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Original Article

Research Progress on Wilson's Disease

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Abstract:
Hepatolenticular degeneration, also known as Wilson's disease, is an autosomal recessive genetic disease caused by ATP7B on chromosome 13q14.3. Due to abnormal copper metabolism, copper ions accumulated in the body accumulate in the liver, brain, kidneys, cornea, and other organs, causing different clinical symptoms and onset ages. Early diagnosis plays a crucial role in subsequent treatment, but due to the significant differences in clinical symptoms, accurate diagnosis is still challenging at present. This review summarizes the etiology and pathogenesis, clinical characteristics, diagnostic methods, imaging features, pathological changes, and treatment methods of Wilson's disease.

Keywords: ATP7B; Copper; Diagnosis; Pathogenesis; Wilson's Disease

1 Introduction

Wilson's disease(WD) is an autosomal recessive genetic disorder, named after a doctor named Kinnear Wilson who first discovered and summarized it in 1912 [1]. Abnormal copper metabolism was gradually established as the cause of the disease, and its genetic mode was established as autosomal recessive inheritance in the following decades [2]. The location of the gene was basically determined in 1985, and it was discovered that its pathogenic gene was the ATP7B gene located at 13q14.3 in 1993, which is a P-type ATPase mainly expressed in the liver and responsible for transporting copper ions in liver cells [3].With the continuous advancement of molecular biology and genetic related technologies, puzzles are also constantly being solved. However, there are still many unexplainable issues with this disease, such as some patients being found to carry only one pathogenic gene or even no pathogenic gene through gene sequencing, and some patients having common gene mutation sites but no commonality in clinical manifestations, which still require further exploration by researchers.

The prevalence rate of WD is 1/10,000-1/30,000 shown in epidemiological investigation, the incidence rate is 0.5/100000, and the disease gene carrier rate is about 1:90 [4]. WD is relatively rare in most European and American countries, but it is more common in certain countries and regions such as Sardinia in Italy, Israel, Romania, etc. Among the Asian yellow population, the incidence rates are higher in China, Japan, and South Korea [5]. There are no epidemiological reports that cover bulk data on this disease in China , but according to the research of Hu et al. [6], they investigated a total of 153370 people in three counties of Anhui Province and detected 9 WD patients, the estimated prevalence rate is 5.87/100000.

WD is one of the few neurogenetic diseases that can be treated. Most patients have a good prognosis if diagnosed and treated in a timely manner in the early stages of onset or symptoms, many manifestations of WD can be prevented and reversed, and life expectancy can be restored to near normal levels. Conversely, it can lead to severe disability and even endanger life if the condition gradually worsens [4,7]. However, many patients have complex and diverse early symptoms due to the varying rates and degrees of copper deposition in different organs, which can

easily be misdiagnosed as other diseases. False positive or false negative results also existed in laboratory copper metabolism tests. Therefore, it is a great challenge to diagnosis this disease, especially in the early stages of symptoms.

In this review, we mainly discussed the etiology and pathogenesis, clinical characteristics, diagnostic methods, imaging features, pathological changes, and treatment methods of Wilson's disease.

2 Etiology and Pathogenesis

WD is an autosomal recessive copper metabolism disorder, with its related gene located at 13q14.3, encoding a P-type adenosine triphosphatase consisting of 1411 amino acids that participates in the transmembrane transport of copper, known as the ATP7B gene [8].

Due to a mutation in the ATP7B gene, the ATP7B enzyme located on thrans-Golgi network (TGN) in liver cells and on the side of the bile duct membrane is functionally impaired, resulting in copper ion transmembrane transport disorders, impaired ceruloplasmin (CP) synthesis, and restricted copper excretion in bile. Excess copper cannot be excreted from the body and deposits in the liver, brain, kidneys, cornea, and other areas, causing corresponding tissue and organ damage [9]. Patients may present with clinical manifestations such as decreased serum copper levels, cirrhosis, neurological and psychiatric symptoms, and Kayser Fleischer ring (K-F ring)[10].

Most of the copper in the normal human body is distributed or stored in proteins and blood of different tissues, with the highest content in the liver and brain, where the liver is the center of copper metabolism [11,12].Normal people consume copper from their diet daily, mainly through the stomach, duodenum, and upper jejunum [13].Copper in human blood enters the bloodstream through the portal vein through the action of transporter proteins located on the intestinal cell membrane, and then loosely binds with albumin and is transported to the liver. Copper entering liver cells is divided into three parts: one part firmly binds to a2 globulin to form ceruloplasmin, another part binds to important copper proteins such as cytochrome oxidase and superoxide dismutase, and the other part is excreted into bile by liver lysosomes and further excreted from the body [12]. Many enzymes in the body contain copper, which plays various roles in the body's metabolism [14].

ATP7B protein has a dual function of absorbing and secreting copper ions in the liver. Under normal circumstances, the intake and excretion of copper maintain a dynamic balance. When liver cells have low copper levels, ATP7B protein moves to the Golgi apparatus, and the endoplasmic reticulum transfers copper ions into the Golgi apparatus; When there is an excess of copper in liver cells, ATP7B protein moves towards the tubular surface of liver cells, secreting copper ions into the biliary tract to expel copper [15].When ATP7B undergoes genetic mutations, it loses the aforementioned functions, preventing excess copper from being excreted smoothly and depositing in the central nervous system, liver, kidneys, cornea, and other organs, resulting in structural damage and functional changes to the corresponding organs. ATP7B mainly has three modes of losing copper transport: ①ATP7B is still located within TGN, but when copper concentration increases, it loses its response to copper and cannot transport copper out of the cell. The typical mutation site is G943S, and this pattern of lesions does not affect the formation of ceruloplasmin, which is also the reason why ceruloplasmin does not decrease in a few patients [15] . ②ATP7B aggregates at the cell edge rather than within the normal TGN, resulting in the inability to bind excess copper and transport it out of the cell [15].③ ATP7B is stored in the endoplasmic reticulum and cannot complete the transport of copper. The most common mutation sites are H1069Q and R778L [16].

There are approximately 300 different ATP7B gene mutations described in the International Human Genome Organization database, and different mutation types determine different onset ages, clinical manifestations, and severity of the disease [17]. The most common mutation type among Caucasians is H1069Q (where the histidine at position 1069 of ATP7B is replaced by glutamate), the more common mutation type is R778L in Chinese (the arginine at position 778 is replaced by leucine) [18].

3 Clinical Symptoms

The clinical manifestations of WD are diverse, and the onset age is mostly between 7 and 14

years old. Usually, younger individuals tend to develop liver damage, while older individuals tend to develop neurological or psychiatric symptoms. And those with neurological symptoms often have liver damage that has not yet caused clinical symptoms [19].

3.1 Hepatic Symptoms

The clinical manifestations vary greatly, including loss of appetite, fatigue, jaundice, abdominal distension, abdominal pain, and other symptoms similar to acute or chronic hepatitis, or asymptomatic persistent mild elevation of transaminase, and even sudden liver failure such as severe hepatitis, cirrhosis, ascites, etc. Clinically, a large proportion of patients have no obvious discomfort and have already developed to the stage of cirrhosis when they first visit [4,19]. From this, it can be seen that WD is often overlooked during the asymptomatic period or early stages of liver cirrhosis, resulting in delayed diagnosis and treatment. If patients with only elevated transaminase levels in the early stages are not treated in a timely manner, they may eventually develop into cirrhosis, which can further progress to decompensated cirrhosis, hepatic encephalopathy, and liver failure [20,21].

3.2 Neurological Symptoms

It can be the first symptom of the disease, and some may occur several months or years after the manifestation of liver damage [22]. The earliest neurological symptoms can be subtle, such as mild tremors, language and writing disorders, which typically progress most rapidly in the age range of 10 to 20 and are easily confused with other neurological and psychiatric disorders. A small number of patients may not develop symptoms until the age of 45 to 70, and the main manifestation is extrapyramidal motor disorders, which are characterized by changes in muscle tone, difficulty with fine motor movements, articulation disorders, difficulty chewing, limb tremors, chorea like symptoms, and common Parkinson's like symptoms [23]. Common changes in mental behavior include dull facial expressions, slow thinking, and academic setbacks. Rare mental depression, impulsivity, schizophrenia, and personality changes, even manifested as epilepsy, hemiplegia, etc. [24].

3.3 Ocular Symptoms

The corneal K-F ring was first named after the reports of German ophthalmologists Kayser (1902) and Fleischer (1903) [25]. The K-F ring is formed due to excessive copper deposition in the stratum corneum, located in the posterior elastic layer of the corneal edge. It appears gray, brownish green, or brownish yellow, with a width of approximately 1.3mm, and can be seen by slit lamp examination [26,27]. The K-F ring is a unique sign of this disease, present in 95% of patients with neurological symptoms, while only 50% -60% of patients without neurological symptoms have K-F rings, and 10% of asymptomatic patients have K-F rings. Individuals who are young, have mild symptoms, and mainly present with liver disease or hemolytic anemia may not have a K-F ring. For patients with clinical symptoms, if the K-F ring is present and ceruloplasmin is reduced, the clinical diagnosis can be confirmed [28,29]. However, it should be noted that the K-F ring is not unique to Wilson's disease. Some chronic cholestatic diseases, such as primary biliary cirrhosis, sclerosing cholangitis, biliary atresia, etc., can also cause corneal copper deposition due to copper excretion failure in bile [26]. In addition, some WD patients may have sunflower shaped cataracts, often coexisting with K-F rings [30]. The presence or absence of K-F rings may not necessarily be related to the severity of the condition or the effectiveness of treatment.

3.4 Hematological System Symptoms

Intravascular hemolysis may occur during the course of WD, which is often transient and self limiting, and can be seen in mild, moderate, and severe cases. The blood Coombs test of WD hemolytic patients is negative, indicating non spherical red blood cell hemolysis. Therefore, for patients with spontaneous hemolysis without obvious causes, the possibility of the disease should be considered and used as a differential diagnosis [19].

3.5 Renal Symptoms

Kidney damage mainly affects the glomerulus and proximal tubules. Copper accumulation in the kidney causes impaired reabsorption of renal tubules, resulting in increased levels of urinary amino acids, proteins, uric acid, calcium, kidney stones, renal diabetes, and even renal acidosis. There are also reports of hematuria as the initial manifestation [19,31].

3.6 Skeletal Symptoms

WD can manifest as early-onset osteoporosis, arthritis, unexplained joint pain, skeletal deformities, spontaneous fractures, bending deformation of both lower limbs, cartilage degeneration, etc. Knee joint is the most susceptible joint [32].

3.7 Cutaneous Symptoms

WD can be manifested as skin pigmentation, increased skin lines, hirsutism or abnormal hair distribution [33].

3.8 Endocrine Symptoms

WD can also manifest as symptoms such as pancreatitis, hypoparathyroidism, menstrual disorders, and even infertility [34].

4 Diagnosis

The prognosis is mostly good if WD can be diagnosed early and treated appropriately, so early diagnosis is particularly important. However, due to its rarity in clinical practice, complex and diverse symptoms, and unfamiliarity with many medical personnel, misdiagnosis and missed diagnosis often occur. Accurate diagnosis requires comprehensive judgment based on clinical manifestations, biochemical examination, pathological examination, genetic examination, etc [35].

For patients who cannot rule out WD, the following auxiliary examination methods can help confirm the diagnosis.

4.1 Liver Function Examination

Mild liver function abnormalities are the most common auxiliary examination abnormalities in the early stage. For patients with liver function abnormalities who exclude viral hepatitis, autoimmune hepatitis, fatty and non fatty alcoholic hepatitis, this disease should be highly suspected.

4.2 Serum Ceruloplasmin

The normal serum ceruloplasmin content is 250-400mg/L. When the ceruloplasmin content is below 200mg/L, it is highly suspected to be a WD patient. If the K-F ring is also positive under slit lamp, the diagnosis is confirmed.

Serum ceruloplasmin <80mg/L is strong evidence for the diagnosis of WD [36]. It is worth noting that 10% to 20% of WD heterozygotes (carriers of disease causing genes) may have serum ceruloplasmin levels lower than the normal reference value, but most are between 150-250mg/L and very few are less than 100mg/L [3]. According to Sass Kortsak et al., approximately 2.5% to 4% of WD patients have normal serum CP values, which are mainly found in children [3]. CP has the activity of oxidase in the body and is the most important copper oxidase. In clinical practice, serum CP can be directly measured, or serum copper oxidase can be indirectly used to determine serum CP values. These two tests can replace and complement each other in the diagnosis of WD [37].

4.3 Serum Copper

Although WD is a disease characterized by excessive copper content in the body, patients often exhibit a decrease in serum copper levels. In the case of decreased ceruloplasmin, normal or increased serum copper levels indicate an increase in non ceruloplasmin copper. The concentration of non ceruloplasmin bound copper in the human body can be used as an auxiliary diagnostic method for WD, the concentration is greater than 25ug/dL for most untreated patients [38].

4.4 24-hour Urinary Copper

The 24-hour urinary copper content reflects the amount of non ceruloplasmin bound copper in the body. The upper limit of copper content in normal 24-hour urine is 40ug/24 hours, if it exceeds 100ug/24 hours, it is of great significance [39]. For children with suspected WD and corresponding clinical symptoms, penicillamine stress test can help clarify the diagnosis [35].However, it lacks specificity for non pediatric patients [40].

4.5 Liver Copper Content

Measuring the copper content in dry liver tissue remains the most accurate method for diagnosing WD to this day. Normal liver copper content is generally less than 50ug/g. If its content is greater than 250ug/g, it can be diagnosed as WD [41].

4.6 Ceruloplasmin Oxidase

The sensitivity and specificity of diagnosing WD are superior to the determination of serum ceruloplasmin content, and the optimal critical value for diagnosing WD is around 7U/L [42].

4.7 Cerebrospinal Fluid Copper

As an auxiliary diagnostic indicator to evaluate the prognosis of patients with brain type, it has reference value for distinguishing between liver type and brain type patients [43].

4.8 Neuronal Specific Enolase

It can determine whether the neurological symptoms worsen during copper removal therapy [44].

4.9 Genetic Examination

Genetic diagnosis can use polymerase chain reaction technology to detect relevant gene mutations, single strand conformation polymorphism technology for gene sequencing, and restriction fragment length polymorphism and microsatellite marker polymorphism technology analysis for indirect diagnosis, playing an irreplaceable role in screening the relatives of diagnosed patients [45]. However, the current technology and cost issues of gene sequencing hinder its widespread application.

4.10 Liver Biopsy

In the early stages of the disease, ultrastructural changes include mitochondrial enlargement, separation of mitochondrial inner and outer membranes, widening of mitochondrial cristae spaces, increased cytoplasmic density, and formation of vacuoles. Without cholestasis, HLD can be diagnosed based on these changes. In the middle stage of disease progression, pathological features include portal vein inflammation, monocyte infiltration, hepatic lobular necrosis, and bridging fibrosis [46].

5 Imaging Features

5.1 Abdominal Ultrasound Examination

The main manifestation is liver cirrhosis changes, including increased and thickened echo spots in the liver parenchyma, star shaped distribution, uneven density, and abnormal enlargement or reduction of liver size. May be accompanied by splenomegaly, ascites, cholecystitis, etc, many patients also have thickening of renal cortex echoes [47].

5.2 Liver and Spleen CT and MRI Examination

Fikkhan et al. [48] found that in patients with WD, multiple, slightly high-density nodules of varying sizes can be seen on liver CT scans, which may show slight enhancement after enhancement. As the condition progresses, CT re-examination can reveal that these nodules have significantly increased density and liver volume gradually decreases. Many patients also have splenic enlargement, and in some cases, portal vein thickening or /and ascites can be seen, presenting typical CT signs of portal hypertension. The main manifestation of liver MRI is multiple intrahepatic nodules of varying sizes, with slightly high signal intensity on T1WI and slightly low signal intensity on T2WI.

5.3 Head CT and MRI Examination

The abnormality rate of cranial CT is as high as 85%, mainly manifested as decreased density in the bilateral symmetrical basal ganglia and thalamus, often accompanied by varying degrees of cortical and white matter atrophy. Head MRI examination is superior to CT [49]: (1) Abnormal signals are most common in the bilateral basal ganglia, mainly in the lentiform nucleus, especially the putamen nucleus, followed by the caudate nucleus, thalamus, midbrain, pons, globus pallidus, and less common in the cerebellar dentate nucleus (2) T1WI is mostly low signal or slightly low signal, while T2WI is often high signal. The appearance of the latter may be due to copper ion deposition in the basal ganglia area, causing focal brain tissue edema, nerve demyelination, glial cell proliferation, and even nerve cell necrosis, leading to increased local water content (3) rain atrophy is common, seen in the cortex and white matter (4) The brain lesions are basically symmetrical on both sides.

5.4 X-ray Examination of Bone and Joint

The abnormality rate of X-ray examination is 83% to 92%, and it can be seen that the distal ends of the limbs, cones, pelvis, wrist joints, interphalangeal joints, etc. are affected [32]. Common manifestations include osteoporosis, focal demineralization, osteoarthritis, osteomalacia, bone edge fragmentation, spinal osteochondritis, periarticular or intra-articular calcification, spontaneous fractures, etc.

5.5 Nuclear Medicine Examination

The results of positron emission tomography (PET) examination in WD patients showed a general decrease in local glucose metabolism rate in the brain, with the most significant decrease

observed in the lentiform nucleus. Piga M et al [50] used MRI and Single-Photon Emission Computed Tomography (SPECT) to examine 25 patients with WD, and compared them with 24 healthy individuals,the results was that SPECT showed pathological changes, which was much higher than the positivity rate of MRI. The study showed that SPECT examination is of great help in early detection of WD brain damage and guiding treatment.

6 Pathological Changes

6.1 Liver

Under the light microscope, hepatic steatosis and necrosis can be seen, and the nuclei are vacuolated [51]. The earliest changes in liver cells can only be detected under electron microscopy [52]. The pathological diagnostic criteria for early WD (asymptomatic) in the liver include: ① mitochondrial enlargement, polymorphism, and increased matrix density; ②An increase in the number, volume, and polymorphism of peroxisomes; ③Formation of smooth endoplasmic reticulum vesicles; ④The number of bubbles in triglycerides increases;⑤Lipid droplets and copper deposition within the lysosome. Its pathological changes can be classified into four stages, from mild to severe: hepatic steatosis, hepatitis, hepatic fibrosis, and cirrhosis. Patients with rapid disease progression may present with subacute yellow liver atrophy. Under the light microscope, copper like (brown granular) deposits can be seen in the cytoplasm of liver cells around the pseudo lobules of the liver. The most characteristic change during the cirrhosis phase is the appearance of Mallory bodies [53].

6.2 Spleen

The volume increases, the capsule thickens, and under light microscopy, the splenic sinus is highly congested, the splenic capsule and trabecular connective tissue proliferate, and there are many small brownish yellow particles (copper like substances) inside the cells [40].

6.3 Brain

The lesions are mainly located in the basal ganglia, with the putamen being the most obvious, followed by the globus pallidus and caudate nucleus. Other areas such as the cerebral cortex, thalamus, red nucleus, substantia nigra, dentate nucleus, midbrain, pons, and cerebellum can all be affected. The shell nucleus shrinks, and in severe cases, it forms a cavity. Under light microscopy, degeneration and necrosis of nerve cells, reactive proliferation of glial cells, and formation and edema of glial nodules were observed. Under electron microscopy, it was observed that the neurons in the lentiform nucleus exhibited degeneration and necrosis, with a ruptured cytoplasmic membrane and a significant increase in electron density of the capillary basement membrane [54]. Bertrand et al. [55] found that the type and quantity of degenerated astrocytes are related to the clinical classification and tissue damage characteristics of this disease.

6.4 Kidney

Under electron microscopy, the interstitial space between renal tubular epithelial cells significantly increased, cell connections decreased, some microvilli curved into branching shapes, fusion occurred, and the rough endoplasmic reticulum decreased [21].

6.5 Eyes

Under electron microscopy, copper can be seen to deposit in the cytoplasm of endothelial cells in the posterior elastic layer of the cornea, forming brownish green or brownish green K-F rings [26 ,27].

7 Treatment methods

The treatment methods include dietary therapy, medication therapy, surgical treatment, and symptomatic treatment [55].

7.1 Dietary Therapy [55]:

(1) Avoid eating foods high in copper, such as chocolate, beans, nuts, potatoes, mushrooms, and shells.

(2) Try to eat less copper rich foods such as millet, buckwheat flour, wheat flour, potato flour, brown rice, fragrant fruit, and pomegranate.

(3) Do not use copper utensils and utensils.

(4) Suitable low copper foods: refined white rice, refined noodles, pork, beef, chicken, duck, goose, eggs, milk, formula, condensed milk, cheese, fresh vegetables, radish, apples, peaches, pears, etc.

(5) Patients should be given a high amino acid or high protein diet, which can promote urinary copper excretion and repair organ function.

7.2 Medication Therapy

(1) Penicillamine

Based on clinical data and years of experience, penicillamine has always been the first choice for treatment. Currently, it is the most commonly used potent metal chelating agent, and its thiol group in the structure can chelate with copper to clear copper. It can also induce the production of an endogenous metal scavenger metallothionein, which not only increases the excretion of copper in urine but also reduces free copper in cells [56]. The adverse reactions of this drug may include fever, rash, neutropenia, thrombocytopenia, and proteinuria. There are reports that 20% to 50% of patients with neurological symptoms may initially experience worsening symptoms when taking medication [57].

(2) Trientine

However, some patients may experience adverse reactions and worsening of neurological symptoms after taking penicillamine, more and more studies have confirmed that trientine is effective and has fewer adverse reactions, the drug has been considered as a first-line alternative to penicillamine for WD [57], but its ability to clear copper is not as good as penicillamine. Trientine has few side effects, occasional skin damage, and decreased whole blood cells. Due to its ability to chelate iron, it should be avoided when taken with iron supplements. During the treatment process, it is necessary to monitor the amount of copper excreted in urine to determine the efficacy and adjust the dosage, as copper deficiency caused by excessive treatment with trientine can lead to liver iron overload in WD patients [58].

(3) Tetrathiomolybdate (TM)

There are two mechanisms of action for TM: one is that TM forms a complex of copper and albumin in the intestinal mucosa (both endogenous copper and copper in food can form this complex), which cannot be absorbed by the intestinal mucosa and excreted with feces; another is that TM can limit the absorption of copper by the intestinal mucosa [59]. TM has fewer adverse reactions [59]. Research has found that TM has a better therapeutic effect on WD patients' neurological symptoms than trientine [59].

(4) Zinc preparations

Oral zinc preparations can induce intestinal mucosal cells to synthesize metallothionein, which binds to copper in food within duodenal epithelial cells, reducing the free radicals produced by high concentrations of copper in cells, thereby reducing copper absorption, and copper can be excreted from the body with the shedding of intestinal epithelial cells. In addition, zinc can induce the synthesis of metallothionein in liver cells, thereby reducing copper induced liver damage [59,60]. The main adverse reaction is indigestion, which can be reduced by changing the dosage form and adjusting the administration time. There are reports that zinc supplements and penicillamine also have good effects in HLD patients with neurological disorders as the main manifestation [61]. For patients with severe liver damage, maintaining treatment with zinc preparations after initial application of zinc and trientine therapy also has significant therapeutic effects [62].

(5) Sodium dimercaptosulphonate (DMPS), Sodium dimercaptosuccinate(Na-DMS),Dimercatosuccinic acid(DMSA)

DMPS contains two thiol groups and is a low toxicity and efficient heavy metal chelating agent. After entering the human body, it can bind with free copper ions in the blood and also with copper ions bound to the ketolase system in tissues, forming thiol compounds with low dissociation and toxicity that are excreted through urine [63]. Na-DMS and DMSA can be used alternately with penicillamine as long-term maintenance therapy, with the main adverse reactions being gastrointestinal symptoms and allergies [64].

（6）Traditional Chinese Medicine

The main formula is Gandou Decoction which includes drugs such as Radix et Rhizoma Rhei, turmeric, rhizoma coptidis, lysimachia herba, Alisma orientale, and Sanqi. It promotes copper excretion in bile, urine, and feces. Yang et al. developed Gandou Decoction and found that patients treated with Gandou Decoction had an average increase in 24-hour urinary copper content compared to before treatment. At the same time, it had no significant effect on the patient's

liver and kidney function or peripheral blood count, and could promote copper excretion through bile from the digestive tract. This indicates that there are fewer adverse reactions and it is suitable for long-term maintenance and adjuvant therapy of WD [65]. In addition, basic research has also confirmed that Gandou Decoction can promote the outward excretion of copper from cells, thereby reducing patient symptoms and minimizing organ damage [65].

7.3 Liver Transplantation

The mortality rate of WD patients with liver symptoms is five times higher than those with neurological symptoms. When the disease progresses to liver decompensation or severe viral hepatitis occurs, liver transplantation is the only effective treatment measure [66]. However, for WD patients with severe neurological and psychiatric symptoms that continue to develop and are ineffective in copper treatment, liver transplantation is no longer possible to restore copper stability and organ function status in the body. Therefore, liver transplantation is not recommended for such WD patients. Since the implementation of liver transplantation for WD patients in 1969 , this technique has been widely used around the world for decades [67]. Liver transplantation can correct patients' genetic defects in phenotype, not only providing them with a healthy liver, but also improving their existing copper metabolism disorders to varying degrees after the recovery of new liver function, without the need for copper replacement therapy after surgery. So far, there have been no reported cases of copper deposition damage in transplanted livers both domestically and internationally. In a sense, liver transplantation has fundamentally cured WD.

7.4 Cell Transplantation

Cell transplantation therapy is the transplantation of normally functioning liver cells or stem cells into the damaged liver of humans, fundamentally improving and restoring liver cell function. It is currently an ideal treatment method for WD. The transplanted cells include liver cell transplantation, bone marrow cell transplantation, and embryonic stem cell transplantation.

Yoshida et al. [68], Irani et al. [69], and Park et al. [70] performed liver cell transplantation techniques by injecting allogeneic newborn rat liver cells into the liver of pre-diseased rats. The results showed that the transplanted group expressed normal ATP7B enzyme mRNA, and the copper storage in the liver also significantly decreased, bile copper excretion increased significantly. Generally speaking, mature liver cells have limited proliferation ability and are often limited by HLA typing, while fetal liver cells have stronger proliferation ability in the host liver than adult liver cells [71]. Allen et al. [72] transplanted bone marrow stem cells from mice into allogeneic mice and found that the copper content in the liver of successfully transplanted mice was significantly lower than that of non expressed mice.

7.5 Gene Therapy

As a monogenic genetic disease, gene therapy is the most fundamental treatment for WD. The current basic research mainly focuses on gene correction therapy mediated by plasmids, adenovirus, lentivirus and other vectors.

Plasmids are a type of vector that have the ability to replicate autonomously and can be stably transfected by recombining into the genetic material of host cells. Meng et al [73]. transferred cDNA from WD patients into WD animals, and successfully established transgenic rats with mature oocytes in WD animal models. This experiment confirmed that human ATPTB enzyme can promote copper excretion in rats, effectively improve their symptoms, and prolong their survival cycle compared to other pathological rats.

Adenovirus is a linear double stranded DNA virus and is currently one of the most commonly used viral vectors for gene therapy research in animal laboratories. Ha Hao et al [74]. conducted research on recombinant adenovirus expressing ATPTB cDNA and obtained transient expression of ATPTB protein. Therefore, they found that the target protein ATP7B enzyme expressed by adenovirus can increase copper excretion in the liver of LEC rats.

The most common lentivirus (LV) vector is human immunodeficiency virus-1 (HIV-1). In 2006, Merle et al. [75] transfected the human WD gene into rat liver cells using a chronic viral vector and constructed recombinant lentivirus rats containing human ATP7B cDNA. The results showed a significant decrease in serum copper

levels. Liver fibrosis is reduced, and liver function and liver damage are improved to a certain extent.

7.6 Other Treatments

The toxic effects of copper can produce lipid peroxides, causing oxidative damage to mitochondria. In experiments, the application of vitamin E can inhibit this process [76], but there is no further research to support it. The effect on N-acetylcysteine is also similar to that of vitamin E.

8 Conclusions and Future Perspectives

WD is one of the few genetic diseases that can be treated, but its clinical symptoms are complex and diverse, including symptoms of multiple systems such as the liver, neuropsychiatric system, eyes, kidneys, hematologic system, skeletal system, skin, and endocrine system. Early diagnosis is relatively difficult and has a high misdiagnosis rate, so it is necessary to make a comprehensive judgment based on clinical manifestations, biochemical examinations, imaging and pathological examinations, genetic examinations, etc. Chelating agents such as penicillamine and trientine are still the main means of drug treatment. Traditional Chinese medicine's Gandou Decoction also has certain therapeutic effects. Liver transplantation is the only way to cure. Cell transplantation therapy and gene therapy are still in the developmental stage. At present, gene therapy is mainly conducted in animal experiments and has not yet been clinically studied in humans. Although gene therapy is widely recognized as a fundamental method for curing human genetic metabolic diseases, there are still many insurmountable obstacles to gene therapy for WD at this stage, and the safety and long-term effectiveness of gene therapy need to be further confirmed.

Abbreviations

WD, Wilson's disease; TGN,thrans-Golgi network; CP, ceruloplasmin;

K-F ring, Kayser Fleischer ring; PET, positron emission tomography; SPECT, Single-Photon Emission Computed Tomography; TM, Tetrathiomolybdate; DMPS, Sodium dimercaptosulphonate; Na-DMS, Sodium dimercaptosuccinate; DMSA, Dimercatosuccinic acid; LV, lentivirus; HIV-1, human immunodeficiency virus-1.

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