Young female pregnant mother initially treated as viral hepatitis finally diagnosed and sucessfully treated as Wilson disease

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July 25, 2023

Abstract

Successful pregnancy is a rare phenomenon in women with Wilson's disease (WD). We report a case of a primigravid 19 -years old woman who presented with hemolytic anemia and was later diagnosed with Wilson's disease for the first time during pregnancy. With prompt treatment, she delivered a healthy albeit pre-term child.

Introduction

Wilson's disease, also known as hepatolenticular degeneration, is an autosomal recessive disorder of defect in copper transport due to a mutation in the adenosinetriphosphatase copper transporting beta (ATP7B) gene. Impaired copper transport results in the accumulation of copper in the liver, brain, and cornea, thereby causing symptoms. It presents as liver disease, neurological, neuropsychiatric symptoms, and non-immune hemolytic anemia [1]. Kinnier Wilson first described the disease in 1912. It affects between 1 in 30000 individuals to 1 in 100,000 individuals [1,2]. The mean age at diagnosis is 13.2 years [3]. The diagnosis may be overlooked owing to its numerous presentations of non-specific symptoms of fever, fatigue, and change in behavior to fulminant hepatic failure. Kayser-Fleischer ring is found more commonly with the neurological presentation, up to 95 % of cases [4]. Hemolytic anemia, which may be seen as a distinctive clinical feature with jaundice or acute liver failure in Wilson disease, is a rare presentation in isolation [5]. The diagnosis is often based on the constellation of clinical findings, serum ceruloplasmin, urinary copper excretion, Coombs negative hemolytic anemia, and liver biopsy [5].

We report a case of a 19 years old pregnant lady who presented for the first time in her life with Coombs negative hemolytic anemia in the third trimester of pregnancy. Jaundice, as a presentation in pregnancy, can be due to hemolysis with or without hepatitis secondary to Wilson's disease.

Case Presentation

A 19-year-old normotensive primigravida from a rural area presented to our center in the third trimester at 30 weeks of gestation with a history of fever, yellowish discoloration of eyes and urine, malaise, generalized weakness, and fatigue for ten days. She also had moderate pain in the upper abdomen, more localized on the right side, decreased appetite, and a few vomiting episodes. She received symptomatic care as she was treated with the diagnosis of acute viral hepatitis in her local hospital initially. However, she did not have clinical improvement. She did not have a history of altered sensorium, itching, pale-colored stools, or bluish patches on the body. She never had any similar illness in the past. Movement disorders, behavioral and personality changes were not noted in the past. She had uneventful home delivery and childhood. She was good at her academic performance and there was no history of any known liver or neurological disorders in family members.

On examination, she had pallor and icterus with no palpable lymph nodes. She had a fever of the recorded temperature of 101 degree Fahrenheit with a blood pressure of 100/60 mmHg on bilateral arms . A firm, tender liver with regular margin and surface, with a distinct border, was palpable 4 cm below the right subcostal margin. The fundal height of the patient corresponded to 28 weeks of gestation. Fetal heart sound was audible, and the rest of the systemic examinations had normal findings.

Her hemoglobin was 5 g/dl on the initial presentation at the district hospital, where she was transfused 2 pints of fresh blood. Peripheral blood smear showed a microcytic hypochromic picture with anisocytosis and poikilocytosis. Liver function test (LFT) was abnormal with unconjugated hyperbilirubinemia, transaminitis but a normal prothrombin time and international normalized ratio (PT/INR), with the platelet count always in the normal range. Her viral serology profile was send and was found to be negative . She had a high lactate dehydrogenase (LDH) value and a negative Direct-Coomb's test. Her lab reports are mentioned in the table 1.

Table 1

Parameters	**At the time of admission**
Hemoglobin	5.8 gm%
Total count	11200/cubic mm
Platelet count	371000/cubic mm
Direct Coombs test	Negative
PT/INR	12sec/0.85
Total bilirubin	668 µMol/L
Direct bilirubin	172 µMol/L
SGOT	133 U/L
ALP	141 U/L
SGPT	55 U/L
LDH	2532 U/L
Serum ceruloplasmin	63 mg/dl
24 hr urine copper	298.8 mcg
USG abdomen and pelvis	Fetus of 28 weeks, cephalic EFW 1400 gm; AFI 5.3 cm Hepatomegaly; portal vein 9 m
Hepatitis A, B, C, and E IgM/IgG	Negative

The presence of Coomb's negative hemolytic anemia suggested a non-immune etiology of hemolysis. Her glucose-6-phosphate dehydrogenase (G6PD) activity was normal. On suspicion of Wilson's Disease, we sent a 24-hour urine collection for copper quantification, which came out to be 298 mcg/24 hr. However, her ceruloplasmin was 76 mg/dl (20-60 mg/dl). The patient deferred the liver biopsy. The abdominal ultrasonography revealed a fetus of 28 weeks gestation with normal heart rate and fetal movements, hepatomegaly with perihepatic cuffing suggestive of acute hepatitis. With strong suspicion of Wilson's disease, she was again sent to a senior ophthalmologist for KF ring evaluation. She was then found to have the KF ring on a slit-lamp examination.

Her treatment began with tab penicillamine 250 mg twice a day and tab zinc 40 mg twice a day, where the gap of two hours between penicillamine and zinc tablet administration was assured. She was also given a pyridoxine tablet of 10 mg /day. She had gradual improvement in her clinical symptoms of jaundice and anemia. Her hemoglobin level improved to 8.2 g/dl, and her LFT and LDH were normalizing. After two years of follow-up, she does not have jaundice or anemia, and her lab parameters are within the normal range with no hemolytic features. She is currently under penicillamine 250 mg once a day and a copper restricted diet. She had pre-term delivery of a 2.3 kg baby by cesarean section at 34 weeks of gestation. Her baby weighs 12 kg at present. The 24-hour urine copper analysis could not be sent because of financial reasons. Neither the genetic analysis could be done for the same reason.

Discussion

Progressive hepatolenticular degeneration or Wilson's disease is a rare, potentially treatable autosomal recessive disorder of the copper transport caused by ATP7B gene mutation in the long arm of chromosome 13 [1]. WD's prevalence was thought to be 1 in 100,000 people. However, with the advancement of studies, the estimated prevalence is now considered 1 case per 30,000 live births [1,2]. Although virtually no data is available from Nepal but neighboring country India sheds some light on WD . Taly et al. have presented a cohort study that reported approximately 15-20 cases of WD are registered annually at one of India's major neurological hospitals at NIMHAMS, Bangalore [6].

Defective ceruloplasmin synthesis, impaired copper excretion, and accumulation of copper in the tissues, mostly in the liver and brain, as a result of a mutation in the ATP7B gene, are the main hallmarks of this disease that presents itself as a broad spectrum of clinical manifestations.

Acute intravascular Coombs negative hemolytic anemia is a characteristic feature of acute hepatic failure in WD. Oxidative injury, altered erythrocyte metabolism, and severely compromised antioxidant status is caused by the toxic effects of copper that is released from necrotic hepatocytes, which in turn results in Wilsonian hemolysis [7,8]. WD has a myriad of clinical manifestations ranging from asymptomatic to chronic liver diseases, neuropsychiatric diseases, acute liver failure, hemolytic anemia, or combinations of these problems. It often poses as a diagnostic challenge to the physicians. The finding of a KF rings is an essential indicator of critical copper overload and is present in 95% of patients with neurological symptoms and 50-60% of patients without neurological symptoms of WD [4].

There is no single confirmatory test for WD; a score was developed at the eighth International Conference of Wilson's Disease based on clinical and laboratory abnormalities, which helps diagnose WD [9].

The presence of KF rings, low serum ceruloplasmin levels, and high urine copper excretion is enough to make a diagnosis of Wilson's Disease [9]. WD is an easily overlooked rare clinical entity because it resembles other common disorders like viral hepatitis. However, if detected early, effective treatments are available to manage the disease that may help prevent or reverse the many manifestations of Wilson's disease.

The majority of patients with Wilson's disease are diagnosed between 5 and 35 years of age, the mean age being 13.2 years [3]. Children are more likely to present with hepatological symptoms considering the neurological manifestations develop only after the slow accumulation of copper in the brain [10]. The mean age at presentation for patients with neurologic symptoms ranges between 15-21 years. Our patient presented with hepatological symptoms of jaundice and hepatomegaly, mimicking viral hepatitis. No neurological symptoms were observed, but the classical ophthalmic manifestation of WD: the KF ring was present at the age of 19 during the third trimester of her pregnancy.

24-hour urine copper excretion >100 mcg holds an important diagnostic aid and is also used for the therapeutic monitoring of Wilson's disease. The patient had elevated 24-hour urine copper excretion, which can be seen in various liver diseases, but it is most often below 100 mcg/24 hrs [11,12].

A liver biopsy could not be done, which is essential for quantifying the hepatic copper concentration. The common observation in the liver function test of a Wilson disease patient, as seen in this case, is the elevated serum aminotransferase, which is typically less than 2000 with an AST/ALT ratio of >2, wherein this patient AST/ALT ratio is > 2.2 [11]. The ALP level is usually normal or subnormal with an ALP: total bilirubin ratio of <4 as seen in this particular case [13].

Apart from the common liver diseases that present in pregnancy, such as jaundice, hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome, intrahepatic cholestasis, and viral hepatitis, Wilson's disease is also a very real possibility that may present itself as hemolytic anemia with normal platelet count in pregnancy, as seen in this case.

WD and pregnancy have a complicated relationship; the outcome of pregnancy with WD in the past has not been great. Untreated WD can lead to significant morbidity and mortality. Excessive copper accumulation

in the liver and uterus leads to metabolic disturbance and recurrent miscarriage.

The normal range of ceruloplasmin in pregnancy is 300 to 1200 mg/L, while it is 250 to 600 mg/L in a non-pregnant adult [14]. Despite the less likelihood of KF rings in a hepatic presentation; the patient was found to have them.

During pregnancy, ceruloplasmin levels are elevated. Because of the fetus, the physiological copper demand is also increased. There might be an improvement in the symptoms of WD, and patients may experience a period of remission [15]. However, in symptomatic and asymptomatic patients alike, life-threatening complications such as preeclampsia, placental abruption have been experienced during pregnancy regardless of the medications [16,17]. The exact mechanism is not known, but it is believed that increased copper in the uterus prevents the successful implantation of the fetus, similar to a copper-containing intrauterine contraceptive device [18]. The outcome of Wilson's disease in pregnancy has improved in recent years with the therapeutic evolution and better understanding of the disease in asymptomatic women [18]. Although a pre-term delivery, this case is one such example of a successfully treated Wilson disease diagnosed during pregnancy.

Currently, the treatment of WD consists of lifetime therapy aimed at primarily copper detoxification by the chelators and prevention of copper accumulation in the body by zinc salts or chelators themselves. The primarily used chelator is D-penicillamine, while Trientine is considered to be the second-line agent. Research suggests that although teratogenous in animals, D-penicillamine is safe in pregnancy, which is given with zinc acetate/ zinc sulfate, pyridoxine, and a low copper diet for the maintenance of pregnancy [19,20]. We started the treatment of the patient with D-penicillamine and zinc. As shown in this case, the correct diagnosis and appropriate management of WD can lead to a favorable outcome even in pregnancy.

Conclusions

To sum up, WD is an inheritable metabolic liver disease associated with the accumulation of copper in the human body. Pregnancies in patients with WD are considered high risk, not only because it poses an obvious risk to the mother but also because the accumulating copper could affect the unborn fetus. The proper treatment of the mother with Zinc and Penicillamine is said to be relatively safer and has a lower risk of congenital disability. We have tried to establish that successful pregnancy while suffering from WD is possible through the data collected from our case, although it does require continuous treatment and good compliance.

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