WILSON DISEASE ASSOCIATED WITH MESANGIOCAPILLARY GLOMERULONEPHRITIS. A CASE REPORT.

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OVERVIEW

Wilson's disease (hepatolenticular degeneration) is an autosomal recessive disorder of copper transport. It is characterized by the accumulation of copper in the liver and subsequently other organs, mainly the central nervous system and the kidneys because of a deficiency of the copper-binding protein ceruloplasmin. The gene for Wilson's disease has been mapped to chromosome 13 at the q14 region. The approximate homozygote prevalence of 1 in 30,000 (13,16).

The most common clinical manifestations are hepatic (47%), neurologic (34%) or psychiatric (10%). A hematologic (12%) or renal (1%) presentation is occasionally observed. Hepatic involvement encompasses a broad spectrum of acute and chronic liver diseases. The course is most commonly long term, characterized by signs of postnecrotic cirrhosis or chronic active hepatitis. In a few patients, Wilson's disease can present as fulminant hepatic failure or acute hepatitis accompanied by acute renal failure. Abnormalities of renal function can also occur. They have been recognized as result from impaired proximal renal tubular reabsorption which may produce glycosuria, hyperphosphaturia, hyperkaliuria, hypercalcuria, tubular proteinuria, and uricosuria. That group of characteristic tubular dysfunctions may be classified as acquired Fanconi syndrome.

CASE REPORT

A 36-year-old woman was admitted to Saint Marina Hospital. She presented with a four month history of aching pain on left side of the lower back and intermittent passage of café au lait dark urine. She had noticed a brief episode of periorbital oedema that had resolved spontaneously. The patient had been diagnosed as having haemolytic anaemia upon occasion of a haemolytic crisis after administration of Analgin-Chinin 18 years ago. The Coombs test gave a negative result. Electrophoresis didn't establish any abnormal

hemoglobins. The patient didn't have family history of Wilson's disease.

Physical examination revealed scleral jaundice and peripheral lower limb discrete oedema. On palpatory assessment of the abdomen, the woman appeared to have left flank pain. There was palpable hepatosplenomegaly. The edge of the liver was palpable 2 cm below the right costal margin in inspiration. Neurological examination showed slight nystagmus of left gaze. There was an irregular flapping tremor of the extended hands, which persisted throughout intended movements. Examination further revealed postural tremor of the arms (the left was affected more) and a plastic rigidity of the limbs upon passive movement.

Fig. 1 Kayser-Fleischer ring

The diagnosis of Wilson's disease was suggested by the presence of Kayser-Fleischer rings (10,11) (figure 1) at the periphery of the cornea on examination by slit lamp and when biochemical examination showed normal plasma copper concentration of 15,64 $\mu\text{mol/l}$ (12-24 $\mu\text{mol/l}$) but low level of ceruloplasmin 3,3 ME (normal 36-74 ME) and an increased urine copper concentration 13,63 $\mu\text{mol/l}$ (normal <1,1 $\mu\text{mol/l}$) (19). D-penicillamin was administered to the patient in a provocative test. A significant increase in urinary copper excretion was established upon induction with the chelating agent (1000 mg/24h) – 23,54 $\mu\text{mol/l}$. A

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liver biopsy was refused by the patient. Therefore, liver copper content wasn't evaluated. Her liver function tests were however within normal limits: serum SGOT 33 IU/l and SGPT 20 IU/l (normal <40 IU/l). Alfa-1 antitrypsin deficiency was excluded by measuring the serum levels of 1820 mg/l (normal 785-1881 mg/l). The patient was tested negative for markers of HBV and HCV.

The diagnosis was verified though genetic evaluation that identified an abnormal gene on chromosome 13 (mutation at position 1070), encoding copper-transporting ATPase, also known as the Wilson disease protein. This protein directs the incorporation of copper into apo-ceruloplasmin thus facilitating biliary excretion of excess copper (17,18). Laboratory results were consistent with the presence of hemolysis: serum bilirubin concentration was 19,7 $\mu\text{mol/l}$ (normal <17,0 $\mu\text{mol/l}$), conjugated – 7,310 $\mu\text{mol/l}$ (normal <4,38 $\mu\text{mol/l}$). The haemolysis was associated with hypercupraemia, a manifestation of Wilson's disease. It is believed to be transient and self-limiting (9,12). Laboratory tests revealed 120 $\mu\text{mol/l}$ of serum creatinine, 7,5 mmol/l serum urea, and 115 mmol/l of hemoglobin. Serum albumin concentration was 38 g/l with total protein 67 g/l. No laboratory evidence of hypoalbuminemia and azotemia was established.

At admission, increased excretion of proteins (1,16 g/l, or 2,08 g/24h) indicated glomerular injury. The urine was positive for hematuria (+) and hemoglobin (+); the sediment contained 15-20 WBC and many erythrocytes. Creatinine clearance was below normal limits – 62,3 ml/min. A renal biopsy was proposed to the patient upon evaluation of laboratory results and performed lately.

Fig. 2 Glomerulus with increased cellularity of mesangial regions, matrix accumulation and apparent thickening of the basement membranes; heavy degeneration of tubular epithelium

On abdominal ultrasound was revealed non-homogeneous liver structure with various in their size hyperechoic areas. Renal ultrasound demonstrated normal kidney size with lobular contour. Both kidneys exhibited homogeneously

hyperechoic parenchyma and a blurred pelvic parenchymal border. No abnormality was detected in the kidney drainage system. A solitary concrement was revealed in the right kidney and a peripelvic cyst in the left kidney.

Ultrasound-guided renal biopsy showed fifteen glomeruli with increased cellularity of mesangial regions, matrix accumulation and apparent thickening of the basement membranes (figure 2). Half of the glomeruli showed generalized involvement leading to congestion of the capillary lumen. In four a segmentary extracapillary proliferation in the fibrocellular stage was observed. Three of the glomeruli were totally hyalinised. Arterioles were with segmental endothel proliferation and thickening of the wall. The interstitium exhibited a dense inflammatory infiltrate and foci of fibrosis. The renal tubules showed evidence varying degrees of epithelial alternations and erythrocyte casts in the tubular lumina (figure 3). Immunofluorescence findings - epimembranous IgG and IgA granular depositions along basement membrane. The immunohistological changes were suggestive of mesangio-capillary glomerulonephritis.

Fig.3 The renal tubules showed evidence varying degrees of epithelial alternations and erythrocyte casts in the tubular lumina.

We attained forbearance in pathogenetic treatment of the glomerulonephritis and administered chelating agent. However, the assessment of treatment in one year revealed a slight tendency to improvement of proteinuria also.

DISCUSSION

Although impairment of renal tubular and glomerular function may frequently be shown on testing, it is rare for the renal disturbance to predominate in the clinical picture. The atypical presentation and course with this patient prompted this clinical brief.

Patients with Wilson's disease can have a variety of renal disturbances. Renal manifestations may involve the tubules, and the glomerulus resulting in azotemia and glomerular filtration rate reduction (13,14). It is unclear

whether the change in the glomerular filtration rate is a primary result of copper toxicity or is due to the renal disease associated with cirrhosis or both. Tubular disease is more clearly related to copper excess as evidenced by usual improvement with chelation therapy (15). In this view the renal abnormalities described are secondary to a disturbance in copper metabolism.

The present case report suggests that glomerulonephritis may be yet another manifestation of Wilson's disease instead a bare coincidence of pathological processes affecting the kidneys simultaneously.

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