

Unusual presentation of wilson's disease in children : recurrent gross hematuria

Ben Rabeh. R ^(1,2), Ben Ismail. A ^(1,2), Bouyahia. O ^(1,2), Missaoui. N ^(1,2), Atitallah. S ^(1,2),
Yahyaoui. S ^(1,2), Mazigh. S ^(1,2), Boukthir. S ^(1,2)

⁽¹⁾ University Tunis El Manar, Faculty of medicine of Tunis, Tunisia

⁽²⁾ Pediatric Department C, Bechir Hamza Children's hospital Tunis, Tunisia

ABSTRACT :

Wilson's disease is an autosomal recessive inherited disorder of copper metabolism. It has a variety of presentations. We reported a case of 14-year-old boy who presented with a history of recurrent macroscopic hematuria and flank pain. He had signs of chronic liver disease and dysarthria. He had kidney stones and hypercalciuria. The diagnosis of Wilson's disease was confirmed by low serum ceruloplasmin level, high 24 hours Urinary copper excretion and genetic testing.

Keywords: Wilson's disease, ATP7B gene, gross hematuria, hypercalciuria, kidney stones, Child

INTRODUCTION :

Wilson's disease is a genetic disorder of copper metabolism caused by excessive deposition of copper in various organs, particularly in the liver and brain. Excessive copper deposition may also involve the eyes, the heart, the kidney, and other organs [1].

It's a monogenic, autosomal recessive disease, due to mutations in the Adenosine Triphosphatase (ATP) 7B gene. This gene encodes a P-type copper-transporting ATPase [2].

Clinical presentation of Wilson's disease is very heterogeneous, and can involve several organs, which makes diagnosis challenging [3].

We reported a pediatric case of Wilson's disease diagnosed in a child presented with recurrent macroscopic hematuria secondary to kidney stones.

CASE REPORT :

A 14-year-old male child was admitted to pediatric department for recurrent macroscopic hematuria associated with acute left flank pain. He was born from consanguineous marriage. His family history was unremarkable. His psychomotor and mental development was normal. However, parents had reported problems with skill acquisition, a decline in school performance and hand-

writing deterioration noted for few months.

He had no medical history apart from hepatic cytolysis at two times upper limit of normal (ULN), three years ago. Cytolysis was discovered on laboratory tests performed to explore abdominal pain with asthenia. Levels of both serum alanine transaminase (ALT) and serum aspartate transaminase (AST) returned to normal within one month. The diagnosis was viral hepatitis but it was not confirmed by serological tests.

The child presented with recurrent left flank pain associated with macroscopic hematuria of two months duration.

Physical examination on admission, showed normal temperature, blood pressure at 115/75 mmHg, hepatomegaly (liver length of 13.5 cm in the midclavicular line), splenomegaly and knocking tenderness over the left flank. Neurological examination showed dysarthria with no other abnormalities, mainly no dystonia or extra pyramidal rigidity.

Urinary analysis showed gross hematuria. Urinalysis test strip found a urine specific-gravity of 1020, pH of 6, blood of 3+ and no protein, glucose of 1+ without ketosis. Microscopic examination of urine revealed a red blood cell (RBC) count of 300 000/mL (normal value <5000/mL) with 90% dysmorphic RBC. Laboratory tests revealed

Corresponding author :

Rania Ben Rabeh

Complete postal address: N°14 Rue Hédi Noura, 1001, Tunis – Tunisie

Phone number: (+216) 52 85 70 24

E-mail: zayani.seyfeddine@gmail.com

ORCID : 0000-0003-2674-6049

normal blood urea (3.2 mmol/L, normal value 1.6–6.5 mmol/L), normal serum creatinine level (69 μ mol/L, normal value 35–79 μ mol/L), raised ALT level (173 IU/L, normal value <45 IU/L), elevated AST level (204 IU/L, normal value <40 IU/L), increased gamma-glutamyl transferase (GGT) level (103.6 IU/L, normal value <43 IU/L), high total bilirubin level (44 μ mol/L, normal value <20 μ mol/L), elevated conjugated bilirubin level (32,3 μ mol/L, normal value <4 μ mol/L) and normal prothrombin time (92%, normal value 80%–100%). Complete blood count revealed a hemoglobin level of 11.8 g/dl, with normal white blood cell and platelet counts. Urinary protein excretion was 106.7 mg per 24 hours (normal value <150 mg/24h).



Figure : Urinary tract X-Ray showing a calcified opacity projected next to the left transverse process of the L3 (ureteral stone)

The urinary tract X-Ray showed a calcified opacity projected next to the left transverse process of the L3 suggesting ureteral stone (Fig). Abdominal ultrasound showed signs of chronic liver disease. Kidney ultrasound examination revealed a hyperechoic stone with posterior acoustic shadowing in the lower pole of the left kidney and a moderate dilatation of the proximal ureter due to hyperechoic stone in the lumbar ureter.

Analysis of urinary calcium level found hypercalciuria of 0.18 mmol/Kg/ 24h (>0.10 mmol/Kg/ 24h) and a raised urine calcium/creatinine ratio of 0.97 mmol/mmol (>0.7 mmol/mmol). Tubular reabsorption of phosphate (TRP) was 81.5%.

Antinuclear antibody, anti liver kidney microsomal antibody, anti-smooth muscle antibody, anti-soluble liver antigen antibody, anti-HBs, and anti-HCV were all negative.

Slit lamp examination revealed bilateral Kayser-Fleischer ring. We found low serum ceru-

loplasmin level (0.12 g/L, normal value 0.20–0.50 g/L) and raised level of urinary copper excretion (340 μ g/24h, normal value < 100 μ g/24h).

The diagnosis of Wilson's disease complicated by renal tubular disorders and nephrolithiasis was based on clinical, laboratory and imaging findings and was confirmed by low blood level of ceruloplasmin, high 24 h urinary copper excretion and genetic testing which showed that the patient had one heterozygous mutation of Adenosine Triphosphatase (ATP) 7B gene. Mutations were c.3207C>A (p.His1069Gln) at exon 14.

Cerebral magnetic resonance imaging was normal. Esophagogastroduodenoscopy showed esophageal varices grade 1.

D-penicillamine was prescribed (150–300 mg, titrated until 20 mg/kg/day, given in two or three doses) associated with 50 mg/day of vitamin B6. After three months, we observed improvement of neurological signs and no macroscopic hematuria was observed subsequently, liver function tests returned to normal and calciuria decreased. Urinary copper excretion dropped from 340 μ g/24h to 213 μ g/24h. Abdominal ultrasound showed signs of chronic liver disease and portal hypertension and kidney ultrasonography did not reveal nephrolithiasis.

DISCUSSION :

The most common clinical signs and symptoms of Wilson's disease are hepatic, neurologic and psychiatric disorders and episodes of hemolysis [4]. Kidney involvement of Wilson's disease varies greatly and is relatively rare. Renal manifestations are exceptional inaugural signs of Wilson's disease [3].

We reported an original pediatric case of Wilson's disease diagnosed in a child presented with recurrent gross hematuria secondary to kidney stones. The child had clinical manifestations of liver disease (hepatomegaly and splenomegaly), abnormalities of liver function tests (elevation of the activity of transaminases and cholestasis), imaging signs of chronic liver disease and signs of portal hypertension. He had also neurologic disorders (dysarthria) and ophthalmic signs (Kayser-Fleischer rings). These signs suggested the diagnosis of Wilson's disease.

Kidney involvement is usually seen in elder patients or those with longer course of disease. This was confirmed in our case since the child presented with signs of chronic liver disease. Wilson's renal manifestations are mainly caused by copper deposits in the epithelium of proximal and distal tubules resulting in impairment of tubular reabsorption function with acidosis, glucosuria, aminoaciduria, hypercalciuria, phosphaturia, and proteinuria [5]. The consequence of hypercalciuria is nephrolithiasis [6].

The most common cause of non-glomerular hematuria in Wilson's disease is urolithiasis due to

hypercalciuria [5]. Nevertheless hematuria may be caused by glomerular damage due to secondary IgA nephropathy [7,8].

This case, as well as other published support the hypothesis that urinary calcium excretion disorders start early in Wilson's disease. Hypercalciuria may remain asymptomatic for several years before it causes polyuria-polydipsia and leads to nephrocalcinosis [9].

In this child, we identified two missense mutations at exons 14 and 16. These mutations have been previously reported in patients from Mediterranean and European countries [10].

The His1069Gln mutation is most common on European populations. Genotype-phenotype correlation studies suggested that the His1069Gln mutation was more commonly associated with neurologic manifestations [10,11]. The correlation between genotype and kidney involvement has not been studied [12].

Our patient had a decline in school performance and dysarthria. However brain MRI was normal. Several studies showed that more than 5% of children with hepatic involvement of Wilson's disease already have neurological manifestations and that more than 15% of children with WD develop neurologic disorders during childhood [13,14]. Brain MRI may be normal in children with neurological involvement of WD. Recent studies suggested that magnetic resonance spectroscopy may detect metabolite abnormalities before structural changes become visible on MRI [15,16]. In summary, reports of unique cases with atypical and uncommon clinical presentation of Wilson's disease may improve awareness of the disease and its management. Renal manifestations in Wilson's disease are various, but mostly hematuria or proteinuria. Therefore urinalysis strips and renal function tests should be performed regularly in children with Wilson's disease, particularly those who are receiving D-penicillamine treatment.

Conflicts of interest: None declared

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