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Case Report

Wilson's Disease, Etiology and Treatment

Feryal Rada[1]

1. Department of Clinical Biochemistry, College of Pharmacy, Al-Nahrain University, Baghdad, Iraq.

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ABSTRACT

Background: Wilson's disease is a chronic, gradually developed disease. Its concern is as an autosomal recessive inherited metabolic disorder. The deposition of copper in many organs, such as the liver, eyes, kidneys, and basal ganglia in the brain is the main cause of this disease.

Case Presentation: A 13-year-old male patient was admitted to the Children's Department in Al-Kadhimae Hospital, Iraq with chief complaints of vomiting, abdominal pain, pallor, icterus, fever, and chest complaints. The laboratory data showed elevated levels of total bilirubin, alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase and reduced levels of globulin (α2 and β), ceruloplasmin, and serum copper. Additionally, high urine copper was reported. After that the patient was diagnosed with Wilson disease and treated with D-penicillamine drug (copper chelation) and zinc acetate tablet.

Conclusion: Wilson's disease is a metabolic error of copper, if undetected and untreated immediately, it causes declining in the function of many organs, such as the liver and brain.

*** Corresponding Author:**
Feryal Rada, Professor.
Address: *Department of Clinical Biochemistry, College of Pharmacy, Al-Nahrain University, Baghdad, Iraq.*
E-mail: *fermsc33@yahoo.com*

Introduction

Copper is a crucial metal for many processes in the body, such as the improvement of the brain, energy output, connective tissue growth, melanin formation, and others. Wilson's disease is a metabolic disorder related to the defect in the transport and elimination of copper. It is inherited by autosomal recessive. The symptoms of this disease vary depending on the amount of copper in which organ deposits more. It ranges from hepatic to neurological or psychological symptoms or may be asymptomatic with cirrhotic biochemical changes of the liver [1].

Moreover, the increased levels of interleukins and other inflammatory cytokines that may accompany Wilson disease may affect other organs, such as the cardiovascular system [2, 3].

The hepatic symptom is mostly found in children and adults with Wilson disease and begin with hepatitis that may be confused with other types of hepatitis, such as viral hepatitis, and progress to liver cirrhosis and may be accompanied by neural degeneration of the brain (lenticular nuclei) that lead to a state called hepato-lenticular degenerative state [4].

Neurological symptoms of Wilson's disease involved dysarthria, dystonia, dementia, and defect in cognition, and behavior. The most common symptom of movement disorder occurring in Wilson's disease is tremor, which appears early and latterly progresses to spastic dystonia and reflects a lenticular degeneration [5]. Many studies found that the neurological symptoms were prolonged from onset to diagnosis compared to hepatic symptoms [6].

While the Kayser-Fleischer ring is a feature of accumulation of copper in the eyes [7], kidney or gastrointestinal defects are less common in Wilson's disease. Copper accumulation inside the body occurs either due to the decreased ceruloplasmin level (α2 globulin), which is responsible for copper transport and conserving hepatic copper level, or due to mutation in the adenosine triphosphate 7B (*ATP7B*) gene that is present on chromosome 13q and lead to encoded of nonfunctional protein ATP7 base (transporter protein) that regulate the integration of copper with apoceruloplasmin to form ceruloplasmin and then excreted into the bile. Another mechanism reported that the ATP7 base is localized in biliary canaliculi and accelerates copper elimination [8].

This mutation caused impairment in the copper transport by liver lysosomes. After that it leads to a decrease in the hepatic elimination of copper into the bile causing more deposition of the copper in the liver and more cell damage. Then, necrotizing hepatocytes release copper into the blood and accumulate in other organs, such as the eyes, kidneys, and brain, especially the basal ganglia [9].

Diagnosis of distrusted cases of Wilson's disease depends on many factors summarized in three steps by Aggarwal and Bhatt and illustrated in Figure 1. The features of the first step lead to the second step and so on until a definite diagnosis of the disease is made [10]. Another approach used for the diagnosis of Wilson's disease is called the Leipzig scoring system summarized in Table 1 [7]. It depends on many factors and tests to confirm the diagnosis, at which a score of 4 or more is considered as a probable diagnosis of this disease. Leipzig's scoring system was documented at the eighth international conference on Wilson's disease and Menkes disease. A revised Leipzig scoring system was documented by Nagral et al. It involves extra points suggested for diagnosis of Wilson´s disease, which are typical brain changes presented on magnetic resonance imaging (MRI) and a positive family history of deaths due to hepatic or neurological complications [11].

Treatment of Wilson's disease involves the use of chelating agent drug, such as D-penicillamine, or Trientin, which chelate copper from the body and eliminates it by the urine. Additionally, zinc acetate tablets can be used with the above drugs and act by inhibiting the intestinal absorption of copper contained in foodstuff [12]. Many approaches for diagnosis and prognosis of Wilson disease are predominant by the clinical analysis of liver functions, and copper levels in serum and urine. Moreover, the genetic detection of *ATP7B* mutation is the most definitive diagnosis for Wilson's disease but it is costly test [13]. This report was designed to outline the details of causing and treatment of Wilson's disease to decrease the incidence of misdiagnosed cases.

Case Presentation

A 13-year-old male patient was admitted to the Department of Children in Al-Kadhimae Hospital, Iraq with chief complaints of vomiting, abdominal pain, pallor, icterus, fever, and chest complaints. The laboratory data showed elevated levels of total bilirubin, alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase and reduced levels of globulin (α2 and β),

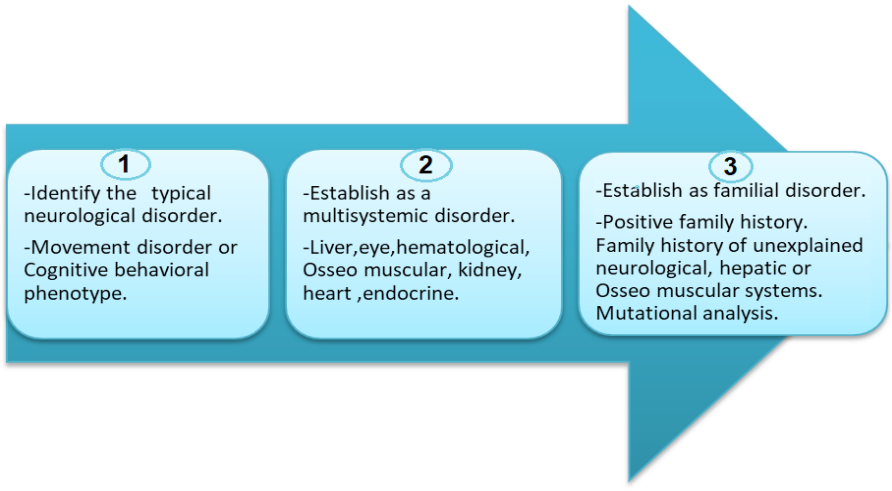

Figure 1. Clinical approach for diagnosis of Wilson's disease

ceruloplasmin, and serum copper. Additionally, high urine copper was reported, see Table 2.

The patient and his family were urban, had a negative family history of Wilson disease, and had negative consanguinity of the patient's parents. Initially, the patient was sent for hepatitis C virus-ribonucleic acid (RNA) detection, and the result was negative for hepatitis C virus-RNA viral load. The abdominal ultrasound scan reported early portal hypertension at which the liver is mildly enlarged in size, and coarsening, with no evidence of mass lesion, no intrahepatic biliary tree dilation, and spleen is slightly enlarged. The ophthalmologist reported no evidence of Kayser-Fleischer ring and a brain MRI report showed no neurological deficit.

After that the patient was diagnosed with Wilson disease and treated with a D-penicillamine tablet (250 mg) four times daily that made chelation of copper and excreted with it in the urine. A zinc acetate tablet (25 mg) two times daily is also used with the above drug to diminish the absorption of copper from the intestine. For monitoring and adjusting the doses of drugs, the patient sends monthly for serum and urine copper measurements. Moreover, the patient was informed to avert the intake of diets with high copper levels, such as chocolates, nuts, and others.

Discussion

The disease associated with inherited defect in copper metabolism is called Wilson's disease commonly recognized at age 7-35 years. Copper deposits in many organs especially the liver, brain, eye, and other. Thereafter, it causes defects in the function of these organs and cellular toxicity that may lead to elevated levels of interleukins and other cytokines of inflammation [9].

In Iraq, the prevalence of Wilson's disease approximately was 1:30,000, and the incidence of heterozygotic carriers nearly was 1:90. No specific region exists for the presence of Wilson's disease in Iraq, it can appear in cities or villages. Moreover, the initial symptoms of the disease in Iraq have a resemblance to chronic liver diseases and are assumed for all inexplicable cases of liver disease. Utmost of the patients initially revealed hepatic clinical features, such as jaundice or hepatosplenomegaly [14].

The patient and his family in this case report were urban, have a negative family history of Wilson's disease, and have negative consanguinity of the patient's parents. The presence of consanguineous parents increases the incidence of Wilson disease because this disease is inherited autosomal recessive and this inheritance increases with offspring of consanguineous marriages [15].

Many situations may enhance the incidence of Wilson's disease, such as family history, consanguineous parents' state, ambience factors (air, soil, water, food, or others) affected by industrial west products, cooking in copper tools [16]. Likewise, the misdiagnosis of psychiatric patients as teenage variation [17].

In this medical case, the outcome of liver function tests reported high levels of total bilirubin, transaminase, and alkaline phosphatase enzymes. Moreover, a high level of serum and urine copper and a low level of serum ceruloplasmin were determined. All of these features are consis-

Table 1. Leipzig score used for detection of Wilson's disease

Typical Clinical Symptoms and Sign		Score
Kayser-Fleischer rings	Present	2
	Absent	0
Neurologic symptoms or typical abnormalities at brain MRI	Severe	2
	Mild	1
	Absent	0
Serum ceruloplasmin (g/L)	>0.2 (normal)	0
	0.1-0.2	1
	<0.1	2
Coombs-negative hemolytic anemia	Present	1
	Absent	0
Liver copper (in the absence of cholestasis) (µmol/g)	>4	2
	0.8-4	1
	<0.8 (normal)	-1
	Rhodanine-positive granules*	1
24 hr. Urinary copper (in the absence of acute hepatitis) (xULN)	Normal	0
	1-2	1
	>2	2
	Normal, but >5 xULN after D-penicillamine	2
Mutation analysis	On both chromosomes detected	4
	On one chromosome detected	1
	No mutation detected	0

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MRI: Magnetic resonance imaging; ULN: Upper limit of normal.

*If no quantitative liver copper available.

Notes: Total score (evaluation): ≥4: Diagnosis established, 3: Diagnosis possible and more tests needed, ≤2: Diagnosis very unlikely.

tent with the symptoms documented in Leipzig scoring system for diagnosis of Wilson's disease.

Kayser-Fleischer ring was not observed in this case and this feature is consistent with the many studies, which they documented that the presence of the Kayser-Fleischer ring was definite for the utmost of patients with neurological or neuropsychiatric manifestations and not definite for hepatic manifestations [18]. Features of hemolytic anemia are observed in the test of blood pictures and slightly enlarged spleen, and these features are concomitant with many cases of Wilson's disease [19].

Many FDA and liver disease guidelines approved the usage of penicillamine drug for curing Wilson's disease, cystinuria, and critical rheumatoid arthritis. Penicillamine has an ability to make chelation with metals like copper, lead, and mercury and with cysteine giving a product with higher water solubility that is eliminated easily by the urine and prevents the formation of stones [20].

Table 2. Laboratory analyses of the patient

Parameter	Results	Reference Range
Serum copper (µg/dL)	90	80-150
Urine copper (µg in 2000 mL urine/day)	225	<40
Serum ceruloplasmin (mg/dL)	2	Male: 15-30 Female: 16-45
Serum ALT (U/L)	63	10-49
Serum AST (U/L)	39	<34
Serum ALP (U/L)	293	46-116
Serum total bilirubin (mg/dL)	1.5	0.2-1.0
INR	1.08	0.9-1.0
PT (s)	14.5	11-15
PTT (s)	32	26-36

Abbreviations: ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase; INR: International normalization ratio; PT: Prothrombin time; PTT: Partial thromboplastin time.

Penicillamine is present as a 250 mg tablet or capsule. Its t ½ was 4-6 days, protein bounding percent was 80%, and eliminated by urine. In adult patients, the daily dose was 750-1500 mg divided into 3 or 4 doses. While in pediatric patients, the daily dose was 20 mg/kg divided into 2 or 3 doses.

Penicillamine is properly taken on a fasting stomach, 1 hour earlier than mealtimes, or 2 hours later than mealtimes. Moreover, it is preferable to intake separately from other drugs or food. Other medications can be prescribed with penicillamine, such as zinc acetate 25-50 mg daily and pyridoxine 25-50 mg daily [21]. For the first six months of Wilson disease treatment, the patient needs follow-up every 2 weeks to monitor the adverse events and doses of drugs by making complete blood analysis, and urine analysis to measure copper level in the urine [22].

Wilson's disease can be treated by another approved drug, Trientine (triethylene tetramine dihydrochloride), which is used for patients with penicillamine warning because penicillamine may cause earlier immune-related hypersensitivity and serious adverse events. It has a chelation activity for copper and forms a complex that is eliminated by urine and can decrease the absorption of copper from the intestine. For children, a daily dose of 500-750 mg is divided into 2-4 doses, taken 1 hour earlier or 2 hours later than the mealtimes because it is less absorbed in the presence of food [23].

Concerning the adverse events of drugs, many studies reported that Trientine has lower side events than penicillamine and can be used for initial treatment either alone or with zinc acetate. The main adverse event of drugs that reduce the copper level in the blood is sideroblastic anemia.

Trientine adverse events include dyspepsia, muscle spasms, and dystonia. Whereas penicillamine adverse events include nephritis and arthritis [24], neurological events , fever, cutaneous eruption, neutropenia, and thrombocytopenia. Therefore, penicillamine is not used to treat patients with neurological origin of Wilson disease [25]. Zinc acetate has limited adverse event, especially neurologically types but cannot be used as a single therapy because it is not efficient for the chelation of copper from the body, which declines hepatic worsening [26].

Conclusion

Wilson's disease is an inherited disease affecting on metabolism of copper leading to the deposition of copper in many organs and causing symptoms mainly of hepatic origin or neural origin or both. Earlier diagnosis is crucial to prevent further deterioration of organs and depends on many diagnostic tools and clinical parameters that are documented in the Leipzig scoring system. It can be treated by many guidelines depending on the state and response of the patient and requires monthly follow-up to monitor the doses and the type of drugs,

limit the adverse events, and evaluate the function of an organ, especially liver.

Ethical Considerations

Compliance with ethical guidelines

All ethical values are considered in this study. The author obtained all appropriate patient consent forms that related to the patient and his family's agreement to publishing his clinical information with the secrecy of his name and identity.

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Conflict of interest

The author declared no conflict of interest.

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