Wilson’s Disease

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ABSTRACT
Wilson disease is an inherited autosomal recessive disorder due to mutations of ATP7B gene. ATP7B gene is responsible for encoding copper-transporting P-type ATPase. As ATP7B gene undergo mutations, incorporation of cu into ceruloplasmin is blocked. So, amount of cu gets elevated. This further leads to accumulation of cu at various organs like kidney, cornea, and brain causing damage. This condition includes toxicity of copper. ATP7B gene is relatively large (about 80kb, with 21 introns). It encodes a metal-transporting P-type ATPase, known as the Wilson ATPase that is responsible for moving copper across intracellular membranes, principally in hepatocytes. The symptoms involved in WD might be hepatic or neurological disorders like liver cirrhosis, liver failure, amenorrhea, ovarian dysfunction, dysarthria, and choreoathosis. Clinical manifestations of WD include neurological symptoms such as dystonia, tremor, dysarthria, psychological disturbances. It also includes hepatic diseases like liver disease/ cirrhosis. Early recognition by means of clinical, biochemical or genetic examination is very important in order to prevent the progression of WD. So, early diagnosis requires a high index of suspicion. D-penicillamine, Vit c, Zinc, trientine, liver transplantation is used to treat Wilson disease. The purpose of present review is to summarize pathophysiology, clinical manifestations, diagnosis and treatment of Wilson disease.

Key words: ATP7B gene, copper, diagnosis, treatment, wilson disease.

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INTRODUCTION
Wilson’s disease
Wilson’s disease is an inherited autosomal recessive disorder. It occurs due to mutations of ATP7B gene that encodes copper transporting P-type ATPase expressed in liver, kidney [1-4]. this condition includes toxicity of copper [5]. Clinical manifestations of WD include neurological symptoms such as dystonia, tremor, dysarthria, psychological disturbances. It also includes hepatic diseases like liver disease/ cirrhosis [1,6,7]. Other manifestations like sunflower cataract, hemolytic anaemia, thrombocytopenia, renal tubular dysfunction, hypercalciuria, hyperphosphaturia, hypokalemia, gynecological abnormalities, cardiovascular dysfunction can be seen in WD [8]. Impairment in biliary excretion of copper and improper accumulation of copper into ceruloplasmin leads to progression of WD. This further leads to accumulation of cu in extrahepatic sites like liver, kidney, brain, cornea causing several diseases [9, 10].

Copper and its physiology
Copper is a very prominent nutrient involved in various pathways like mitochondrial respiration, melanin biosynthesis, dopamine metabolism, iron homeostasis, anti-oxidant defense, connective tissue formation, peptide amidation. [9, 11] Daily cu intake is 1 to 2mg per day [12]. Daily uptake of copper in the proximal parts of the small intestine ranges between one and two milligrams, this amount is adequate for the needs of the human body [13,14]. It is absorbed in stomach and duodenum, binds mainly to circulating albumin and is taken up by various tissues [15]. The liver plays a
pivotal role in copper uptake, distribution, and excretion in the human organism. ATP7B, a copper-transporting P-type ATPase (Wilson disease protein) is the central regulator of hepatic copper metabolism [16]. As the food containing copper moves along the digestive tract, it gets absorbed at small intestine. In the blood, copper is bound to amino acids, proteins and then transported to liver and peripheral tissues [17]. Low concentration of copper result in incomplete development as it is required for various pathways and high conc of copper is injurious [18,19]. Copper generally first enters from digestive tract to absorption system through CMT-1. Then copper enters the cells. This copper later binds to melathionein. As copper concentration gradually moves on increasing, ATP7A gene releases copper through portal vein into liver. Liver cells also contain CMT for copper transport. The liver cells contain ATP7B gene that function as binding of copper to ceruloplasmin and eliminating excess copper into bile [20]. Biliary excretion is the only mechanism for copper elimination[9].

**ATP7B gene**

ATP7B gene is relatively large (about 80kb, with 21 introns). It encodes a metal-transporting P-type ATPase, known as the Wilson ATPase that is responsible for moving copper across intracellular membranes, principally in hepatocytes [21]. It normally resides in trans-golgi netework in hepatocytes, where it mediates incorporation of six-copper molecules into apoceruloplasmin forming ceruloplasmin. Under high copper conditions, however, ATP7B is also redistributed to cytoplasmic vesicles where it transports excess copper across the hepatocyte apical membrane into the bile canaliculus for subsequent biliary excretion [8].

WD gene codes for copper-transporting ATPase (ATP7B gene). In hepatocytes, ATP7B gene deliver copper to apoceruloplasmin and mediates excretion of excess copper to bile. It contains 6 copper-binding domains, a transduction domain involved in transduction of energy of ATP hydrolysis to cation transport, cation channel, phosphorylation domain, nucleotide binding domain, 8 hydrophobic transmembrane sequences. The six-N-terminal MBS metal binding sites are required for trafficking and are essential for copper transport function [22].

**Epidemiology**

The prevalence of WD is approximately 1 in 30000 worldwide, many times greater than global prevalence [23]. Approximately 1 in 90 carries mutated ATP7b gene. Its prevalence is high from small mountain village on the island of crete, where the disease was diagnosed as 1 in 15 births. [24].
Etiology
Mutations of ATP7B gene is the main cause for MD. This mutated gene further leads to accumulation of cu at various sites causing severe damage [1].

Signs and symptoms
The symptoms involved in WD might be hepatic or neurological disorders like liver cirrhosis, liver failure, amenorrhoea, ovarian dysfunction, dysarthria, choreoathetosis, [1] kayser-Fleischer ring, 25 others like asymmetric distal accentuated tremor of hands (postural tremor), wing beating tremor, intention tremor, tremor of trunk and head can also be seen [15,26].
Neuro psychological disorders like irritability, obsession, and loss of inhibition, memory and attentional impairment, difficulty in planning [27].

Pathophysiology
Malfunction of ATP7B gene caused by alteration or mutations of ATP7B gene leads to WD, characterized by hepatotoxicity and neurological degeneration. Mutations of this gene further cause change of the aminoacid sequence associated with alterations of protein structure and function, followed by cu accumulation in liver [20]. The loss of ATP7b gene result in production of apoceruloplasmin, which is rapidly degraded in plasma, resulting in reduced cu carrying capacity [28].
In WD patients, the absorbed cu first into liver can’t be easily excreted to bile due to mutations of ATP7B gene. As the gene is mutated, its functions like binding of cu to ceruloplasmin and eliminating excess cu into bile are blocked. So, more and more cu gets accumulated in liver, causing death of hepatocytes, leading to liver disease, cirrhosis. It later slowly releases excess cu into blood that is transported to several sites like kidney, brain, cornea causing neurological disturbances and KF rings [21,29]. kayser- Fleischer rings is a pathological condition that occur due to accumulation of cu in cornea. Cu gets deposited at Descemet membrane. They may be golden brown, ruby red or blue green. This is the main indication for WD [30].
Neuropathological changes of WD include spongy degeneration, nerve cell loss, demyelination in the putamen, globus pallidus, and dentate nucleus, as well as marked hyperplasia of the protoplasmic astrocytes in the cerebral cortex, basal ganglia, brain stem, and cerebellum [31].

ATP7B gene mutations
There are at least 300 distinct mutations. Mutations of E1064A and H1069Q drastically reduce nucleotide affinities. R1151H mutant exhibits 1.3 fold reductions in affinity for ATP [32].

Diagnosis
Early recognition by means of clinical, biochemical or genetic examination is very important in order to prevent the progression of WD. So, early diagnosis requires a high index of suspicion. If the disease is elucidated at initial stages, comorbidities of WD could be hastened to certain extent. Diagnosis involves clinical findings and biochemical examination. D-pencillamine challenge test is one of the diagnostic test useful especially for children to diagnose WD [33].
As WD involves several neurological abnormalities, MRI for brain can be considered as a factor for diagnosis [1, 34, 35].
Abnormalities such as the “face of the giant panda” in the midbrain, the “face of the miniature panda” in the pons, and the “bright claustrum” sign are present in only a relatively small percentage of individuals with Wilson’s disease [35-37].

Measurement of 24-hour urinary copper excretion
The 24-hour urinary copper measurement may be the single best screening test for Wilson’s disease, especially in individuals with neurological or psychiatric dysfunction. Urinary copper levels in symptomatic Wilson’s disease patients typically exceed 100 mg/d. They may also be elevated in several liver disorders. This distinguishing between diseases is important during diagnosis [8].
WD patients have abnormal liver enzymes. So, various liver function tests like aspartate transaminase, alanine transaminase, bilirubin levels need to be diagnosed. WD patients are indicated with decreased albumin levels and prolonged prothrombin time [38].
The biological test for copper must include ceruloplasmin and copper in the blood, as well for the amount of copper excreted in urine during a 24-h period [3].

Table 1: Copper evaluation in healthy subject and patient with Wilson’s disease

<table>
<thead>
<tr>
<th></th>
<th>Healthy patients</th>
<th>Wilson’s disease</th>
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<tbody>
<tr>
<td>Ceruloplasmin in plasma</td>
<td>0.2-0.4g/l</td>
<td>&lt;0.1g/l (normal in 10% of patients with Wilson’s disease)</td>
</tr>
<tr>
<td>Serum copper</td>
<td>13-22µmol/l or 0.8-1.4mg/l</td>
<td>&lt;10µmol/l or &lt;0.6mg/l can be normal if acute hepatitis or haemolysis</td>
</tr>
<tr>
<td>Urinary copper</td>
<td>&lt;0.8µmol/24h or &lt;0.05mg/24h</td>
<td>&gt;1.5µmol/24h or 0.096 mg/24h</td>
</tr>
<tr>
<td>Copper in liver</td>
<td>&lt;0.9µmol/g of dry tissue or &gt;56µg/g of dry tissue</td>
<td>&gt;4µmol/g of dry tissue or &gt;250µg/g of dry tissue</td>
</tr>
</tbody>
</table>

Basal 24-hour urinary excretion of copper reflects the amount of non-ceruloplasmin-bound (‘free’) copper in the blood and is indirectly related to the total body copper load. It is more than 0.6 µmoles/24 hours in nearly all affected individuals. Measuring 24-hour urinary excretion of copper while giving D-penicillamine is a useful provocative test; more than 25 µmoles/24 hours is considered diagnostic of Wilson’s disease [21].

In WD patients, steatosis, increased glycogen in nucleus, area of necrosis is seen at initial stages. Infiltration by inflammatory cells, piecemeal necrosis, and fibrosis are seen at advanced stage. At late stage, it is further converted to cirrhosis [34].

Treatment

Penicillamine
Penicillamine is the first drug used for the treatment of WD. It later became standard drug therapy. After treatment, Cu is quickly mobilized by tissues and eliminated in urine. But due to its adverse effects, its use is limited.[38] The normal dosage of penicillamine for initial treatment is 250-500mg 4 times daily [39,40]. It causes several adverse effects like steven-Johnson syndrome, myasthenia gravis, pseudoxanthoma elasticum, [41] skin disorders, protein-losing nephropathy, lupus-like systemic inflammatory conditions, and bone marrow suppression including aplastic anaemia, [21] skin rash, fever, eosinophilia, thrombocytopenia, leucopenia, lymphadenopathy,[8] good-pasteur’s syndrome and dermatomyositis [42].

Zinc
Zinc role in WD is increasing gradually. It is used as maintenance therapy following initial treatment with more potent decoppering agents. Zinc reduces intestinal absorption of dietary copper via induction of metallothionein formation in intestinal enterocytes. The increased metallothionein further binds to both Zinc and copper, trapping them within intestinal mucosal cells, further excreted in feces [8, 29].

Trientine
It is used as an alternative for penicillamine. It is good therapy for patients who are intolerant to penicillamine. [21, 41]. It is copper chelating agent similar to penicillamine. The daily dose is 750 to 2000 mg, divided into 3 doses [8]. It acts by increasing renal copper elimination. It is also responsible for neuronal degeneration [43]. Side effects are lupus nephritis and sideroblastic anemia [8].

Liver transplantation
If WD cannot be treated by mediations at advanced stage, orthotopic liver transplantation has proved to be an effective treatment for WD. [44] Liver transplantation is an effective treatment for fulminant hepatic failure in WD. But OLT is under investigation because of its neuropsychiatric symptoms [44-47].

Summary
WD is an inherited autosomal recessive disorder of Cu balance leading to hepatic damage and neurological disturbances. This occurs due to mutated ATP7B gene. Generally ATP7B gene is responsible for incorporation of Cu into ceruloplasmin and passing excess Cu into bile which is further eliminated from feces. Biliary excretion is
Early recognition of WD is essential for its management. A genetic condition, WD involves the accumulation of copper (Cu) in the liver. When the copper concentration exceeds levels that the liver can manage, toxic levels result. There is no cure for Wilson's disease and the only mechanism for Cu elimination is through the kidney. As liver undergo cirrhosis, Cu slowly released into blood. This Cu further move to different parts of the body like kidney, brain and cornea and gets accumulated there. KF rings, neurological disturbances and hepatic failure are the outcomes of WD. Early diagnosis is very critical in this disease. Early recognition of WD is essential in order to avoid long term clinical manifestations. D-penicillamine, Vit c, Zinc, trientine, liver transplantation is used to treat WD. But as there are several adverse effects included in these agents, further research is required in order to elucidate new molecules that may be useful to treat WD.

REFERENCES