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Case Report Open Access

Wilson's Disease Presenting with Severe Thrombocytopenia and Urinary Symptoms: Case Report and Literature Review

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Abstract

Wilson's disease is inherited copper metabolism defect with primarily hepatic and also extra hepatic copper accumulation. Liver and other end organs damage - mainly cornea, brain and kidney, present with wide variety of symptoms, often resulting to misdiagnosis and delayed treatment. Liver manifestations range from asymptomatic liver and spleen enlargement to acute liver failure. Renal disturbances are rather usual and basically attributed to toxic effects of copper, leading to tubular dysfunction with impaired urate, calcium, phosphate, amino acids, potassium and glucose tubular handling. Thrombocytopenia is uncommon and happens mostly along with haemolytic anaemia. Here we present a case of Wilson's disease, manifested with severe thrombocytopenia, splenomegaly and dark urine without haemolytic anaemia.

Keywords: Wilson's disease; Thrombocytopenia; Urinary symptoms

Introduction

"Progressive lenticular degeneration: a familial nervous disease associated with cirrhosis of the liver" was the title of S.A. Kinnear Wilson doctoral thesis, published in 1912 and describing the condition, actually bearing his name – Wilson's disease [1,2]. The role of copper metabolism in the pathogenesis of Wilson's disease, the genetic defect and autosomal recessive pattern of inheritance were determined more than 3 decades later - between 1948 and 1993. It was shown, that loss of function of the metal-transporting P-type adenosine triphosphatase (ATPase), caused by mutation of ATP7B gene, leads to decreased excretion of copper into bile, and in hepatic copper accumulation and damage.

Excess of copper is released into the bloodstream and deposited in also in the brain, cornea and kidneys. In addition, this defect results in decreased copper incorporation into ceruloplasmin, increasing the total copper load in these organs. As a consequence, clinical presentation in the patients with Wilson's disease includes extrahepatic manifestations, such as neuropsychiatric symptoms, renal abnormalities, and many others [2-10].

Hepatic manifestations is the initial clinical manifestation in 40-50% of patients and include asymptomatic liver and spleen enlargement with or without slightly elevated liver enzymes, acute transient hepatitis, acute liver failure, which may be complicated by severe Coombs-negative haemolytic anaemia, and progressive cirrhosis. Neurologic manifestations present at the onset in 40-60% of cases, with the wide range of symptoms: tremor, dysarthria, chorea, tics, myoclonus, seizures, headache, peripheral polyneuropathy, emotional lability sleep dysfunction etc. Psychiatric manifestations include personality changes, depression, cognitive impairment and other changes. Ophthalmologic manifestations are typically presented by pigmented corneal rings, also known as Kayser-Fleischer rings, due to the copper deposition within Descemet's membrane. Another manifestation is sunflower cataract. Bone and joint involvement may manifest with spontaneous fractures and joint pain. Haemolytic anaemia due to the copper-induced damage of erythrocytes may be accompanied by thrombocytopenia; the latter may also be seen without anaemia. Thrombocytopenia was described in a patient with combination of Wilson Disease and antiphospholipid syndrome [9-19].

Early studies demonstrated excessive urinary excretion of copper, and renal damage was attributed to the deleterious effect of accumulation of copper in the kidneys, resulting into progressive deterioration of tubular functions and also renal plasma flow and glomerular filtration rate, similar to the effects of other heavy metals. Renal tubular dysfunction with consequent aminoaciduria, hypercalciuria and hyperphosphaturia inducing nephrocalcinosis, uricosuria with decreased serum urate level, nephrolithiasis, glucosuria in the absence of hyperglucemia, hypokalaemia and renal tubular acidosis are documented [9,20-30].

Variety of extrahepatic clinical presentation often lead to diagnostic errors, and delays in diagnosis and initiation of treatment are common even in patients with a positive family history [14].

Case Presentation

Here we present a case of Wilson's disease, manifested with thrombocytopenia and urinary symptoms.

Caucasian male 17 years old admitted to our clinic in July 2015, referred from local nephrology unit with the diagnosis "Systemic lupus erythematosus, lupus nephritis".

Main complains: General weakness, headache, myalgia, back pain.

Previous medical history: Unremarkable but childhood infections and flu.

Family history: Father's sister has unspecified chronic illness since childhood, disabled.

History of present illness: January 2015 he developed unexplained weakness, headache, nasal bleedings, face swelling and palpitations. April 2015 he noticed dark urine, work-up in the local outpatient clinic showed anemia, thrombocytopenia, hematuria and splenomegaly. May 2015 during school exams he became irritated, complained for fatigue

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and sleep loss. Patient's mother reported his emotional lability and aggressiveness. He also had high-grade fever, resolved on antibiotics within 3 days.

June 2015, after the second episode of dark urine, repeated work-up found Hb 11.7 g/dL, Plt 50x10^9/L, WBC 4.4 x10^9/L, ESR 15 mm/h, serum total protein 51 g/L, creatinine 72 μmol/L, AsAT and AlAT within normal range, proteinuria 0.67 g/L, urine sediment - RBC >200 hpf. Abdomen CT: splenomegaly, nonspecific diffuse liver changes. Patient was seen by local nephrologist and referred to our clinic.

At admission: Conscious, oriented, slightly confused. Body temperature was 37.2°C, RR 18 per minute, pulse regular 78 per minute, BP 120/80 mm Hg. Slightly obese (BMI 29). Skin is pale, with multiple purple striae on back and hips, palmar erythema, single vascular spiders on the chest wall, Mild pedal edema, HEENT and neck otherwise normal. No palpable peripheral lymph nodes.

Joints: no swelling, movements not restricted; **Lungs:** clear; **Heart:** regular rate and rhythm, no murmur; Abdomen was soft, non-tender, bowel sounds normal. Liver +3 cm below rib arch, non-painful, spleen and kidneys not felt. Urination is free, urine normally coloured, urine output 1500 ml/day. **Neurologic exam:** No signs of cranial nerve disorder, pupils round, S<D. No paresis, tendon reflexes S<D. Coordination tests were normal, right-side positive Babinski's symptom.

Clinical Manifestations (Tables 1-3)

Infections screening: RPR-test for T. Pallidum, HBsAg, anti-HCV and anti-HIV-antibodies negative; **Lupus serology:** Anticardiolipin antibodies IgG 0,1 GPL, IgM 0,1 MPL, anti-β2-glicoprotein antibodies IgG 0,1 U/mL, IgM 0,1 U/mL, anti ds-DNA antibodies 0,3 U/mL, C3 complement 0,76 g/L, C4 complement 0.14 g/L, ANA – negative, LA – negative, RF 5 IU/ml; **Coombs-test:** Negative; **Coagulation tests:** ATTP 31.2", PTA 65%, PTT 14.7", fibrinogen 1.58 g/L, INR 1.33

WBC (x10^9/L)	RBC (x10^{12}/L)	Hb (g/dL)	Plt (x10^9/L)	PMN %	Lymph %	Mon %	Eos %	ESR (mm/h)
3.36	4.23	124	37	66	26	6	2	6

Table 1: Total blood count.

Color	SG	pH	Protein g/L	Glucose mmol/L	WBC hpf	RBC hpf	Casts hpf	Urobilin μmol/L	Crystals
Yellow	1024	6.5	0.35	abs	2-3	1-2	0-1	70	abs

Table 2: Urinalysis.

Bilirubin Total mmol/L	28	Urea μmol/L	7.1
Bilirubin Direct mmol/L	5	Uric acid μmol/L	105
Bilirubin Indirect mmol/L	23	Creatinine μmol/L	87
AlAT U/L	45	Fe μmol/L	8.8
AsAT U/L	53	Transferrin g/L	1.92
AP U/L	96	Ferritin μg/L	157
GGT U/L	38	Ca total mmol/L	2.18
LDH U/L	144	Phosphate mmol/L	0.98
Glucose mmol/L	6.3	K^+ mmol/L	4.1
Total Protein g/L	56	Na^+ mmol/L	140
Albumin g/L	32	Cl^- mmol/L	110
Cholesterol mmol/L	5.89	pH	7.40
Lactate mmol/L	2.3	CRP mg/L	3

Table 3: Blood chemistry.

ECG, Chest X-Ray, ECHO-CG, Low extremities DV Doppler ultrasound and EGDS: Normal

Abdomen, kidney and lymph nodes ultrasound

Liver enlarged, with parenchymal hyperechogenicity and coarse texture. Vena Porte diameter 14 mm, cholehepatic d`uct diameter 3 mm. Gall bladder and pancreas otherwise normal. Spleen enlarged up to 187x88 mm, normal echogenicity and structure, splenic vein diameter 8 mm. Kidneys enlarged with parenchymal hypoechogenicity: RD 140x65 mm, RS 154x65 mm; parenchyma 28 mmмм. No cyst, stones or dilatation of renal pelvis. Ascites, retroperitoneal or peripheral lymph nodes not found

Diagnostic considerations and additional work-up

Teenager male presented with the symptoms of systemic disease with CNS, skin, liver, spleen and kidneys involvement and severe throbocytopenia. As the first step we ruled out systemic lupus erythematosus, suspected on the basis of thrombocytopenia, neuropsychiatric disturbances, proteinuria, microhaematuria, and palmar erythema (patient did not meet ACR criteria), primary antiphospholipid syndrome (absence of thrombotic events, negative serology) and infectious endocarditis (ECHO-CG did not show any valvular abnormalities). There were no data favoring any kind of thrombotic microangiopathy (LDH normal, no anemia) or autoimmune hemolysis (no anemia, Coombs test negative). Neuropsychiatric symptoms, "dark" urine at the onset and urobilinuria were suggestive for acute porphyria, but Erlich test turned to be negative. Due to severe thrombocytopenia, idiopathic thrombocytopenic purpura or haemoblastosis were suspected, but bone marrow smear showed all three hematopoietic lineage enhanced proliferation.

Final diagnosis

Finally, combination of hepatosplenomegaly with the dilatation of vena portae and splenic vein, palmar erythema, vascular spiders, encephalopathy, urobilinuria with slightly elevated serum bilirubin level, decreased serum uric acid level lead us to the putative diagnosis of Wilson's disease. Patient was seen by ophthalmologist and slit lamp investigation confirmed presence of Kayser-Fleischer rings. Serum ceruloplasmin was tested and proved to be as low as 43 mg/L (normal range 200-600 mg/L). Serum copper test and urine 24-hour copper excretion were ordered, and the patient, diagnosed with Wilson's disease, was referred to the Hematology Research Center, Division of Orphan Diseases, for specific treatment. Subsequently additional tests showed decreased total serum copper level, and increased urinary copper excretion. The patient was started on penicillamine and his condition markedly improved within 2 months.

Discussion

This case demonstrates the difficulties in diagnostics of Wilson's disease due to unusual initial presentation. Asymptomatic liver disease and relatively mild neuropsychiatric abnormalities did not allow considering Wilson's disease as a "first choice" diagnosis. Severe thrombocytopenia as a leading symptom demanded differential diagnosis with systemic lupus erythematous, thrombotic microangiopathies and idiopathic thrombocytopenic purpura. Acute hepatic porphyria could not be excluded because of "dark" urine at the onset in combination with neuropsychiatric abnormalities, absence of hematuria at admission and urobilinuria without significant bilirubin elevation, this diagnosis was canceled only after negative Erlich test. Thus, Wilson's disease was suspected only after step by step rule out

of all above mentioned conditions, and confirmed by ceruloplasmin decrease, Kayser-Fleischer rings detection, and increase of urinary copper excretion. Family history with unspecified disabling illness of patient's aunt was also confirmative to the diagnosis.

Kidney damage, presenting with "dark" urine (probably due to uraturia, rather than to hematuria), moderate proteinuria and transient microhaematuria, is confirmed by low serum uric acid level. Absence of uric acid crystals in urine, kidney stones and electrolyte disturbances do not exclude tubular dysfunction, typical for Wilson's disease.

The most interesting finding is severe thrombocytopenia without anemia, rarely reported in the literature, and probably may be explained by hypersplenism, as no proof for DIC or antiphospholipid syndrome was found during detailed investigation.

Conclusion

Wilson's disease has to be considered in differential diagnostics of cases with even mild urinary abnormalities combined with extra renal symptoms like hepatic, CNS, skin, skeletal and blood involvement, along with other systemic diseases.

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