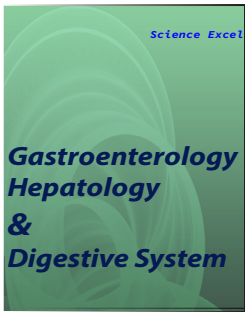
Gastroenterology Hepatology and Digestive System

Review Article



Review Article on Wilson's disease

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Vignette

A 24-year-old female presented to the emergency department (ED) with a history of feeling unwell for the last few days in the form of nausea, vomiting, abdominal pain, and jaundice. Her past medical history is unremarkable apart from repeated miscarriages in the past. She was investigated before for antiphospholipid syndrome and was negative. She has two children, a boy aged 9 and a girl aged 6.

On examination, she was hypotensive with a blood pressure of 90/60 mm Hg; heart rate of 110/min regular, and oxygen saturation of 99% on room air. She was icteric without any other signs of chronic liver disease.

Initial Investigations revealed the following-

Normal kidney function

Liver Function Tests (LFTs)-

- Total Bilirubin - 2.1 milligram/dl (0.1-1.2)
- Fractionation of Bilirubin- 100% unconjugated
- AST 500U/L(8-48)
- ALT 200U/L(5-55)
- ALP(150 U/L(40-129)
- GTT 68 U/L(6-61)
- LDH 300 U/L(122-223)
- Albumin 2.5 g/dl (3.5-7.9)
- Total protein 6 grams/dl (6-8)

Coagulation Profile-

- Prothrombin time (25 sec) (9-13)
- INR 1.8

Full Blood Counts

- HB 70 g/L (11.6-16); MCV 100fl(80-100fl); MCH 32 pg (27-32)
- Reticulocytes 10% (0.5-2.5%)
- WBC 11000cells/microL) (4000-11000 cells/microL)
- Platelets 380,000 cells/microL (150-400 cells/microL)

Viral Serology- HepB/C/HIV/CMV/EBV: Negative

Coombs test negative

Serum Immunoglobulins

- Immunoglobulin IGG 18 g/L (6-16)
- IgA 3.3 g/L (0.8-3 G/L)
- IgM 2.6 G/L (0.4-2.5)

U/S abdomen-

Normal liver architecture, no organomegaly, no hydronephrosis or renal obstruction.

The patient was admitted to the hepatology team and subsequently treated with fluids and steroids for autoimmune hepatitis pending the results of the autoimmune screen. However, the LFTs and the patient's clinical status did not improve.

How will you establish the diagnosis and management?

The Clinical Problem

Although Wilson disease may cause liver dysfunction (acute/subclinical/chronic), it is not the primary/common cause of acute hepatitis. Due to its rarity and the threat of significant mortality if not diagnosed and treated promptly, diagnosing Wilson's disease in acute hepatitis can be tremendously arduous. Here we discuss the diagnostic challenge of Wilson's disease in acute hepatitis as well as the diagnostic and management approach according to three guidelines - the American Association for the study of liver diseases (AASLD) updated in 2008, the European Association for the study of the liver (EASL) updated in 2012 and the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) updated in 2014..

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Introduction

Wilson Disease (WD), discovered by Samuel Kinner Wilson about 100 years ago [1,2] is an uncommon autosomal recessive disease leading to hepatic copper deposition affecting mainly the liver, brain, and eyes. Rarely other organs can be affected like joints, kidneys, heart, thyroid, parathyroid, and red blood cells.

The diagnosis of WD is very challenging as the signs are very nonspecific and failure to get the diagnosis and to start the treatment in a timely manner might result in the death of the patient either from acute liver failure or decompensated liver disease.

The worldwide prevalence of Wilson Disease is 1 case in 30,000 live births [3]. Most cases of WD are diagnosed between 5 and 40 years of age. Clinical signs vary considerably and due to the heterogeneity of clinical manifestations, WD has been referred to as the Great Masquerader.

Pathogenesis

Copper is an essential metal that is an important cofactor for many proteins. It is usually absorbed from the stomach and duodenum and transported to various tissues including hepatocytes [4,5]. Where copper is incorporated with apo-ceruloplasmin and converted to ceruloplasmin. When hepatocytes are oversaturated with copper, intact P-type ATP7B enables copper-loaded apoceruloplasmin to be secreted in the plasma and then excreted into the bile.

Wilson disease is an autosomal recessive hereditary disease caused by a mutation of the P-type Adenosine triphosphatase copper transporter gene- ATP7B, which is located on chromosome 13. ATP7B regulates cytoplasmic copper by removing it outside the hepatocyte [2,6].

There are over 500 mutations in ATP7B, and the most common type is the H1069Q mutation [7,8]. Moreover, most of the mutations in patients are heterozygous making diagnosis more challenging.

ATP7B mutation leads to impaired copper transport resulting in excess copper accumulation within the hepatocytes. Initially, the excess copper is bound to metallothionein and is evenly distributed throughout the cytoplasm of hepatocytes. However, extensive copper accumulation leads to the oversaturation of metallothionein, ultimately causing hepatocyte injury [9].

Similarly, the increase in free serum copper leads to its deposition and toxicity in the central nervous system and other tissues. Despite the increase in urinary copper excretion, it is not able to compensate for the reduced biliary copper excretion; as a result, there is progressive extra-hepatic tissue copper deposition and subsequent injury.

Clinical Manifestation

Liver disease

The liver is the initial site of copper accumulation in WD and there are several different clinical manifestations due to hepatic copper accumulation. (5,10). Hepatic manifestation can range from asymptomatic biochemical abnormalities (like the ratio of AST: ALT >2.2 and ALP: Bilirubin <4) to steatosis, acute hepatitis, Coomb's negative hemolytic anemia; chronic hepatitis, acute liver failure, and cirrhosis. Irrespective of clinical presentations, some degree of liver disease is always evident in Wilson's disease [11].

Signs and symptoms of the hepatic manifestation of WD depend upon the degree of liver injury [1,3,6] which may include- Kayser-Fleischer rings, Jaundice, hepatomegaly, splenomegaly, upper gastrointestinal bleeding, and recurrent miscarriages with acute liver failure in pregnancy often mistaken as HELLP syndrome.

Investigations may reveal- Low level of serum ceruloplasmin; elevated aminotransferases; Coagulopathy; thrombocytopenia, Coombs-negative hemolytic anemia, hepatic steatosis, hepatomegally, and splenomegaly.

Neurological manifestation

Neurological manifestation is the second most common clinical presentation of WD after liver disease and can occur earlier/parallel with or after the liver disease [12]. Neurological symptoms could be due to hepatic encephalopathy or due to copper toxicity of the brain, especially in the basal ganglia and brainstem which are very susceptible to copper toxicity.

Neurotoxicity secondary to excess neuronal copper deposition occurs via various mechanisms like mitochondrial toxicity, oxidative stress, cell membrane damage, cross-linking of DNA, and inhibition of enzymes, which eventually causes dysfunction of the blood-brain barrier and demyelination [13].

Neuropsychiatric manifestation can be very subtle in the form of insomnia and mood disorder, or very incapacitating-bradykinesia, drooling, dysarthria, hypersalivation, micrographia, hand tremors, muscle stiffness, and spasms, postural hypotension and autonomic neuropathy, personality changes, dystonia, clumsiness of the face, recurrent falls, ataxia, and chorea. Even patients can present with juvenile Parkinsonism or multiple sclerosis-like symptoms.

Diffuse weighted imaging MRI is the traditional first investigation of choice, which usually shows a positive T2 signal in the putamen and atrophic changes in T1 in the midbrain (Face of the giant panda sign) which is considered almost diagnostic of WD. MR spectroscopy (MRS) of the brain is advised by some guidelines which detect early neurological changes of Wilson disease before it becomes apparent in MRI and also can be used to follow up regarding disease progression.

Psychiatric manifestations of WD

Psychiatric symptoms may precede liver disease, parallel or present later in the course of the disease.

Children may present with the isolated psychiatric disease at a very young age which could be quite challenging to diagnose WD in the absence of liver disease. Psychiatric manifestations include behavior disorders, Schizophrenia-like disorders, cognitive disorders, and affective disease.

Eye manifestation of WD

Kayser -Fleischer rings (KF rings)

Kayser- Fleischer rings are due to the deposition of copper in the Descemet's membrane of the cornea and are accompanied by 98% of neurological disease and about 50% of liver disease and yet, it can be absent in 40% in both liver and neurological disease. Of note, Kayser Fleischer can be present in other diseases like primary biliary cirrhosis and other cholestatic diseases of the liver.

It is usually diagnosed by slit lamp examination however, Anterior segment optical coherence tomography has become a standard of care for the diagnosis and quantification of Kayser -Fleischer rings.

Kayser -Fleisher rings usually decrease in size or even disappear with the treatment of WD, and this could be a marker of a favorable response to treatment.

Sunflower cataract

Sunflower cataract is another ophthalmologic manifestation of WD due to the deposition of copper in the center of the lens causing a formation of a disc with radial strands resembling sunflowers. Like Kayser- Fleischer ring, Sunflower cataract also disappears with successful treatment of WD.

Renal Manifestations

Copper toxicity can lead to Type 1 Renal tubular acidosis (Fanconi Syndrome) and present with glucosuria, aminoaciduria, fructosuria, galactosemia, uricosuria, phosphaturia, calciuria, nephrocalcinosis, nephrolithiasis, hematuria, and tubular albuminuria.

Musculoskeletal and other systems

Wilson disease can cause a few metabolic derangements which affect muscles, bones, and joints. As a result, it can cause multiple musculoskeletal abnormalities which include- osteomalacia, osteopenia, osteoporosis, osteoarthrosis, chondrocalcinosis, chondromalacia, aseptic arthritis, proximal myopathy, hypothyroidism, hypoparathyroidisms, cardiomyopathy, cardiac conduction disease, dermopathy, dermatoses, skin pigmentation, bluish coloration of the base of nails, infertility, recurrent miscarriages, and pancreatitis.

Psychiatric manifestations of WD

Rarely, Coombs negative intravascular hemolysis could be the initial manifestation of WD, and it may not be uniformly associated with acute liver failure [2]. Other hematological manifestations can be neutropenia, thrombocytopenia, and coagulopathy because of chronic liver disease.

How to Diagnose Wilson disease

Wilson disease is a very rare disease and has a wide range of phenotypes. It affects mainly the liver and brain but can extend to other organs. We are not aware of sizable randomized controlled studies on Wilson disease and most guidelines are extrapolated from case series and expert consensus to complement the very limited data from available studies. Most of the guidelines have focused on liver disease. The three most available guidelines are the American Association for the study of liver diseases (AASLD) revised in 2008, The European Association of the study of the liver (EASL) updated in 2012 and recently the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN).

In our approach to the diagnosis, we will follow the commonalities in the three guidelines. We acknowledge that there is a recent trend to deviate from liver histology because of the invasiveness and sampling error with the progress at the same time with genetic testing and molecular analysis.

All three guidelines agreed that few clinical signs and chemical tests score high for the diagnostic pathway mainly Keyser -Fleisher ring, Coomb's negative hemolytic anemia, low serum ceruloplasmin, and 24 hours urinary copper.

Leipzig score

Is adapted by EASL and ESPGHAN. It includes KF rings, Serum ceruloplasmin, Coomb's negative hemolytic anemia, 24 hours urinary copper, Mutation analysis, liver copper in the absence of cholestasis, and neurological symptoms.

Serum ceruloplasmin

It is usually lower in WD. However, its concentration is elevated by acute inflammation, pregnancy, and estrogen supplementation. On the other hand, it is decreased in patients with neurologic Wilson's disease, malabsorption syndromes, or with severe end-stage liver disease of any etiology. Additionally, in patients with aceruloplasminemia, they do not have a copper deposition. Hence, serum ceruloplasmin alone is not sufficient to diagnose or exclude Wilson's disease [14].

Serum copper

Elevated serum copper in the presence of decreased serum ceruloplasmin indicates that non Ceruloplasmin-bound copper is elevated, this is considered a diagnostic test by EASL [14]. This can be calculated by subtracting ceruloplasmin-bound copper from the total serum copper concentration. However, non-ceruloplasmin-bound copper can be elevated in acute liver failure of any etiology, chronic cholestasis, and copper intoxication.

Urinary copper

Urinary copper >1.6 umol/24 hours is helpful in diagnosing and monitoring the treatment of WD. Low 24 hours urinary copper raises the concern about either non-compliance with treatment or overtreatment.

Hepatic parenchymal copper concentration

It is not agreed by all guidelines due to sampling error and its invasive nature.

Liver histology

Liver biopsy could be considered in situations when other differential diagnoses need to be ruled out like autoimmune hepatitis, toxic hepatitis, and steatohepatitis.

Neuroimaging

Very reasonable test to do and can clinch the diagnosis. MRI is a very sensitive and specific imaging modality in supporting the diagnosis of symptomatic and asymptomatic neurologic disease. Hyperintensity in T2 MRI in the basal ganglia especially the putamen, thalamus, and brain stem is suggestive of WD. Other imaging modalities are- Single photon emission computerized tomography (SPECT) can detect early changes, and transcranial doppler ultrasound can diagnose lenticular nucleus hyperechogenicity even before MRI.

Genetic testing

Direct molecular–genetic diagnosis might be difficult because of more than 500 mutations and in addition, most patients are heterozygotes (i.e., carry two different mutations) and needs a lot of time and resources [14].

However, in difficult cases or when other tests are inconclusive and the dominant disease is the liver or brain, or both, the molecular analysis of the ATP7B gene helps to confirm the

diagnosis and to facilitate the subsequent screening of the family members.

Acute liver failure due to Wilson Disease

All guidelines have agreed that there are some characteristic features in acute liver failure due to WD which should be investigated thoroughly and treated urgently as acute liver failure due to Wilson disease has high mortality without an emergency liver transplant. These features are-

Coombs negative hemolytic anemia, modest rise in transaminases (<200) with AST: ALT >2.2, unconjugated hyperbilirubinemia and low alkaline phosphatase with ALP/Bilirubin <4, coagulopathy refractory to vitamin K. Combination of AST: ALT of >2.2 and ALP: Bilirubin ratio of <4 has diagnostic sensitivity and specificity of 100% [15].

Most guidelines favor liver biopsy for copper quantification and histology before liver transplant.

Family screening

AASLD recommends that siblings be screened with ATP7B mutation analysis and or haplotype studies.

In the absence of the availability of genetic testing, the first-degree relative should have a slit lamp examination, serum ceruloplasmin, 24 hours urinary copper, liver function testing, and liver biopsy.

EASL also recommends ATP7B mutation analysis and where molecular analysis is not possible, EASL recommends pedigree analysis using haplotypes based on known polymorphisms.

ESPGHAN recommends physical examination, all above-mentioned blood testing in addition to ATP7B mutational analysis, and haplotyping.

Treatment

Currently, there are few medications approved for the management of Wilson's disease, which includes- D-penicillamine, Trientine, and Zinc.

D-Penicillamine

D-penicillamine acts by inducing metallothionein [16] and promotes urinary copper excretion.

It is rapidly absorbed from the gastrointestinal tract with a double-peaked curve for intestinal absorption [17,18]. If taken with a meal, its absorption is decreased overall by about 50%, hence it should be taken 1hour prior to the meal.

The adult maintenance dose is usually 750–1500 mg/day (and the pediatric dose is 20mg/kg) to be divided into twice or thrice daily dosing. Side effects include- reduced pyridoxine levels; delayed/poor wound healing (interferes with collagen cross-linking [19], mild immunosuppressive effects, early sensitivity reactions (fever/exanthemas/lymphadenopathy/neutropenia and thrombocytopenia), nephrotoxicity and lupus. About 30% of patients discontinue the treatment due to severe side effects. [20,21].

Treatment sufficiency can be monitored by measuring 24 hours of urinary copper excretion. In the long run, the efficacy of the treatment is assessed by persistent improvement in the clinical signs and laboratory markers.

After ceasing D-penicillamine for 2 days the urinary copper should be <1.6 umol/24 h for adequate therapeutic response. If excretion is >1.6 umol/24hrs after ceasing D-penicillamine may indicate non-compliance. Moreover, with effective treatment, there is the normalization of non-ceruloplasmin-bound copper concentration [22].

Multiple studies have shown the efficacy of D-penicillamine in Wilson's disease [20,23,24]. Improvement of liver function is more rapid as compared to neurological improvement. In Neurologic WD, improvement is slower and may take over three years [24].

Trientine

Trientine is a chelating agent chemically different than D-penicillamine however, acts by promoting urinary copper excretion and is considered an effective treatment for WD [25,26]. It is poorly absorbed from the gastrointestinal tract [27]. Its potency as a copper chelator, when compared to D-penicillamine, is controversial [20,28]. It is used in patients who are intolerant to D-penicillamine, yet, it has shown to be effective initial therapy, even with patients with decompensated liver disease [29,30].

Adult dosage is 900–2700 mg/day in two or three divided doses and pediatric dosage generally used is 20 mg/kg/day in two or three divided doses. Side effects include- Skin rash; Muscle spasms, sideroblastic anemia, and lupus-like reaction. Avoid co-administration with iron as Trientine also chelates iron.

Treatment adequacy is monitored by measuring 24-hour urinary copper excretion and non-ceruloplasmin-bound copper levels.

Ammonium tetrathiomolybdate

Ammonium tetrathiomolybdate (TM) prevents the intestinal absorption of copper by forming a complex with copper and reduces its cellular uptake [31].

Potential side effects include- bone marrow depression, hepatotoxicity [32], and neurological dysfunction due to excess copper removal. TM also has anti-angiogenic effects due to its extensive decoppering effect [33].

However, it is an experimental drug and is not commercially available yet.

Zinc

In the early 1960s, Schouwink used Zinc for the first time to treat Wilson's Disease [34]. Zinc acts by interfering with copper absorption in the gastrointestinal tract. It induces metallothionein in the enterocytes which preferentially binds with copper and prevents its entry into circulation [35]. Moreover, it prevents hepatocellular injury by inducing hepatocellular metallothionein which binds excess of toxic copper in the hepatocytes [36,37].

The adult dose is 150 mg elemental zinc/day, and the pediatric dose is 75mg/d in three divided doses.

Adequacy of treatment is monitored by measuring 24-hour urinary copper excretion and non-ceruloplasmin-bound copper levels. Side effects include- gastric irritation, increased lipase, and immunosuppressant effects.

It is considered less effective than chelating agents in managing WD; yet, the data are limited and uncontrolled [38].

Zinc is commonly used as a maintenance therapy however; it has also been used as the first-line therapy in asymptomatic patients as it is better tolerated. Monotherapy with Zinc in symptomatic hepatic Wilson Disease is controversial as there have been reports of hepatic deterioration when commenced on Zinc [39].

Other treatment modalities

- **Liver Transplantation:**

Indicated in the acute liver failure/decompensated cirrhosis due to WD [40]

- **Vitamin E and antioxidants:**

Vitamin E levels were found to be low in WD [41-43]. Vitamin E and antioxidants have an adjunctive role in the treatment of WD [44,45]

All three guidelines agreed on decreased copper content in diet and starting on chelating medication which includes penicillamine and trientine. AASLD and ESPGHAN advocate for adding zinc therapy.

EASL includes zinc for neurological manifestation and is also to be considered for maintenance therapy.

EASL and AASLD guidelines include tetrathiomolybdate as a potential emerging strong chelating agent although not yet approved. They also advocate for Vitamin E as a potential adjacent therapy.

All three guidelines agreed on lifelong treatment and monitoring with 24 hours hour urine copper and non -ceruloplasmin copper level. The target for 24-hour urinary copper should be 3-8umol per 24 hours. EASL recommends that 24 hours of urinary copper after two days of cessation of treatment be less than 1.6 umol per day and normalization of non -ceruloplasmin bound copper is the target on treatment which is agreed by all three guidelines. Regular blood and urine should be done twice a year for all patients on treatment.

EASL and AASLD recommend liver function testing, serum copper, serum ceruloplasmin, urinary copper, and physical, exam twice yearly and urinary copper once a year.

All three guidelines advocate for liver transplant in decompensated cirrhosis but not for neuropsychiatric disease.

EASL and ESPGHAN recommend using the revised Kings College Wilson Disease Prognostic Index score (Bilirubin, AST, INR, WBCs, and Albumin) to assess patients' prognosis and mortality. A score of 11 should be considered for a transplant.

AASLD and EASL recommend treating pregnant women as other patients, although teratogenicity is a concern, the benefit outweighs the harm. Penicillamine could be reduced in the third trimester as it causes delayed wound healing and can cause a decrease in fetal copper supply. It has been shown that patients who are successfully treated can get pregnant [46,47]. Regarding contraception, only barrier/progesterone only preparation/spermicidal agents are indicated as estrogen can interfere with biliary copper excretion [48].

AASLD also recommends reducing the dose of chelator before surgery because of the concern of poor wound healing.

All guidelines recommend following up on patients with cirrhosis for hepatoma and cholangiocarcinoma surveillance despite the reduced incidence of malignancy in WD with cirrhosis.

Patient in the vignette

The patient was admitted to the high-dependency unit for stabilization and close monitoring. She was treated with intravenous thiamine, albumin infusion, fresh frozen plasma, vitamin K and careful saline infusion.

Further investigations:

- 24-hour urinary copper was 6 umol
- Serum ceruloplasmin was almost undetectable
- Transjugular liver biopsy showed extensive micro and macrovascular steatosis, extensive glycogen inclusion bodies, periportal fibrosis, and extensive fatty infiltration
- Hepatic copper was 300 mcg per gram of dry weight (normal values are less than 50mcg per gram of dry body weight)
- MRI did not show any T1 or T2 changes
- Genetic Testing confirmed Homozygous mutation for H1069Q (Results received after about 3 months)
- Remaining Hepatitis Auto-immune Panels: Anti LKM1 Ab/Ant SM Ab/AMA- Negative

Hence, acute liver failure due to Wilson's disease was confirmed. A geneticist was involved to counsel the first-degree relative for genetic testing and mutational analysis.

The patient was listed for a liver transplant. While waiting for a transplant, she was started on D-penicillamine. However, it was stopped due to the development of skin reaction and lymphadenopathy, and it was changed to zinc which was tolerated very well by the patient. Three weeks later, the patient received a cadaveric liver transplant.

Subsequently, the patient improved and was discharged home 4 weeks later for regular follow-up with the transplant hepatologist and WD specialist.

Conclusion

Wilson disease is a genetic disease with multiple phenotypes and variable clinical presentation. It mainly affects the liver and the brain although any other organ can be affected. It can present acutely or can be primarily progressive and has got significant mortality if not diagnosed and treated in a timely manner.

Because of its rarity, there are only very few small non-randomized controlled studies. Moreover, guidelines are few and based mainly on few clinical cases and expert consensus. Diagnosis needs a high index of clinical suspicion, a thorough physical exam, and a cascade of uncommon investigations. Treatment is life-long and a liver transplant can cure liver disease.

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