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Wilson's Disease in Children (About 52 Cases): Diagnostic and Therapeutic Difficulties

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Abstract **Original Research Article**

Wilson's disease is an autosomal recessive inherited metabolic disease. It is characterized by toxic accumulation of copper in the body, mainly in the liver, central nervous system, and cornea. The aim of this work was to report our service's experience regarding the diagnostic, therapeutic, and evolutionary management of Wilson's disease. We conducted a descriptive and analytical retrospective study at the Pediatric B department of the Mohammed VI University Hospital Center in Marrakech over a period of 13years. Fifty-two cases of Wilson's disease were identified, with of which the average age at diagnosis was 10 years with extremes varying between 5 and 15 years. A male predominance of 54% was found, with a sex ratio of 1.15. Consanguinity was present in 32 cases. Clinical signs at admission were predominantly cholestatic jaundice in 38% of patients. Neurological signs, within an extrapyramidal syndrome, were found in 18 patients. Kayser-Fleisher rings were found in 35 children. Five patients were diagnosed through family screening. Biologically, a decrease in prothrombin levels at the time of diagnosis was found in 46 patients with cytolysis in 50 cases. Serum ceruloplasmin level was lowered in 46 patients, serum copper level was decreased in 41 patients, and urinary copper excretion was increased in 49 patients. Hemolytic anemia was found in 14 patients. Abdominal ultrasound revealed signs of portal hypertension on cirrhotic liver in 26 patients. Genetic testing was performed in 12 patients, revealing six different homozygous mutations in the ATP7B gene, except for 2 patients in whom no mutations were detected. Regarding treatment, D-Penicillamine is the cornerstone of Wilson's disease treatment, initiated in all patients along with adjunctive therapy and a low-copper diet, except for patients diagnosed through screening who were directly started on zinc acetate.

Keywords: Copper metabolism - D-Penicillamine - Copper test.

INTRODUCTION

Wilson's disease is a copper toxicosis resulting from an anomaly in the biliary excretion of copper, leading to excessive copper deposition in the body, initially with a hepatic tropism before affecting other organs. It is a rare genetic disorder inherited in an autosomal recessive manner. The disease can be observed in children typically after the age of 3 years. Its positive diagnosis relies on a combination of factors. The clinical presentation is varied and nonspecific, ranging from asymptomatic discovery to fulminant hepatitis. Without treatment, copper accumulation in the liver can cause damage that may jeopardize prognosis, highlighting the importance of adequate and early management.

In this article, based on our study, we aim to illustrate the epidemiological, clinical, therapeutic, and evolutionary aspects of this condition.

MATERIALS AND METHODS

This work is based on a descriptive and analytical retrospective study conducted in the Pediatric B department of the Mohammed VI University Hospital Center in Marrakech. Fifty-two cases were included in this study over a period of 13 years, from January 2008 to December 2020.

RESULTS

The average age at diagnosis of the disease in our patients was 10 years, with age ranging from 5 to 15 years. Consanguinity was found in 32 cases, accounting for 63%. Gender distribution showed a male predominance of 54%, with a sex ratio of 1.15. Among the medical history of our patients, we noted the presence of mental retardation in one patient. The history of similar cases or chronic liver disease in siblings was found in 9 patients, accounting for 17% of cases.

The most common reason for consultation was cholestatic jaundice in 22 cases, accounting for 47%, followed by neurological signs in 18 patients, including dystonia, tremors, and gait disturbances. Edematous syndrome was reported in 6 cases, and gastrointestinal bleeding in 2 patients. Five patients were diagnosed through family screening.

Clinical signs at admission were predominantly jaundice in 38% of patients. Portal hypertension features, including ascites, were found in 21 patients, and splenomegaly in 17 patients, accounting for 32%. Hepatomegaly was observed in 15 patients. Generalized edematous syndrome was found in 6 patients. Fulminant hepatitis was the initial expression of the disease in 2 cases. Neuropsychiatric examination revealed the presence of an extrapyramidal syndrome in 18 patients and learning difficulties in 16 patients. Ophthalmological examination using a slit lamp, performed in all our patients, revealed the presence of Kayser-Fleischer rings in 35 patients, accounting for 68%.

Hepatic involvement	Number of cases	Percentage (%)
The jaundice	20	38 %
Ascites	21	40 %
Generalized edematous syndrome	6 .5	11.5 %
Hepatomegaly	15	30 %
Splenomegaly	17	32 %
Epistaxis	5	9 %
Fulminant hepatitis	2	4 %
Neurological involvement	**Number of cases**	**Percentage (%)**
Tremors	12	24 %
Gait disturbances	12	24 %
Dystonia	11	22 %
Dysarthria	10	20 %
Academic difficulties	16	30 %
Ocular involvement	**Number of cases**	**Percentage (%)**
Kayser-Fleischer ring	35	68 %

Table 1: Clinical signs of Wilson's disease

A decrease in PT (prothrombin time) below 50% at the time of diagnosis was found in 33 patients (63% of cases), between 50% and 70% in 15 cases, while PT was normal in the other 4 patients. Transaminases were normal in 4 patients. Moderate cytolysis was noted in 18 patients and very high in 30 patients, accounting for 58%. As for the copper assessment; Serum copper levels were indicated for all our patients, but due to its unavailability, it was only performed in 18 patients. Thus, serum copper levels were found to be decreased in 14 patients, accounting for 79%. Serum ceruloplasmin levels were decreased in 46 patients, or 88%, and normal in the remaining 6. Urinary copper excretion was increased in 49 patients, accounting for 94%, and normal in the other 3 patients. Hemolytic anemia was found in 14 patients (27%), with 11 undergoing the Coombs test, which returned negative.

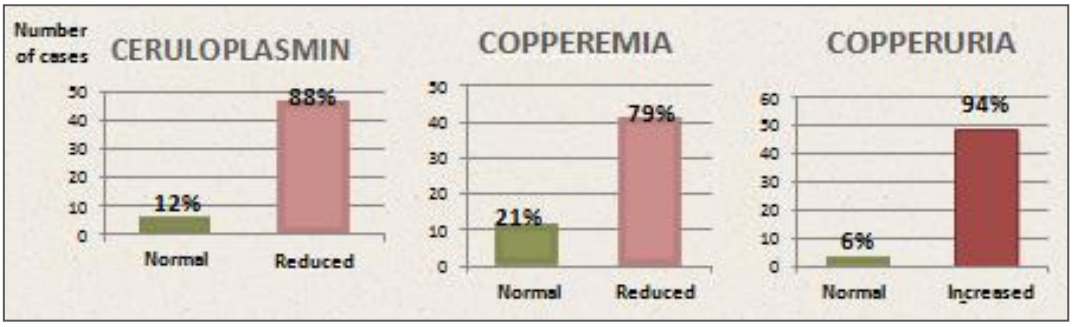

Table 2: Copper profile in our study

Abdominal ultrasound revealed signs of portal hypertension on cirrhotic liver in 26 patients, accounting for 50% of our patients. Digestive endoscopy, performed in 20 patients, showed esophageal varices in 96% of them, or 19 patients. Brain MRI conducted in the 18 patients with neurological signs revealed T2 hyperintensity and flair of the central gray nuclei. Liver biopsy was not performed in any patient in our series.

Genetic study of ATP7B was conducted in 12 patients meeting the clinical and biological diagnostic criteria of Wilson's disease, with a Leipzig score higher than 4. Ten patients exhibited six different homozygous mutations of the ATP7B gene. However, no mutation was detected in the promoter and exon regions of the ATB7B gene in the other two patients. The most frequently observed mutations were missense mutations, found in 4 patients. Other mutation types included two nonsense mutations, two splice mutations, and two frameshift mutations.

All our patients were initially treated with D-Penicillamine in combination with adjunctive therapy and a low-copper diet, except for those diagnosed through screening, who were directly started on zinc acetate. Two patients had an indication for liver transplantation due to fulminant hepatitis with hepatic encephalopathy but died before they could undergo the procedure. Among patients treated with D-Penicillamine, 16 of them (31%) required a therapeutic change to zinc acetate due to poor compliance in 11 patients and unavailability of the treatment in the Moroccan pharmaceutical market in the remaining 5 patients, after passing the initial phase of the disease. Trientine was indicated for one patient who did not respond to either D-Penicillamine or zinc acetate but was unavailable. Treatment-related side effects with D-Penicillamine were noted in 15 patients, accounting for 30% of cases. These side effects were primarily dominated by hematological disorders such as thrombocytopenia in 8 patients, followed by severe hypersensitivity in one patient. Neurological worsening was reported in 8 patients, manifested by hypertonia, gait disturbances, dysarthria, aphasia, total functional impairment, and swallowing difficulties.

The outcome of Wilson's disease was favorable in 35 patients (67%). These patients showed regression or disappearance of clinical signs, with normal growth without pubertal delay and normalization of copper levels. One patient experienced acute pancreatitis during the course of the disease. Seventeen patients (31%) died, including 12 from decompensated cirrhosis, 2 from fulminant hepatitis, and 3 from neurological deterioration, with one patient dying due to rapid neurological worsening caused by severe hypersensitivity to D-Penicillamine necessitating treatment discontinuation.

DISCUSSION

Wilson's disease is a recessive genetic disorder linked to mutations in the ATP7B gene located on chromosome 13. It is characterized by dysfunction of the transmembrane ATPase enzyme crucial for copper transport and metabolism in the body [1]. Due to ATP7B deficiency, copper gradually accumulates, initially in the liver, then in other organs, particularly the eyes, brain, and kidneys [1]. In the brain, chronic copper toxicity causes demyelination, astrocyte damage, and tissue breakdown, primarily localized in the central gray nuclei, thalamus, cerebellum, and brainstem [1]. Excess free copper in the blood leads to oxidative damage to hemoglobin and the cell membrane, resulting in hemolysis with a negative Coombs test [1, 2]. Additionally, excess copper can damage other tissues in the body.

We reported 52 cases of Wilson's disease out of 3200 hospitalized patients over 13 years, corresponding to an incidence of 1.6%. The exact incidence of the disease in Morocco is not precise. However, the worldwide prevalence of Wilson's disease appears to range between 1 in 30,000 and 1 in 50,000 individuals [3]. In France, an epidemiological study conducted in 2013 identified 906 cases of Wilson's disease, corresponding to a prevalence of 1.5 cases per 100,000 inhabitants, according to the Reference Center for Wilson's Disease and other rare copper-related diseases [4, 5]. In South Korea, the average prevalence and incidence of Wilson's disease between 2010 and 2020 were 3.06 per 100,000 inhabitants and 0.11 per 100,000 inhabitants, respectively, based on data from the National Health Insurance Service (NHIS) [6].

We found a clear male predominance of 54% in our study, consistent with the results of the study by Lakhdar conducted in Fes [7] and the study by Rukunuzzaman conducted in Bangladesh [8]. However, we noticed no sex difference in the study by Couchonnal [9]. Regarding consanguinity, in our study, the majority of patients were from consanguineous marriages, which is similar to the findings of the Fes series. Consanguinity significantly increases the incidence of Wilson's disease due to its autosomal recessive nature.

Copper deposition in Wilson's disease occurs from birth, but clinical manifestations exceptionally appear before the age of 3 years, reflecting the liver's capacity to store excess copper [1]. This is consistent with the findings of our study as well as those of Couchonnal [9] and Lakhdar [7]. However, a clinical study conducted in China on an 8-month-old infant presenting severe hepatic cytolysis and low serum ceruloplasmin levels. Genetic analysis of the ATP7B gene detected two heterozygous mutations responsible for Wilson's disease. Zinc administration normalized the elevation of serum transaminases in this infant. This represents the youngest recorded case of a patient with

Wilson's disease associated with increased hepatic enzymes [10].

Patients may be asymptomatic in the early stage of the disease. Therefore, discovery may be incidental in the presence of abnormal liver function tests or signs of hepatopathy on ultrasound or during family screening [1]. In our study, family screening; performed solely through cupriuria, ophthalmological examination, and liver function tests; identified 5 cases of Wilson's disease.

In our study, hepatic involvement of Wilson's disease was the most frequent, representing 90% of clinical signs, followed by ocular involvement in 68% of cases, which is consistent with the findings of the Couchonnal *et al.,* series. However, there is a predominance of ocular involvement at 70% in the study by Lakhdar *et al.,* followed by hepatic involvement in 45% of cases.

Neurological involvement ranks third in frequency in our study as well as in those of Couchonnal and Lakhdar. It rarely occurs before the age of 10 years, characterized by mild cognitive impairments such as memory disorders and dysarthria [11]. Graphomotor disturbances in children are an early and crucial sign of extrapyramidal involvement. Brain MRI remains the reference imaging examination for visualizing brain lesions indicative of copper accumulation. These lesions are symmetric hyperintensities seen on T2 and FLAIR sequences in the central gray nuclei (especially the putamen and caudate nuclei), thalamus, midbrain, and pontine white matter. In our study, MRI was performed in all patients with neurological signs, accounting for 36% of cases, revealing signs of copper overload.

Psychiatric manifestations can range from behavioral and personality problems (aggressive and impulsive) or mood disorders (depression, anxiety, and bipolar) to psychosis [1, 12]. In our study, signs of psychiatric involvement were noted in 32% of patients.

The most frequently observed ophthalmological abnormalities in Wilson's disease are Kayser-Fleischer rings and sunflower cataracts [2]. The Kayser-Fleischer ring is highly suggestive of Wilson's disease but is not pathognomonic. It can be observed in other liver conditions, notably in the context of primary biliary cirrhosis, biliary atresia, or chronic cholestasis. The Kayser-Fleischer ring corresponds to a precipitation of copper salts in irregular granules on the posterior surface of the Descemet membrane. It presents as a brownish-greenish pericorneal ring [2]. In 68% of our patients, Kayser-Fleischer rings were visualized during slit lamp examination.

Wilson's disease can manifest with other conditions, and hemolysis can be an initial presentation of Wilson's disease [12]. In our study, hemolytic anemia was a revealing mode of Wilson's disease in 2 patients, one of whom, a girl, required weekly transfusions even under treatment, suggesting another etiology, notably Congenital Disorder of Glycosylation (CDG syndrom). Genetic studies showed a mutation in favor of Wilson's disease. Improvement in anemia was achieved 6 months after the start of treatment.

The Specific biological disturbances in Wilson's disease rely on copper balance analysis, including measurement of ceruloplasmin levels, serum copper, and urinary copper excretion, although interpretation of these tests does not always lead to a definitive diagnosis [7]. A low ceruloplasmin level less than 20 mg/dL is indicative of Wilson's disease [13, 2]. In our study, 88% of patients had significantly reduced ceruloplasmin levels, consistent with the findings of the Fes series (Lakhdar *et al.*,). Measurement of 24-hour urinary copper excretion is essential for Wilson's disease diagnosis. A level exceeding 100 µg/24 hours (> 1.6 µmol/24 hours) strongly suggests Wilson's disease in an untreated individual [1, 14]. In our study, urinary copper excretion was elevated in 94% of patients, consistent with the study by Lakhdar *et al.,* which reported a rate of 89% of cases.

Genetic analysis is crucial for the diagnosis of Wilson's disease (WD). Given the diversity of mutations in the ATP7B gene, over 900 variants have been identified. In our study, genetic analysis was performed on 12 patients. We identified six different homozygous mutations in the ATP7B gene in ten of the patients, while no mutations were detected in the other two patients [15].

Diagnosing Wilson's disease can often be challenging due to the diversity of clinical and biological manifestations. Currently, no single test definitively confirms the diagnosis of Wilson's disease outside of genotyping. Due to the lack of well-defined diagnostic criteria, scoring systems have been developed based on clinical symptoms, laboratory test results, and genetic mutation analysis, such as the Leipzig score. This scoring system has been validated in studies involving both adults and children. A score above 4 indicates an increased likelihood of a diagnosis of Wilson's disease [2].

In the absence of adequate and early treatment, the progression of liver involvement towards chronicity or hepatic insufficiency can be rapid, with a risk of irreversible brain lesions. The European Society for Pediatric Gastroenterology, Hepatology, and Nutrition recommends the use of copper chelators as first-line treatment, particularly D-Penicillamine, which is the most widely chosen treatment for symptomatic cases [9]. This aligns with the findings of our study. Digestive copper absorption inhibitors, primarily zinc salts, represent another possible approach, indicated for asymptomatic cases or as maintenance therapy [13, 16]. Liver transplantation remains a therapeutic alternative

indicated in cases of fulminant hepatitis [17]. In our study, two patients had indications for liver transplantation but died before being able to undergo the procedure.

The effectiveness of treatment is linked to the difficulty of obtaining D-Penicillamine in our country since it is still not available in the Moroccan market. Thus, the prognosis of Wilson's disease depends on the speed of diagnosis and the timeliness of treatment initiation.

CONCLUSION

Wilson's disease can be challenging to diagnose. A combination of clinical, biological, and genetic evidence is necessary for early diagnosis and adequate management. Wilson's disease should be considered in any acute or chronic liver disease or neuropathy in a child beyond the age of 10 years. It is also important to consider screening for family members, with genetic counseling provided for family planning purposes.

Conflicts of interest: None

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