Clinical Manifestations with Different Treatment Protocols for Iraqi Patients with Wilson's Disease

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Abstract

Wilson disease (WD) is an autosomal-recessive disorder of copper metabolism caused by mutations in the *ATP7B* gene. ATP7B is also essential for biliary excretion of copper when cytoplasmic levels are high. Dysfunction of ATP7B therefore leads to accumulation of copper in the liver giving rise to cellular damage and disease, and the release of non-ceruloplasmin bound copper into the systemic circulation. Clinical presentation of Wilson disease can vary widely; therefore diagnosis is not always straight forward. Wilson disease is not just a disease of children and young adults, but may present at any age. The key features of Wilson disease are liver disease and cirrhosis, neuropsychiatric disturbances, Kayser–Fleischer rings, and acute episodes of hemolysis, often in association with acute liver failure. Diagnosis is particularly difficult in children and in adults presenting with active liver disease. None of the available laboratory tests is perfect and may not be specific for Wilson disease. To overcome the diagnostic challenge, several clinical signs (Kayser–Fleischer rings(KF.), neurologic symptoms) and laboratory features (copper in serum, urine, liver; serum ceruloplasmin ; genetic testing) are scored 0 (absent) to 2 (present) and the Leipzig score is calculated. If the score is >4, the diagnosis of Wilson disease is very likely. For asymptomatic siblings of index patients, mutation analysis is the most reliable approach.

Keywords: *WD.(Wilson disease), ATP7B gene, Kayser–Fleischer rings(KF); toxicity; Iraqi patients*

Introduction

Wilson disease (WD) is an autosomal-recessive disorder of copper metabolism caused by mutations in the *ATP7B* gene [1,2]. It presents in childhood, adolescence or adulthood with a wide range of clinical manifestations. The disease prevalence has previously been estimated as 1 in 30,000 [3,4], but some recent analyses have suggested a genetic prevalence of 1 in 7,000 [5,6].

Copper is absorbed from the stomach and duodenum, taken up by the liver, and secreted by the liver into the systemic circulation bound to ceruloplasmin [7]. ATP7B transports copper through the trans-Golgi network in hepatocytes before it is incorporated into apoceruloplasmin which is secreted as holoceruloplasmin. ATP7B is also essential for biliary excretion of copper when cytoplasmic levels are high. Dysfunction of ATP7B therefore leads to accumulation of copper in the liver giving rise to cellular damage and disease, and the release of non-ceruloplasmin bound copper into the systemic circulation.

Copper also accumulates and is associated with cellular damage and disease in other organs, most notably the brain [8]. The extent to which disease in the brain relates to high levels of free circulating copper and/or underlying dysfunction in neurons, which also express ATP7B [9], is not clear.

Originally referring to this condition as progressive lenticular degeneration, Samuel Alexander Kinnier Wilson first described the combination of neurologic disease with cirrhosis in 1912. He recognised that psychiatric manifestations were common but stated that the cirrhosis was rarely symptomatic during life [10].

Barnes and Hurst subsequently reported in 1925 that WD can present with symptomatic liver disease in the absence of neurologic features [11]. It is now accepted that symptomatic involvement of the liver or brain can occur in isolation or in combination at presentation. Asymptomatic, or pre symptomatic, liver and brain disease in siblings can be identified and studied through family screening [12].

A working party at the 8th International Meeting on WD in Leipzig in 2001 revised the phenotypic classification and differentiated cases into neurologic (N), hepatic (H) or other (O) presentations [14]. Any patients in whom neurologic and/or psychiatric symptoms are present at the time of diagnosis are classified as a neurologic presentation. They are then subdivided into those with (N1) or without (N2) symptomatic liver disease, or not investigated for liver disease (Nx). This classification requires a detailed neurologic examination to exclude neurologic symptoms at diagnosis and a liver biopsy to confirm the absence of marked liver disease. Hepatic presentations are subdivided into acute (H1) or chronic (H2) depending on the presence of acute jaundice due to hepatitis and/or hemolysis in a previously healthy subject (H1), or any type of chronic liver disease, with or without symptoms (H2). The presence of any biochemical evidence of liver disease indicates a hepatic (H), as opposed to other (O), presentation.

The relative frequency of neurologic and hepatic presentations has been examined in several large cohorts over the last three decades. The proportion of patients that would, under the 2001 classification, be referred to as neurologic, either N1 or N2, ranges from 37% to 80% [13]. While there is likely to be some variation in phenotype between individual populations, comparing these cohorts may be problematic for other reasons.

Firstly, selection bias may affect the relative frequency of different presentations in individual cohorts; centres of excellence for neurology are likely to report a higher number of cases with neurologic involvement. Secondly, neurologic and hepatic features may be subtle or identifiable only through specific investigations. The classification of presentations may therefore have been inconsistent in some cohorts, especially before the introduction of rating scales for WD such as the Unified Wilson's Disease Rating Scale in 2008 and the Global Assessment Scale in 2009 [15,16].

The majority of neurologic presentations consist of a movement disorder associated with bulbar symptoms. The movement disorder is usually characterized by tremor ,dystonia or parkinsonism. These 'core' movement disorders often occur in combination and may initially be subtle. Bulbar symptoms consist of dysarthria, drooling and/or dysphagia. There are a range of additional neurologic features, including cerebellar dysfunction, chorea, hyperreflexia, seizures and cognitive impairment, which can also co-exist.

Material and Methods

A total of 42 Iraqi patients diagnosed with Wilson disease (20 males and 22 female) with age range between 10 – 20 years, who attended the Rare Disease clinic of the Al-Imaamin AL-Kadhmian medical city Hospital – Baghdad/Iraq .The diagnosis of WD was established by clinical features ,low serum ceruloplasmin and copper and increased 24 h urinary copper excretion, Liver function tests.

Inclusion Criteria

· Patients age from 10-20 years old.

· Asymptomatic patients with WD with hepatic involvement diagnosed by screening method.

· Patients referred for unexplained elevation of liver enzymes and $^{+}$ve Leipzig scale score.

· Patients with positive family history of Wilson disease.

Exclusion Criteria

.Patient >20 years old.

· Patients with other co-moribids.

· Pregnancy and breast feeding.

· Patients allergic to any of the study medications.

The eligible 42 patients were allocated into three groups:

Group (1); include **23** asymptomatic Iraqi patients with WD and hepatic involvement diagnosed by screening method treated with Dietary Supplement: **Zinc acetate**(100-150 mg/ d) in 2-3 divided dose for 90 days.

Blood tests will be performed(before and after the treatment): ALT, AST, ALP, Ca., s.Albumine, Total Albumin, PT,IRN, s.Copper,s.Ceruplasmine,24-hr. urine copper.

Group (2); included **10** Iraqi Patients referred for unexplained elevation of liver enzymes and (+ve) Leipzig scale score treated with **d-PCA** (20mg/kg/d for Ped.,750-1500 mg for adult) for 90 days**.**

Blood tests will be performed (before and after the treatment): ALT, AST, ALP, s.Albumine, Total Albumin, PT,IRN, s.Copper,s.Ceruplasmine,24-hr. urine copper.

Group (3); included **9** Iraqi patients referred for unexplained elevation of liver enzymes and (+ve) Leipzig scale score treated with **Trientine** (20mg/kg/d for Ped.,1500-2500 mg for adult) for 90 days.

Blood tests will be performed(before and after the treatment): ALT, AST, ALP, s.Albumine, Total Albumin, PT/IRN, s.Copper,s.Ceruplasmine,24-hr. urine copper.

Results

Patients in this study were classified according to clinical manifestations into the following groups: pre-clinical (pre symptomatic, identified by family screening),hepatic manifestations (H1:acute hepatic WD;H2:chronic hepatic WD) and neurological manifestations (N1:associated with liver disease;N2: not associated with WD) as mentioned in table (1). No significant p.value were identified between these three groups.

Table (1) Clinical manifestations between the study groups.

	(D-Penicillamine)	(Trinetin)	(Zn-Acetate)	P.value
PRE-CLINICAL Yes	7 (70%)	6 (67%)	16 (70%)	0.9846 NS
No	3 (30%)	3 (33%)	7 (30%)	
Hepatic Manifestation - H1: Acute Hepatic	7 (70%)	3 (33%)	17 (74%)	0.0895 NS
- H2:Chronic Hepatic	3 (30%)	6 (67%)	6 (26%)	
Neurological Manifestation : -N1: Associated with liver disease	7 (70%)	6 (67%)	10 (43%)	0.2343 NS
-N2: Not associated with liver disease.	3 (3%)	3 (33%)	13 (57%)	

NS=Non-significant, * significant at p value ≤ 0.05, ** significant at p value ≤ 0.01

Discussion

Patients in this study were classified according to clinical manifestations into the following groups: pre-clinical (pre symptomatic, identified by family screening),hepatic manifestations (H1:acute hepatic WD;H2:chronic hepatic WD) and neurological manifestations (N1:associated with liver disease;N2: not associated with WD). The clinical presentations of patients with WD can involve multiple organ systems and vary from subtle to life-threatening. Diagnostic testing for WD is essential for patients of any age with unexplained hepatic, neurologic, or psychiatric abnormalities. Diagnostic testing algorithms for WD, the Leipzig scoring system because of its quantitative, systematic nature[17]. Pre symptomatic patients identified through genetic screening: Chelators and zinc have been proven effective in preventing development of symptoms or laboratory test abnormalities of WD in pre symptomatic patients identified by testing for WD in a pro band's first-degree relatives. Zinc is preferred treatment, based on its low cost and minimal adverse event profile[18] . Patients with hepatic manifestations: WD patients with acute liver failure, notably those with classic Wilsonian acute liver failure, do not spontaneously recover and require urgent liver transplantation for survival (despite occasional single patient reports to the contrary) [19,20-22]. These patients must be transferred to a transplant center for management. In contrast, WD patients with or without evidence of advanced hepatic WD should be treated with a chelating agent[23] .Such patients typically respond to therapy in the first 2_6 months, and progressive improvement can continue for up to 12 months. Responses often include improvement of complications of portal hypertension in cirrhotic patients. Thus, whenever possible, patients with decompensated cirrhosis should be observed for evidence of a therapeutic response to chelation prior to performing liver transplantation[22]. Patients with neurologic signs and symptoms: The initial goal of chelation or zinc therapies is elimination of excessive total body copper causing end-organ dysfunction. The subsequent goal is to prevent re accumulation of toxic concentrations of total body copper using maintenance therapy. Rapid removal of excessive copper from the central nervous system must be avoided, as it can worsen symptoms and result in irreversible neurologic deficits[18]. In contrast, gradual removal of copper from the central nervous system, achieved by using lower doses of D-penicillamine or Trientine, has a higher probability of resolving signs and symptoms long term. Patience in using lower doses and de coppering slowly is key. Improvement in neurologic symptoms is a slow process and may require up to 3 years after starting chelation therapy. Unexpectedly, zinc therapy has also been implicated in the worsening of neurologic WD. A recent series reported neurologic worsening in 9.1% of patients treated with D- penicillamine, 8.8% on Trientine, and 7.3% on zinc salts [19]. Approximately 10% of WD patients treated with either D- penicillamine or zinc had neurologic worsening during the first 6 months of therapy [24].Since liver transplantation rapidly restores biliary copper excretion in WD, it also markedly accelerates depletion of total body copper. Thus, liver transplantation is relatively contraindicated for active neurologic WD prior to removal of substantial amounts of brain copper. In selected patients with neurologic WD, liver transplantation has reversed the neurologic deficits[25].

Conclusion

The WD clinical phenotype includes hepatic, neurological, and psychiatric manifestations that can present with a wide range of severity and can be combined in unpredictable ways. Copper accumulation in WD is due to a genetic defect affecting the hepatic copper transporter ATP7B, the Wilson ATPase, but clinical and experimental evidence indicates that genetic mutations are just one component of the pathogenesis and clinical presentation of WD.Specifically, two types of evidence indicate there are likely other factors that can affect disease presentation: first, the lack of convincing genotype-phenotype correlation; second, several case reports indicating that homozygous twins with the same ATP7B mutation can present with different phenotypes. Diagnostic tests include serum ceruloplasmin, neurologic exam, and slit-lamp examination for Kayser Fleischer rings. However, additional testing for basal 24-hour urinary copper excretion, hepatic copper concentration

,or sequencing of the ATP7B gene may be required for diagnosis. Family screening is recommended for first-degree relatives of patients and may detect the disease prior to the appearance of signs or symptoms. With improved methods of diagnosis, WD has become an important disease in childhood. The hepatic manifestations are varied, and the neuropsychiatric manifestations may be subtle or nonspecific. Treatment needs to be individualized; comprehensive follow-up is important for all patients. Scoring systems may assist with diagnosis or clinical decisions relating to need for liver transplantation.

Clinical presentation may be chronic liver disease, acute liver failure with distinctive features (ALF-WD) or it may be "silent" liver disease. A broad spectrum of neurologic or psychiatric conditions can occur in childhood or adolescence. While hepatic presentation is more common than neurologic in the pediatric population, manifestations of WD are characteristically multi systemic. WD can resemble autoimmune liver disease clinically. Particularly when there is inadequate response to immunosuppression therapy in autoimmune hepatitis, every effort must be made to ensure that a diagnosis of WD is not being missed.Current management includes chelators like D-penicillamine or trientine; zinc has multiple effects exclusive of chelation.As an oral chelator, D-penicillamine is specified as a first-line drug for use in symptomatic WD patients according to recommendations published by the European Association for the Study of Liver (EASL) (Grade II-1, B, 1) and the American Association for the Study of Liver Diseases (Class I, Level B).

Ethical Clearance: The Research Ethical Committee at scientific research by ethical approval of both MOH and MOHSER in Iraq

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