Wilson's disease presenting during pregnancy: A diagnostic and therapeutic dilemma

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Abstract

Wilson's disease is an autosomal recessive genetic disorder affecting copper transport leading to hepatic and/or neuropsychiatric manifestations. Changes in pregnancy can mimic certain clinical features of chronic liver disease such as spider naevi, and constraints for the use of various investigation for diagnosis pose a challenge to physicians. A high index of suspicion, multi-disciplinary team approach, use of correct non-invasive testing including viral serology, autoantibodies and copper studies and ultrasonography help to diagnose most of the pre-existing, de novo or pregnancy-specific hepatological conditions. We report a case of Wilson's disease diagnosed during pregnancy and discuss the challenges in diagnosis and treatment in pregnancy.

Keywords

Gastroenterology, hepatology, high-risk pregnancy

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Introduction

Wilson's disease is an autosomal recessive disorder affecting copper transport leading to accumulation of copper in various organs.¹ Physiological changes in pregnancy with added constraints in using certain diagnostic techniques can make it difficult to establish the diagnosis during pregnancy. We report a case diagnosed with Wilson's disease during pregnancy and discuss the diagnostic difficulties and treatment options.

Case report

A 32-year-old Gravida 2 Para 2 (G₂P₁), who conceived spontaneously, presented to the surgical emergency department with repeated episodes of haematemesis at 15 weeks of gestation. On admission mild splenomegaly was noted and her investigations revealed hypoalbuminaemia (21 g/L) and platelet count of 35×10^9 /L. Ultrasonography showed features suggestive of cirrhosis with portal hypertension. Liver function tests showed bilirubin (total/direct): 18.81/10.26 µmol/L, alanine transferase (ALT): 28 IU/L aspartate transferase (AST): 15 IU/L, alkaline phosphatase: 117 IU/L and the international normalized ratio (INR): 1.55. Upper gastro-intestinal endoscopy revealed grade I oesophageal varices and she was started on propranolol (20 mg twice daily). She was given omeprazole 20 mg once daily for two weeks, as the cause of haematemesis was thought to be secondary to a Mallory-Weiss tear. She was advised to attend follow-up with a medical gastroenterologist for further investigation.

She presented again at 27 weeks' gestation with another episode of haematemesis and was admitted for further evaluation. On admission, pulse rate was 90 beats per minute (bpm), blood pressure 120/70 mmHg and there was mild pallor. Her haemoglobin was 9.1 g/dL, serum bilirubin (total/direct): 1.1/0.6 mg/dL and INR: 1.53. Repeat endoscopy showed two columns of grade I varices and she was continued on propranolol 20 mg twice daily in view of portal hypertension. On further evaluation, her viral markers (hepatitis A, B, C & E) and anti-nuclear antibody (ANA) were negative. Kayser–Fleischer (KF) ring was identified on slit lamp examination. Serum ceruloplasmin levels of 13.9 mg/dL (normal: 20–60 mg/dL), urinary 24-h copper excretion

of 471.3 µg/day (normal: 15–60 µg/day) and serum copper (non-ceruloplasmin bound) of 74 µg/dL (normal: 63–150 µg/dL) were noted. Diagnosis of Wilson's disease was made with a Leipzig score of 4. She was started on zinc (Zn) acetate (50 mg three times a day) after gastroenterology opinion at 28 weeks. Subsequently she developed tremor and ataxia at 32 weeks; MR imaging of brain revealed hypointensities in the basal ganglion and pons which was thought to be consistent with the lenticular degeneration seen in Wilson's disease.

She was monitored in hospital for worsening of the disease clinically and also underwent further investigations (reports shown in Table 1). In due course she developed ascites. On serial fetal monitoring, at 28 weeks asymmetric fetal growth restriction with microcephaly and shortening of long-bones of both upper and lower limbs (below 5th centile) was identified.

Pre-labour rupture of membranes occurred at 32 weeks and was managed expectantly with antibiotics and antenatal corticosteroids for fetal lung maturity. Induction of labour was performed at 36 weeks and a female baby of 1.86 kg was delivered, with Apgar score of 9 at 5 minutes. The infant had microcephaly and short upper and lower limbs. The infant also had symptoms of neonatal cholestasis which was managed conservatively. Neonatal echocardiogram showed large patent ductus arteriosus (PDA). The infant required ventilatory support for respiratory distress and she succumbed to cardiogenic shock at 45 days of life. The mother developed wound dehiscence of the episiotomy which required secondary suturing. She was discharged two weeks postnatally taking zinc acetate and was advised to use barrier method of contraception.

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Table 1. The laboratory investigations of the index case since admission.

Approximate gestational age (weeks)	27	30	31	34	36	Postpartum
Haemoglobin (Hb) g/dL	9.1	8.4	8.8	8.3	9.4	10
Platelet $\times 10^9/L$	50,000	58,000	73,000	55,000	69,000	74,000
International normalized ratio (INR)	1.73	1.58	1.54	1.61	1.39	1.44
Bilirubin (total) mg/dL	1.1	1.2	1.3	1.4	1.7	1.3
Bilirubin (direct) mg/dL	0.6	0.6	0.8	0.7	0.6	0.8
Protein (total) g/dL	5.7	5.4	5.6	5.3	5.6	6.0
Albumin g/dL	2.5	2.6	2.9	2.5	2.7	2.8
Aspartate transaminase U/L	28	23	26	22	25	24
Alanine transaminase U/L	11	10	21	14	12	15
Urea mg/dL	14	10	13	19	16	15
Creatinine mg/dL	0.6	0.6	0.6	0.7	0.6	0.7

Discussion

Wilson's disease occurs due to mutation of ATP7B gene in chromosome 13 encoding copper transporting P type ATPase, which leads to accumulation of copper in various tissues. The incidence of Wilson's disease ranges between 1 in 30,000 and 1 in 100,000 live births.¹ Most commonly these patients present in the second or third decade of life.²

Initial manifestations are primarily as hepatic dysfunction (45–58%) or neuropsychiatric (30–33%).^{2–4} Most of the clinical signs are neither sensitive nor specific. A clinical hallmark of Wilson's disease is the KF ring, caused by deposition of copper in corneal Descemet's membrane.² Hepatic dysfunction can be highly variable, ranging from being asymptomatic with deranged liver function test to compensated or decompensated cirrhosis and acute hepatic failure. Many may present with isolated splenomegaly due to clinically non-evident cirrhosis with portal hypertension, as in our case.

In pregnancy hepatic dysfunction may due to pregnancy-specific complications such as hyperemesis gravidarum, pre-eclampsia, HELLP syndrome or acute fatty liver of pregnancy. Changes in maternal physiology such as hyper-estrogenemia may lead to changes in the biochemical parameters which are affected by Wilson's disease, and this also makes the diagnosis difficult. A diagnostic scoring system based on clinical signs and biochemical investigations was proposed by a working party at the International Meeting on Wilson's Disease, Leipzig, 2001.⁵ Since these include non-specific signs/symptoms and the results may be altered due to the pregnant state, its accuracy and usefulness in diagnosing a pregnant woman with Wilson's disease is unknown. However, in a pregnant woman presenting with abnormal liver function a high index of suspicion of the diagnosis of Wilson's disease is required.

Low alkaline phosphatase level or an alkaline phosphatase (AP) to total bilirubin (TB) ratio <4 may help to make a diagnosis of Wilson's disease in patients presenting with acute liver failure. In pregnancy the levels of alkaline phosphatase are elevated secondary to the placental isoform, it therefore may not aid in the diagnosis.⁴ Serum ceruloplasmin levels are usually decreased by nearly 50% of the normal values in Wilson's disease, whereas they may be falsely negative (high) in pregnancy. Serum non-ceruloplasmin bound copper level $\geq 15 \mu\text{g/dL}$ is indicative of the disorder; however, these values depend on the estimation method and may be raised in other causes of acute hepatic inflammation. Increase in 24h urinary copper excretion ($\geq 100 \mu\text{g}/24\text{h}$) is diagnostic in symptomatic patients, but these levels may also be increased in autoimmune hepatitis and hepatic necrosis. Invasive testing using liver biopsy to estimate hepatic parenchymal copper ($\geq 250 \mu\text{g/g}$ dry weight) and histology are not performed routinely in pregnant women due to risks involved and as they are not specific for the diagnosis. Although numerous mutations of the ATP7B are known, routine use of molecular genetic analysis is not recommended

for diagnosis as most patients are compound heterozygotes (they may carry more than one mutation) and it is a laborious, long procedure to identify them.² Neuroimaging may detect structural abnormalities in the basal ganglia.⁶ In our case, when she presented initially with haematemesis the diagnosis of Wilson's was not considered as it was uncommon in the region. Later when she presented with recurrence of her symptoms, evaluation showed KF ring and her subsequent evaluation led to the diagnosis of Wilson's disease.

Most reports of pregnancy outcome are of women who conceived on treatment for Wilson's disease. A study by Sinha et al. observed an increase in incidence of miscarriage especially in untreated women, which may be due to the free intrauterine copper derived from excess non-ceruloplasmin bound copper.⁷ Pregnancy does not seem to have an adverse effect on the clinical course of Wilson's disease, but pre-eclampsia and intrauterine growth restriction (IUGR) have been reported in some cases.⁸ These patients should be counselled against the use of oestrogen and copper-containing contraception; they should preferably be counselled to adopt barrier contraceptives or progesterone only methods.

Concerns regarding treatment during pregnancy include the avoidance of teratogenic medication without affecting the health of mother. Care during pregnancy should utilise a multi-disciplinary team involving an obstetrician with special interest in medical disorders of pregnancy along with a gastroenterologist, neonatologist and obstetric anaesthetist to help optimise the outcome. Interruption of treatment during pregnancy has resulted in acute liver failure and even maternal death, suggesting the need to continue anti-copper therapy during pregnancy.^{2,9,10} Teratogenicity may be due to copper deficiency during the critical time of fetal development, possibly due to pulsatile troughs during therapy with agents such as D-penicillamine or Trientine, which does not occur with zinc therapy. Penicillamine is noted to cross the placenta and can lead to oral clefting, micrognathia, low set ears and hypermobile joints in the developing fetus. Although no well-documented fetal effects are noted with Trientine, animal studies have reported associations with harmful teratogenic effects. Thus, zinc therapy is the preferred agent during pregnancy.¹⁰ Use of non-selective beta-blockers such as propranolol reduces the hepatic venous pressure gradient which helps to reduce the risk of variceal bleeding. Beta-blockers have been reported to be associated with intrauterine growth restriction, although this is confounded by indication for use and in our case it was started after the diagnosis of IUGR.

Mode of delivery in these women may be guided by obstetric indication except in cases with grade 3 oesophageal varices associated with cirrhosis (as they have an increased risk of bleeding during labour/delivery). To promote better wound healing, dosage of chelating agents should be reduced to the minimum, especially for the last trimester.^{2,9} Even with the minimum dose of zinc therapy, in the woman described, wound dehiscence occurred. The fetus was diagnosed with

short limbs, microcephaly and early-onset growth restriction which were diagnosed before starting zinc therapy, the cause of which is unknown. It is possible that initiation of zinc therapy at the initial admission (15 weeks) might have delayed or prevented the progression of disease process which manifested later with neurologic symptoms. Since oestrogen may interfere with copper excretion, only spermicide, barrier methods and progesterone-only preparations can be safely prescribed as contraceptives.

Conclusion

The combination of abnormal clinical signs and biochemical investigations may pose a diagnostic challenge to physicians as the abnormalities may be non-specific and difficult to interpret as a result of the physiological changes in pregnancy.

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Ethical approval

As the details were retrieved from the records without collection of any identifying details, ethical approval was not sought. Patients provided written informed consent for publication in scientific journal.

Guarantor

AK

Contributorship

JD, ES and AK conceived the idea and performed the search. ES and AK wrote the first draft. AK, JD MG and VP reviewed and revised the final draft. AK and JD reviewed and commented on the final draft.

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