

## Case Report

## Hemolytic Anemia: An Uncommon Presentation of Wilson's Disease

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## Abstract

Wilson disease is an uncommon inherited disorder of copper metabolism leading to extensive damage to vital organs like liver and brain. Severe hemolytic anemia is an unusual complication of Wilson's disease. We present a case of Coomb's negative acute hemolytic anemia as the presenting manifestation of Wilson's disease which makes this case worth reporting.

**Keywords:** Wilson's disease, hemolytic, anemia, Copper, metabolism.

## Introduction

The differential diagnoses of haemolytic anaemia is quite wide and Wilson's disease is generally not the first condition to be considered. It can be difficult to diagnose, due to the low specificity of the presenting symptoms. However, because of the potentially fatal consequences, a timely diagnosis is of utmost importance.<sup>1</sup>

## Case report

A 35-year-old female with no prior medical history,

presented with weakness, loss of appetite, on and off fever and yellowish discoloration of skin for one month. On examination pallor and icterus was present. Per abdomen palpation revealed hepatosplenomegaly. Liver function test showed increased total bilirubin-37.86 mg/dl with conjugated and unconjugated bilirubin levels of 19.58 and 18.28 mg/dl respectively. AST and ALT levels were 407 U/L and 157 U/L respectively. A/G ratio was reversed (0.40). Alkaline phosphatase and GGT were normal. Routine urine examination showed presence of bilirubin. Her serum iron was normal and serum ferritin level was elevated. TIBC was reduced. CBC revealed hemoglobin level of 8 gm/dl, haematocrit 24%, MCV- 79 fl, MCH- 27.1 pg, MCHC- 32.3 g/dl and RDW-20.4%. PBS showed normocytic normochromic RBCs along with microcytic hypochromic RBCs with moderate anisopoikilocytosis. Target cells, few fragmented RBCs, few polychromatophils, microspherocytes along with 10-12 nRBC/100 WBC and basophilic stippling was also noted. Total leucocyte count was mildly raised (17470/cumm). Platelet count was

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adequate. On the basis of clinical, biochemical and hematological findings, hemolytic anemia workup was advised. Coombs test was positive LDH was raised (375U/L). Her PT was 29 sec with INR of 2.4. USG examination revealed enlarged liver of size 17cm with coarse echotexture and irregular margins. Portal vein appeared dilated. Spleen was also enlarged (17cm) with prominence of splenic veins. Bilateral kidneys were also enlarged with echogenic parenchyma. Overall features were suggestive of chronic liver disease with bilateral acute kidney injury and moderate ascites. Extensive work up was done to find out the cause of hemolysis with jaundice. Viral Hepatitis markers were negative. LKM1, AMA, ANA and ASMA were negative. The combination of haemolysis and signs of liver failure raised suspicion of Wilson's disease. Her serum ceruloplasmin and copper was decreased (17.40 mg/dl and 75.73µg/dl). Her 24-hour urine copper excretion was increased (105.02µg/day). Neurological examination revealed a slight tremor of the left hand. Liver biopsy was postponed because of the elevated INR and ascites. Diagnosis was confirmed by a mutation analysis of ATP7B. It is the gene associated with Wilson's disease and it showed two heterozygous mutations at these 2 places (2930C>T(p.Thr977Met) and c.3207C>A (p.His1069Gln).

To avoid exacerbation of the tremor, medical treatment began with low dosages of D-penicillamine that were gradually increased. Separately from the D-penicillamine, zinc was added. The patient responded nicely to the treatment. Under ongoing medical treatment, the haemolysis subsided within days, the minor tremors disappeared, and liver functions returned to normal within months.

## Discussion

Because it takes time for copper to build to dangerous amounts in the liver until that age, the condition does not present clinically until 4–5 years of age. Early childhood is when hepatic signs of WD are more common, but adolescent neurological symptoms are more common.<sup>7</sup> Hemolytic anemia is a well-known but rare (10–15%) consequence of this illness.<sup>1</sup> A severe spherocytic hemolytic anemia can be the prodrome to WD. Wilson's disease is a rare inherited disorder with an incidence of about 1 in 35000–100,000 live births.

Wilson's illness causes hemolysis due to a lack of ceruloplasmin, a copper transport protein, resulting in an excess of inorganic copper in the bloodstream, with much of it accumulating in

red blood cells. Although the specific mechanism is unknown, increasing copper accumulation in RBC's may harm the cell membrane and speed up the ageing process.

The WD gene (ATP7B) was discovered on chromosome 13 (13q14.3).<sup>6</sup> Because it takes time for copper to build to dangerous amounts in the liver until that age, the condition does not present clinically until 4–5 years of age. Early childhood is when hepatic signs of WD are more common, but adolescent neurological symptoms are more common.<sup>7</sup> Hemolytic anaemia is a well-known but rare (10–15%) consequence of this illness.<sup>1</sup> A severe spherocytic hemolytic anaemia can be the prodrome to WD. Wilson's illness causes hemolysis due to a lack of ceruloplasmin, a copper transport protein, resulting in an excess of inorganic copper in the bloodstream, with much of it accumulating in red blood cells. Although the exact mechanism is unknown.

The increased copper accumulation in RBC's may harm the cell membrane, accelerate haemoglobin oxidation, and inactivate enzymes in the pentose phosphate and glycolytic pathways, however the specific process is unknown. The presence of an increased number of spherocytes in the peripheral blood in this situation could indicate cell membrane injury. Intravascular hemolysis was not detected. Roche-Sicot et al.<sup>8</sup> previously documented acute intravascular hemolysis and acute liver failure as early signs of WD. The KF ring may be absent throughout the hepatic stage. When a patient has neurologic symptoms, KF rings are almost always present. However, there were no neuropsychiatric signs in our case.

KF rings, low serum ceruloplasmin, and increased baseline urine copper excretion were used to diagnose WD. The most sensitive test for the diagnosis of WD is 24-hour urinary copper, especially when a liver biopsy is not possible due to coagulation abnormalities.<sup>9</sup> However, the most reliable test is hepatic copper estimation, which is not widely available in India. Because of bleeding issues, a liver biopsy may not be performed, and histological characteristics are not always indicative with WD.<sup>10</sup> Hemolytic anaemia usually resolves and may reoccur, but unless treated, copper poisoning in the organs (e.g., cirrhosis) is the most common complication.

## Conclusion

An acute hemolytic anemia may be the presenting episode in some patients of Wilson's disease

although its rare and that's why this case is worth reporting. So in case of spherocytic acute hemolytic anemia (Coomb's negative) associated with liver failure; one should always suspect WD and investigate accordingly. Its early diagnosis can prevent end organ damage preventing liver transplantation.

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