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Wilson's Disease: A Study of 10 Cases

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Abstract **Case Report**

Wilson's disease was described for the first time by the neurologist S.A.K as an autosomal recessive genetic disorder characterized by a toxic accumulation of copper in the body, mainly in the liver, central nervous system and cornea. As early as 1956, patients benefit from an effective treatment, D-penicillamine, copper chelating agent limiting the consequences of the disease. A retrospective study of 10 cases of Wilson's disease followed on the department of pediatric over a period of 12 years having various clinical, biochemical and radiological features. Wilson's disease is an inherited metabolic disorder. Early diagnosis and appropriate management help to prevent the systemic complications. It also points out the need to suspect Wilson's disease in any young patient presented with the unexplained liver disease.

Keywords: Wilson's disease, genetic, metabolic, unexplained liver disease.

INTRODUCTION

Wilson's disease is a rare inherited autosomal recessive genetic disorder. It is a cupric toxicosis characterized by excessive copper accumulation in many organs, predominantly the liver, brain, and cornea.

This disease results from mutations of the ATP7B gene carried by chromosome 13. The diagnosis of Wilson's disease can be difficult to establish because of the heterogeneity of the clinical signs and the lack of specificity of the biological parameters. In the absence of any treatment, the spontaneous evolution is most often fatal.

The aim of this study was to determinate the epidemiological, clinical, paraclinical and prognostic profile of a moroccan series and to underline certain particular circumstances.

PATIENTS AND METHODS

This study was conducted in Mohammed V Military Teaching Hospital, a tertiary care institution in Rabat, Morocco. The medical records of 10 children who had received diagnoses of Wilson's disease between December 2000 and May 2012 in the department of Pediatrics were reviewed.

The diagnostic of Wilson's disease was based on clinical history, physical examination, low serum copper and ceruloplasmin, increased 24-hour urinary excretion of copper, liver enzymes and slit-lamp examination to detect Kayser-Fleischer rings. Brain MRI was realized for patients with neurological symptomatology to detect the abnormalities currently described in Wilson's disease. This study did not include a systematic MRI evaluation for Wilson's disease patients without neurological signs.

RESULTS

The average age of discovery of Wilson's disease is 10 years (range 6-14 years). Males were more affected, with 06 cases. Consanguinity was found in 6 patients (60%), 4 of them had a consanguinity of the first degree. A death in siblings in an array of chronic liver disease was noted in 30% of cases. Clinical manifestations have gradually been established in all patients. However, the average time between the appearance of the first clinical signs and the diagnostic was 7 months. The reason for consultation was pedal oedema, found in 4patients of 10(40%), jaundice in 3 of 10(30%); hepatomegaly in 2 children of 10(20%) and splenomegaly in 3 children of 10(30%). Neurological examination revealed an extrapyramidal syndrome in 3 children (30%). Ophthalmological examination with a slit lamp revealed the presence of the Kayser-Fleischer ring in 4 patients (40%).

Transaminases were normal in 4 patients (40%), moderately high in 2 (20%) and very high in 4 others (40%). Prothrombin level was less than 40% in 1 patient, between 40% and 70% in 4, while it was normal in 5 others patients. Total bilirubin was elevated in 4 cases. Hemolytic anemia was found in 4 patients (40%) and thrombocytopenia in 2 patients (20%). Serum ceruloplasmin concentration was low in 9 patients (90%) and normal in one patient. Urinary copper excretion exceeded 100mg/24 hours in all patients. Fibroscopy showed early oesophageal varices in a single patient. Cerebral MRI performed in 4 patients showed hypersignal of basal ganglia in 2 patients. No molecular studies could be performed in our patients. All patients were treated with D-penicillamine. Evolution was favorable in 6 patients (60%) who are always followed with a mean follow-up of 11 years. Evolution was unfavorable in two patients who died from decompensated cirrhosis.

DISCUSSION

Wilson's disease, known as hepatocellular degeneration, was described in 1912 by the neurologist S.A.K [1]. The involvement of copper overload in the liver and brain was only demonstrated in 1948 by Cumings [2]. Wilson's disease is one of the few inborn errors of metabolism which can be successfully treated by specific and effective pharmacological agent's treatment as early as 1956 when Walshe proposed the use of a copper chelator: penicillamine [3].

Wilson's disease is a rare autosomal recessive disorder of copper metabolism caused by mutation of ATP7B gene on chromosome 13 resulting in a systemic overload of copper. Its incidence is reported as 1 / 30,000 [4, 5]. The incidence of Wilson's disease in the Moroccan population is not known because of the difficulty of its diagnosis.

Accumulation of copper in many organs can produce varied clinical presentation that sometimes make the diagnosis difficult .Clinical manifestations can be hepatic, neurological, psychiatric, ophthalmic, hematological, renal, cardiovascular, musculoskeletal, endocrine and dermatological, the patients generally having a combination of several symptoms. In addition, this disease may progress in an acute mode, patients with hepatic impairment, hemolysis, or a combination of both, or in a chronic mode, patients developing cirrhosis and neurological problems [6, 7]. The clinical manifestations of Wilson's disease are extraordinarily diverse. In the first decade of life, Wilson's disease presents more often with hepatic manifestations. After the age of 20 years, 75% of cases present with neurological manifestations and 25% with both hepatic and neuropsychiatric manifestations. Wilson's disease patients with neurological manifestations have a poorer outcome than do patients with hepatic manifestations. Accidental discovery of a corneal ring or a sudden decrease in visual acuity, pyramidal signs, recurrent neuromuscular damageor or epileptic seizures can also be the modes of presentation.

Liver manifestations can range from a simple elevation of transaminases to fulminant hepatitis [8]. It is worth mentioning the hypothesis of Wilson's disease before any chronic non-viral and non-toxic chronic liver disease. The neurological involvement in Wilson's disease is often unobtrusive at first, but should be routinely sought as an adjunct to the diagnosis of Wilson's disease. Its abrupt installation after a triggering factor such as a derivation, a trauma or especially a surgery under general anesthesia is described [9].

The neurological involvement is observed between 15 and 30 years, it is exceptional at an age less than 12 years. It is manifested by rough signs [9]. It is in fact a delay of school acquisitions, behavior disorders like type of mood disorder. Gradually appear tremors, a slow gait, a poor mimicry with inexpressive facies and salivary flow, a monotone voice, Athetotic and choreic movements. Choreic movements can wrongly lead to Syndehman's chorea [10].

The ophthalmologic manifestations of Wilson's disease are the presence of Kayser-Fleischer (KF) ring. The ring of KF is often bilateral, its color is variable (brown, yellow, blue, greenish or reddish), it appears initially in superior, then in inferior and becomes circumferential and rarely extends more than 5 mm towards the center. The KF ring is formed by infiltrating copper particles present in the aqueous humor through the endothelium to the descemet membrane. The KF ring is found in 95% of patients with Wilson's disease. The treatment leads to the disappearance of the ring in 80% to 90% of the cases; its reappearance despite the treatment signals the non-compliance to the treatment.

A haemolytic anemia with a negative Coombs test is sometimes encountered as an inaugural presentation [11]. Inhibition of erythrocyte enzymes (G6PD, PK), but also the effect of free radicals on its membrane, are considered responsible. Most cases have cirrhosis with chronic, low-level hemolytic anemia, with some acute episodes that may precede the hepatic or neurological symptomatology of a few years.

Thrombocytopenia is secondary to hypersplenism, and direct toxicity of copper. Cirrhosis causes hypersplenism that sequesters all the formed elements of blood, including platelets. There is therefore an acceleration of platelet destruction. In addition, copper is involved in megakaryogenesis, causing an anomaly in platelet production [12].

Screening is for anyone between the ages of 3 and 45 who has symptoms of liver or neuropsychiatric disease. It includes aminotransaminase level, gamma-GT, alkaline phosphatase, total and conjugated

bilirubin, factor V and prothrombin levels. The blood count is performed to detect for cytopenia (anemia, leukopenia and thrombocytopenia) or hemolysis. Serum ceruloplasmin, and urinary copper excretion is necessary for diagnosis. In fact, the cupremia is lowered and the urinary copper excretion is increased (> 0.10 mg / 24 h) and serum ceruloplasmin level is decreased (<20 mg/dL).However these results may be normal. MRI, hepatic ultrasonography and oesophageal fibroscopy are recommended for screening and follow-up level [13, 14].

The treatment is based on chelating agents: D-penicillamine, trientine, climercaprol, tetrathiomolybdate and zinc. D-penicillamine was the first oral treatment; however its toxicity and worsening of neurological symptoms under treatment reduced its use

The prognosis depends on the severity of the disease during the diagnosis and the quality of care. Early treatment allows a reversibility of deficits; once irreversible damage has occurred the effect of treatment is limited; untreated the disease is lethal.

CONCLUSION

The prognosis of Wilson's disease depends on the precocity of the treatment, so Wilson must be reminded of any extra-pyramidal syndrome of the young, but also of recurrent jaundice without obvious etiology.

The ideal would be to initiate treatment at an asymptomatic stage, which avoids all its complications. As a result, the interest of screening and surveys

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