to that in Western countries.

The gene that causes WD is located on chromosome 13q14-21 (*4*). This gene, *ATP7B*, encodes a P-type ATPase that participates in ceruloplasmin synthesis and excretion of copper. Pathogenic mutations in *ATP7B* disrupt the normal structure or function of enzymes and lead to copper deposition in multiple organs, leading to different clinical manifestations. In the light of its various manifestations, misdiagnosis is not uncommon (*5*). Many researchers have focused on determining the relationship between the genotype and phenotype of WD (*6*). From 2004 to 2015, Dong *et al*. identified 58 new mutations and determined the first Chinese *ATP7B* pathogenic mutation spectrum (*7*). D-penicillamine (D-PCA) is recommended for most patients with WD (*8*). However, D-PCA is not suitable for patients with severe spasms, deformities, or dysphonia and patients who are allergic to D-PCA. Dimercaptosuccinic acid (DMSA) is first drug used to treat WD in China (*9*). DMSA is recommended as an alternative for patients with severe neurological symptoms. In addition, monozygous therapy is suitable for asymptomatic WD, as well as maintenance therapy after the use of copper chelating agents (*10*). WD is a genetic disorder that can be alleviated, so most patients have a favorable prognosis. The prevalence of WD in China is higher than that in Western countries, but there are few clinical trials in China and treatment is often based on the experience of experts and evidence from other countries. Therefore, appropriate treatments need to be studied and developed specifically for Chinese patients with WD (*5*). This article describes the clinical features of WD and treatment options.

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2. Epidemiology

2.1. *WD in Western countries*

Sternlieb and Scheinberg first estimated the incidence of WD to be 5/1,000,000 in 1968 (*11*). From 1949-1977, Bachman *et al*. studied WD in Leipzig, Germany and calculated that the prevalence of WD to be 29/1,000,000

births (*12*). In 1981, Saito reported that the prevalence of WD was 33/1,000,000 births (*13*). In 1991, Park *et al*. attempted to determine the prevalence of WD in Scotland by examining computerized hospital records, survey results, and death certificates (*14*). They identified 21 patients with WD in a population 5,090,700, for a prevalence of 4/1,000,000. In 1993, Reilly *et al*. used a similar methodological approach to determine the prevalence of WD in the Republic of Ireland, and they identified 26 cases over a 19-year period (*15*). Patients in 5 of those cases died before being formally diagnosed. Between 1950 and 1969, the adjusted birth rate of individuals with WD was 17/1,000,000, which was equivalent to a gene frequency of 0.41% and the incidence of heterozygotes was 0.82% (*16*). In order to account for the highest level of kinship, the gene frequency was modified to 0.36% and the incidence of heterozygotes was modified to 0.72% to provide a minimum disease estimate.

Sequencing of *ATP7B* in 1,000 control participants in the UK allowed the frequency of an individual carrying two mutant *ATP7B* alleles to be estimated at 1/7,026 (*17*). The most common mutation in Europe and North America is p.H1069Q (*1*).

2.2. *WD in Asia*

The WHO estimates that the global prevalence of WD is 1/10,000 to 1/30,000. The prevalence of WD is higher in China than in the West (*18*). Since the first estimate of WD in 1968, considerable progress has been made in China. Cheng *et al*. conducted two consecutive surveys in three counties of Anhui province (Jinzhai, Hanshan, and Lixin counties) (*19*). A total of 153,370 individuals were examined and 9 individuals with WD were identified. Three of these individuals had neurological symptoms, 1 had hepatic symptoms, 1 had both hepatic and neurological symptoms, and the remaining 4 individuals had other symptoms. Of 8 individuals in whom genetic mutations were detected, 7 had mutations in the *ATP7B* gene. The other individual did not have an *ATP7B* mutation but her copper biochemical test results met the diagnostic criteria for WD. The incidence of WD was 1.96/100,000 and the prevalence was 5.87/100,000. In all of the identified cases, diagnosis was based on clinical features, biochemical parameters, and the presence of Kayser-Fleischer (K-F) rings. Given that K-F rings may be absent, patients may be asymptomatic but have other common biochemical abnormalities, the technical limitations of screening levels, and differences in expertise among physicians, the actual prevalence of WD may be underestimated (*5*). According to a haplotype analysis of 660 participants in Hong Kong, the incidence of WD among Chinese was estimated to be 1/5,400 (*20*), which indicates that the average mortality rate of Chinese patients with WD is higher than that in the American or European population (*5*).

In a survey of 500 healthy Korean participants, the prevalence of WD was lower than 1/3,000 and the frequency of carriers was 1/27 (*21*). The molecular epidemiology of *ATP7B* in these populations has also been confirmed by the fact that WD is more prevalent in Asians than Caucasians (*5*). While the most common mutation in Europe and North America is p.H1069Q, the most common mutation in Asia is p.Arg778L (*1*).

3. Clinical features

3.1. *Nerve damage*

In 1932, Cheng described the clinical history of two patients who are 24 years of age (*3*). The two patients clinically presented with impaired motor movements, involuntary movements (including tremors), cone dystrophy, peristalsis, and "dancing" movements (repetitive, complex, and well-coordinated but involuntary movements). In the 1950s, Zhang summarized recent studies on WD and concluded that the major clinical manifestation of WD was neuropathy, and especially damage to the extrapyramidal system (*22*). Neurological manifestations include involuntary movements, stiffness, tremors, and oropharyngeal dysfunction such as expectoration and dysphonia (*23*). As a patient with WD reaches the age of 20 or 30, the patient's condition may deteriorate and trembling may be evident. Muscle stiffness will develop during movement, fine movement will deteriorate, and the patient is then likely to exhibit "dancing" movements (*23*). Speech difficulties and drooling are the most common manifestations of WD (*23*), and they will appear in the early stages. Other symptoms, including dystonia, dysfunction, gait abnormalities, ataxia, autonomic dysfunction, and memory deterioration (*5*) are also common in Chinese patients with WD. Psychotic symptoms are usually nonspecific, such as depression, mania, personality changes, and mental retardation (*23*).

3.2. *Neurological symptoms*

A review of the medical records of patients with WD at Shengjing Hospital from 1993-2001 indicated that 20.3% (27/133) had neurological symptoms at diagnosis and 69.9% (93/133) had hepatic symptoms at diagnosis (*24*). Hepatic symptoms are mainly liver dysfunction, including acute or chronic hepatitis, cirrhosis, hepatic encephalopathy, and fulminant hepatitis. However, patients without neurological manifestations are likely to be misdiagnosed. According to one figure, only 33.1% (44/133) of patients were correctly diagnosed when initially seen (*5*).

3.3. *K-F rings*

K-F rings are a common ophthalmological sign and

the easiest way to identify WD. The transparent tissue of the eye provides a unique opportunity to observe the deposition of copper in tissue (*23*). A red or green ring forms around the corneal limbus, and copper deposition is greater in the upper portion and lower in the lower portion. Copper is deposited on the surface of Descemet's membrane and the surface of endothelial cells (*25*). At least 50% of patients have this symptom and it is always present when the central nervous system is fatigued (*23*). In a non-randomized case series, K-F rings were found in 23.1% (12/52) of patients with liver disease and a neurological disorder was found in 100% (11/11) (*26*). If patients have overt neurological symptoms, the absence of K-F rings cannot be used to rule out WD (*5*). Bile excretion is the main way that the body reduces the copper concentration and K-F rings are caused by the deposition of copper, so those rings are also found in patients with chronic cholestasis (*27*). Li *et al*. found that patients with K-F rings developed symptoms at maturity and that if the first doctor is poorly informed about WD, then WD may not be identified, possibly delaying diagnosis (*2*). In addition, patients with K-F rings had higher levels of 24 h urinary copper and lower levels of alanine aminotransferase (ALT) (*28*).

3.4. *Osseous findings*

Patients with WD have a lower bone mineral density and are prone to osteoporosis and fractures (*29*). Osteoarthritis is one of the manifestations of WD. Osseous findings include osteoporosis (the most common), facet joint inflammation, osteomalacia, juvenile osteoarthritis, spinal osteochondritis, fractures, and heterotopic ossification. Patients with hypercalciuria had a statistically significant lower bone mineral content (BMC) and bone mineral density (BMD) than those without hypercalciuria (*30-33*).

4. Diagnosis

4.1. *Molecular diagnosis*

The methods of identifying WD include molecular diagnosis (laboratory diagnosis), diagnostic imaging (*2*), and genetic analysis. Molecular diagnosis has increased in use. The clinical manifestations of WD include liver disease, brain and nervous system damage, osteoporosis, and K-F rings (*34*). Liver damage may not be identified. Routine liver function tests are not diagnostic. Tremors can be a clue to the diagnosis of WD affecting the nervous system (*35*). Patients with neurological or psychiatric symptoms tend to be more often identified as having WD. The presence of K-F rings at the edge of the cornea is also diagnostic (*23*). The study of copper metabolism is most important. The loss of more than 200 ug of copper within 24 hours is very serious. The loss of large amounts of proteins can occur in WD and chronic liver diseases characterized by biliary obstruction and biliary cirrhosis, but primary liver disease differs from WD. In WD, the concentration of copper in plasma increases proportional to that in urine (*35*). In 1954, Earl found that copper ion concentration can be detected in urine. In 1996, Ravlin found that a low level or undetectable plasma ceruloplasmin could be a rough indicator of WD. A high level of urinary copper excretion in the absence of proteinuria and in association with a low or low-normal plasma copper level will also confirm the diagnosis. The level of plasma ceruloplasmin that can be determined by laboratory screening is the first step in diagnosing WD, followed by the level of copper ions (*35*).

4.2. *Imaging studies*

Nuclear magnetic resonance imaging (MRI) of the brains of patients with WD revealed abnormalities, and the basal ganglia were the areas most often affected (*36*). The main signs of WD are hypointensity on T1-weighted images and hyperintensity on T2-weighted images in the caudate nucleus, thalamus, midbrain, pons, and cerebellum, although in some rare cases there is hyperintensity on T1-weighted images and hypointensity on T2-weighted images (*5*). Concurrent signal changes are more common in the basal ganglia, thalamus, and brainstem (*2*). Patients with WD have varying degrees of atrophy of the frontal cortex, enlargement of the ventricles, and hydrocephalus. The brain abnormalities identified on MRI can subside after successful treatment (*2*), so MRI is a useful way to monitor the effectiveness of treatment (*5*).

4.3. *Genetic analysis*

Genetic analysis has also become routine. WD is caused by mutations in the *ATP7B* gene. At present, direct sequence analysis is the most accurate way to identify *ATP7B* mutations. The most common mutations are point mutations, but other types of mutations have also been identified, such as small deletions or insertions, total deletions, and splice site mutations. Previous studies have indicated that WD in China seems to have been caused by a number of relatively common mutations and a number of rare mutations (*37*). New *ATP7B* mutations have been reported very frequently. Li *et al*. identified 62 cases of WD, 14 of which involved new mutations (*15*). Dong *et al*. concluded a long-term study of 632 samples of *ATP7B* variants from patients with WD in China between 2004 and 2005, and they detected 173 variants, 58 of which were new types of *ATP7B* (*5*). Common mutations include p.R778L with a frequency of 1.7%, p.P992L with a frequency of 2.6%, p.T935M with a frequency of 1.6%, and p.A874V with a frequency of 3.8% (*23*). The three most prevalent alleles were *p.R778L*, *p.P992L*, and *p.T935M*. A study

Table1. The treatment of WD in Chinese medicine and Western medicine

Items	Medication	Advantages and disadvantages	Suitable patients	*Ref.*
Western medicine	D-PCA	Orally administered; Promotes copper excretion; Causes serious adverse reactions.	Not suitable for the treatment of patients with liver disease, patients with severe neurological disorders, patients with advanced WD, and patients with an allergy to D-PCA.	(*39-40*)
	DMSA	Orally administered; Promotes copper excretion.	Suitable for mild and moderate neurological symptoms and psychiatric symptoms and PCA intolerance.	(*41-43*)
	Na-DMPS	Injected; Low toxicity.	Suitable for mild and moderate neurological symptoms and psychiatric symptoms and D-PCA intolerance.	(*42*)
	TETA	Easily absorbed; Causes mild adverse reactions.	Patients who cannot tolerate D- PCA.	(*40-43*)
	Tetrathiomolybdate (TM)	Promotes copper excretion; Causes mild adverse reactions. Not suitable for long-term use.	Suitable for neurological symptoms, not suitable for long-term treatment.	(*44-46*)
	Zn	Promotes copper excretion.	Treatment of asymptomatic disease and maintenance therapy after the use of copper chelating agents.	(*41*)
Chinese medicine	Gandou Decoction Shugan; Lidan Paidu Decoction	Adjuvant therapy; Not as effective as D-PCA and Na-DMPS; Causes mild adverse reactions; Can be used concomitantly with Western medicine.	Mild and moderate patients.	(*41,47-52*)

DMSA, dimercaptosuccinic acid; D-PCA, D-penicillamine; Na-DMPS, sodium dimercaptosuccinate; TETA, triethylene tetramine; TM, tetrathiomolybdate; WD, Wilson's disease.

has suggested that multiple allele-specific PCR be used to screen for WD (*5*).

5. Treatment

5.1. *D-PCA*

Early and lifelong treatment is the key to the treatment of WD (*5*). WD is mainly treated with Western medicine, surgery, hemodialysis, gene therapy, or cell transplantation (Table 1). Patients with WD have copper deposits and copper is mainly taken in through food, so a low copper diet (such as rice, wheat flour, corn, milk, eggs, white radish, poultry, beef, and rabbit) is second-line treatment after first-line treatment (*38*). Foods high in copper like shellfish, nuts, beans, chocolate, and whole grains should be avoided (*23*). A high protein diet should be consumed because the increased excretion of amino acids can increase urinary excretion, thereby reducing the deposition of copper. Drug therapy is mainly excessive copper chelation (*5*).

D-PCA is the drug of choice for treatment of WD since it can chelate copper *in vivo*, promote its excretion, and effectively reduce the severity of disease. D-PCA has the advantage of inducing a high level of urinary copper excretion, but copper is excreted slowly. Therefore, D-PCA is not suitable for patients with severe or advanced WD. If D-PCA is administered over a prolonged period, adverse reactions are not uncommon, including neurological deterioration, early symptoms of gastrointestinal diseases and allergic reactions, leukopenia, thrombocytopenia, hemolytic anemia, and autoimmune diseases (*39*). When D-PCA is administered to mice, levels of both hydroxyl radicals and free copper in the striatum increase, which may lead to deterioration of the nervous system, so D-PCA should be used with caution. D-PCA is contraindicated for patients with severe neurological symptoms, and especially patients with muscle stiffening. The most serious adverse reaction is anaphylaxis, which is evident as a fever and rash over the first few days. Use of PCA should immediately be halted when a serious adverse reaction occurs (*5*). Similarly, D-PCA should not be administered to patients with liver disease since it will increase the burden on the liver, which may lead to temporary signs of early treatment. Given the impact of adverse reactions and neurological deficits during initial treatment, 20-50% patients may be affected, though those impacts are sometimes irreversible. Some experts contend that PCA should not be the drug of choice for treatment of WD (*40*). In China, however, D-PCA is still the drug of choice because of its effectiveness, prevalence, and low price (*5*).

5.2. *Dimercaptosuccinic acid (DMSA) and sodium dimercaptosuccinate (Na-DMPS)*

DMSA is a broad-spectrum metal antidote and an alternative to maintenance therapy. DMSA was the first drug used to treat WD in China (*5*). Dimercaptopropanol results in a lower level of urinary copper and causes more severe adverse effects than other drugs, so its use

has been discontinued (*41*). Na-DMPS is low in toxicity, but it is ill-suited for patients with advanced WD and critically ill patients. Calcium disodium edetate ($CaNa_2$-EDTA) has a low toxicity, but zinc and iron are easier to chelate than copper, so $CaNa_2$-EDTA causes excretion of a small amount of copper in urine (*4*). DMSA and Na-DMPS are recommended for patients with neurological and psychiatric symptoms, mild to moderate hepatic symptoms, and patients who cannot tolerate D-PCA. Use of DMSA and Na-DMPS is particular to China. Because these drugs are not mentioned in studies of liver disease published by the American Society for Liver Disease Research (*42*) and the European Research Association (*14*). Hu *et al*. conducted a clinical study using several heavy metal poisoning antidotes (GSH, DMS, EDTA, DMPS, PCA, and DMSA) to treat WD (*43*). PCA was the most effective oral preparation, followed by DMSA, while DMPS was the most effective injection, followed by DMS and $CaNa_2$-EDTA (glutathione (GSH) was only mildly effective).

5.3. *Tetrathiomolybdate*

Tetrabromomolybdate (TM) can bind to free copper in serum and food (*4*). The use of PCA can aggravate neurological symptoms in patients with severe symptoms (*44*). However, TM rarely causes further or irreversible nerve damage. Brewer *et al*. treated 55 patients with WD in the brain (*45*), and only two had worsening neurological symptoms. As a result, some experts recommend using TM without PCA to treat WD, and TM is considered to be a fast drug that causes relatively mild adverse reactions. However, excessive amounts of molybdenum are toxic, and therefore TM is not used in long-term maintenance therapy (*46*).

5.4. *Zinc*

Zn has been recognized as an effective adjuvant to reduce copper absorption in patients with WD. Yang used oral zinc sulfate or zinc gluconate to treat patients with WD and found that urinary copper excretion increased significantly (*41*). When patients used zinc sulfate as part of maintenance therapy, their clinical symptoms improved significantly in the third year of follow-up. A study in the US indicated that Zn has good clinical efficacy in asymptomatic patients and preclinical patients and in the maintenance phase after the use of copper chelators (*10*).

5.5. *Traditional Chinese medicine*

As adjuvant therapy, Chinese medicine can promote copper excretion in bile, feces, and urine (*4*). Suitable Chinese medicines include Gandou Decoction (*41*), Shugan Lidan Paidu Decoction (*47*), Xiaoyao Powder (*48*), Chaihuang Gandou Powder (*49*), Bushen Jianpi Decoction (*50*), and Gandou De-Copper Pills (*51*). Xue *et al*. found that DMPS and Gaudou Decoction can improve liver function and delay the progression of liver fibrosis by indirectly enhancing the degradation of metalloproteinase-1 in the extracellular matrix. A systematic review of nine randomized controlled trials indicated that Gaudou Decoction appears to be effective, safe, and well-tolerated as a single therapy or adjuvant therapy (*52*).

5.6. *Surgery*

Surgery mainly involves a splenectomy and orthotopic liver transplantation (OLT). The former can treat patients with WD who have severe spleen hyperactivity (*53*). OLT is suitable for decompensated liver disease or "refractory" disease that cannot be alleviated by medication alone. OLT is the only viable option for patients with WD and fulminant liver disease (FHF) or abdominal problems. However, OLT is not suitable for patients with neurological symptoms alone because long-term neurological damage cannot be alleviated by transplantation (*40*). Although OLT is an effective treatment, surgery is a risk and immunosuppression is painful. Although OLT results in greater long-term excretion of copper, it is extremely costly (*4*).

5.7. *Cell transplantation*

Cell transplantation mainly includes hepatocyte transplantation and stem cell transplantation. Hepatocyte transplantation has become the treatment of choice for abnormal liver metabolism and genetic disorders in recent years. "*In vitro*" gene therapy involves transferring a gene from a donor into the body of a recipient. Compared to "*in vivo*" gene therapy, "*in vitro*" gene therapy has the advantages of little risk and ease. However, mature hepatocytes are highly differentiated somatic cells. Their proliferation capacity is limited and *in vitro* proliferation is particularly difficult. In addition, immune rejection is a possibility (*4*). However, stem cell transplantation can solve this problem. In stem cell transplantation, hepatocytes and bile duct cells can be obtained from bone marrow cells. Stem cells can be obtained from donor bone marrow or peripheral blood and they have greater ability to proliferate than hepatocytes. In addition, stem cells can also differentiate into neurons and other cells, so they may have a therapeutic effect on the neurological symptoms of WD. An animal study has indicated that gene therapy and cell transplantation can eventually restore copper homeostasis and reverse liver disease (*54*), suggesting that cell transplantation is the preferable option.

5.8. *Hemodialysis*

Hemodialysis can reduce the level of copper in patients

with WD in a short period of time and it can also remove other toxic substances. It can be used in patients with severe or end-stage WD (*4*).

5.9. *Genetic counseling*

Genetic counseling is also important. Although heterozygous carriers of defective genes are asymptomatic, they will pass a defective gene to their offspring if they marry someone who has similar symptoms. Twenty-five percent of children of heterozygous carriers are normal, 50% are asymptomatic, and 25% develop WD (*23*).

Symptomatic treatment and rehabilitation training are also indispensable. A daily change in symptoms can also enable patients to actively participate in social activities.

6. Conclusion

At present, the prevalence of WD is higher in China than in other countries, and research has made less progress than it has abroad. Early identification, diagnosis, and preemptive treatment of WD are critical to improving patient outcomes (*1*). A combination of traditional Chinese medicine and Western medicine is the best way to treat WD. An individualized treatment program has been put into practice to study the relationship between the genotype and phenotype of WD, but this is far from enough (*5*). Therefore, appropriate treatments need to be studied and developed specifically for Chinese patients with WD.

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