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Intrahepatic Cholestasis and Eclampsia: A Case Report

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Intrahepatic cholestasis of pregnancy is the most common liver disorder in pregnancy that adversely affects maternal well being and fetal outcome. We present a case of eclampsia that followed intrahepatic cholestasis of pregnancy in a patient who has a sister with the same history in her two former pregnancies despite being treated with ursodeoxycholic acid. Intrahepatic cholestasis and pregnancy is briefly reviewed based on a unique case report presenting with intrahepatic cholestasis complicated by eclampsia.

Keywords Intrahepatic cholestasis, Pregnancy, Eclampsia.

INTRODUCTION

Cholestasis results from abnormal billiary transport from the liver into the small intestine and intrahepatic cholestasis of pregnancy (ICP), also known as obstetric cholestasis, is a liver disorder in pregnancy that adversely affects maternal well being and fetal outcome (1). The true incidence and spectrum of ICP are unknown. The prevalence of ICP seems to vary significantly according to country. Its prevalence is higher in Chile and Sweden (2). It is more common in women of advanced age and in multiple gestations. The consensus is that ICP probably arises from a genetic predisposition for increased sensitivity to normally produced estrogens and progestogens and from altered membrane composition of bile ducts and hepatocytes. In addition, cholestasis may be a response to the production of abnormal metabolites. Genetic predisposition suggests a complex trait, and an exaggerated cholestatic response to estrogen has been documented in women from families affected by ICP (3). The course and severity of ICP are variable, but the

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classical maternal feature is generalized pruritus, becoming more severe with advancing gestation and fortunately resolving spontaneously after delivery. Pregnancies complicated by ICP have increased risks of perinatal mortality, preterm delivery, fetal distress and rarely preeclampsia. Additionally to pruritus, abnormal maternal liver function tests and raised serum total bile acids compared with normal pregnancy are necessary to make the diagnosis of ICP (4).

To our knowledge, coexistence of ICP with eclampsia has not been reported previously. We present a case of eclampsia that followed ICP in a patient who has a sister having the same history in her two former pregnancies despite being treated with ursodeoxycholic acid (UDCA) for ICP.

CASE REPORT

A 20-year-old woman presented to the Obstetrics and Gynecology Department at 11 weeks of pregnancy. G1 P0 and married to a second-degree relative of hers. Her history was unremarkable except for diabetes mellitus in her uncle, sister and paternal aunt. From the detailed history it was also established that her sister had two previous pregnancies characterized by disseminated itching and eclampsia.

The arterial blood pressure measurements, fetal growth, and weight gain were in the normal range until week 28 of pregnancy. Polyhydramnios (amniotic fluid index, = 21 cm) was detected on obstetric ultrasound at the 28^{th} week of pregnancy. The 50 g. glucose tolerance test was 146 mg/dL, and an oral glucose tolerance test revealed the following blood glucose results: fasting 82 mg/dL, first hour 103 mg/dL, second hour 68 mg/dL and third hour 55 mg/dL. The fetal echocardiogram revealed a spontaneous bradycardia during the examination.

The patient presented with disseminated itching without skin lesions at the 29^{th} week of pregnancy. Her laboratory findings were: aspartate transaminase (AST): 59 U/L (normal range, 1 to 32 U/L), alanine transaminase (ALT): 52 U/L (normal, 1 to 31 U/L), Alkaline Phosphatase (ALP): 495 U/L (normal, 0–280 U/L), Gamma Glutamil Transpeptidase (GGT): 16 U/l (normal, 10 to 50 U/L), Total Bilirubin: 0.93 mg/dL (normal, 1.0 to 1.3 mg/dL), Direct Bilirubin: 0.3 mg/dL (normal, 0.0 to 0.3 mg/dL) and erythrocyte sedimentation rate, 100 (normal, 0 to 19 mm/h). The hepatic markers were negative for hepatitis B and hepatitis C virus. The upper abdominal ultrasound detected a gallbladder that contained sludge of 17 mm. in length. Given these findings, the patient was diagnosed as having ICP. UDCA oral therapy 250 mg/d was started. The laboratory findings at day 14 of UDCA treatment were: AST: 48 U/L, ALT: 56 U/L, ALP: 462 U/L, and GGT: 11 U/L. Pruritus decreased progressively until week 34 of pregnancy. When disseminated itching started again, Zyrtec® (cetirizine) 10 mg/d was added to the therapy.

At week 36 of pregnancy, the patient attended our outpatient clinic with nausea, vomiting, and headache of 2 days duration, and also reported suffering from blurred vision for 2 hours as a result of a hypertensive attack in which the arterial blood pressure was measured as 160/110 mm Hg. She had an eclampsia attack during examination and immediate Cesarean section under general anesthesia was performed because of acute fetal distress. A 3020 g. male fetus was born with Apgar scores of 9/10 at 1 and 5 minutes, respectively. The arterial blood pressure was above the normal levels despite glycerol trinitrate and magnesium sulfate given as a continuous 2 g/h infusion. Aldomet® (methyldopa) was added to the therapy, but the hypertensive state continued until the fifth postoperative day. On the first postoperative day, the patient presented features similar to disseminated intravascular coagulation (DIC); she had echimosis in various regions of her body. The thrombocyte (Plt) levels decreased to 88,000. The prothrombin time (PT), activated partial thromboplastin time (aPTT), and international normalized ratio (INR) levels were within normal ranges. Hemoglobin (Hb) levels continued to decrease to 7.3 g/dL. Ultrasonographic examination was performed, and free fluid was shown in the abdomen. Paracentesis revealed defibrinated blood. Three units of blood were transfused, and expectant management was carried out. On the postoperative day 7, the patient was discharged from hospital. On the postoperative day 38, the patient attended our department for review. Itching had disappeared, and her laboratory findings were: Hb: 13.1 g/dL, hematocrit: 39.3%, platelets: 357.000 *10^9/L, ALP: 864 U/L, AST: 34 U/L, ALT: 34 U/L, GGT: 127 U/L. As a result of these parameters, UDCA treatment was continued for 2 months.

DISCUSSION

ICP is the most common liver disorder unique to pregnancy and it is the second most common cause of jaundice (5–8), but its relation to eclampsia has not been previously reported. The onset of ICP is characterized by the development of pruritus in the third trimester as a result of the peak of estrogens generally starting from palms and soles, progressing to arms and legs and involving trunk and face last. Jaundice occurs in 10% to 15% of cases 2 to 4 weeks after the onset of pruritus (4, 6, 9). Serum levels of AST and ALT are commonly elevated 2 to 10 times the upper limit of normal ranges in more than 80% of patients. Serum levels of GGT are elevated in 50 % of patients (10). Steatorrhea is a feature of ICP but it may be underestimated because women do not report changes in their bowel habits. Our patient presented to the antenatal clinic with pruritus on week 29 of gestation with raised serum levels of AST, ALT, and GGT, but no jaundice or steatorrehea had been observed during pregnancy. We were not able to measure serum bile acids, but a recent study has demonstrated that bile acid levels are

important since fetal complications occurred in cases with bile acid levels >40 μmol/L (11).

The retrospective studies from Finland, where a high incidence of ICP is seen, demonstrated that the clinical presentation of hepatic steatosis is atypical (3). Preeclampsia and ICP occurred solely in pregnancy with a long-chain 3-hydroxyacyl-coenzyme dehydrogenase (LCHAD)-deficient fetus and a combined group of hypertensive disorders. LCHAD deficiency is a recently discovered disorder of mitochondrial fatty acid oxidation. A LCHAD deficient fetus was reported in 4 patients with ICP and preeclampsia by Tyni and colleagues (12), but coexistence of ICP and eclampsia has not previously been reported. In those reported four cases, preeclampsia had been detected before week 35 of gestation, and none of these patients had eclampsia. In contrast, our patient presented with eclampsia but without signs or symptoms of preeclamsia during follow-up until the clinical picture at the time of presentation. Also, the sister of our patient had the same obstetrical history with coexistence of ICP and eclampsia, which may indicate a genetic association for their disease. The pathological mechanisms causing hepatic impairment in some women with preeclampsia may predispose to cholestasis. As some women with preeclampsia and abnormal liver function complain of pruritus, the etiology of ICP may overlap with that of preeclampsia, but further evidence must be provided (13).

The pathogenesis of ICP is obscure, although a role of female sex hormone or metabolites with exogenous and genetic factors impairing bile secretion have been suggested (14, 15). Current studies propose susceptibility to derangements in the sulfation of steroid compounds, affecting the metabolism of progesterone and bile acids in the fetal placental compartment; this damages the passage of bile acids from fetal to the maternal circulation through the placenta (10, 16).

ICP also seems to have a genetic etiology. At least 16% of ICP cases are familial, and therefore are likely to be caused by an inherited predisposition (17) and genes for ICP include those that mutate in different types of inherited cholestasis: progressive familial intrahepatic cholestasis types 1–3 (PFIC 1–3), and benign recurrent intrahepatic cholestasis (BRIC). PFIC is characterized by the onset of cholestasis in early childhood, which can progress to cirrhosis and liver failure and necessitating liver transplantation before adulthood. It can be classified in three subtypes: PFIC1 and 2 are characterized by low levels of bile acids and low to normal levels of GGT, whereas PFIC3 has high serum levels of GGT and bile but lacks phospholipids in normal biliary bile concentrations. BRIC results in a transient form of cholestasis, whereas no hepatic failure symptoms exist (18). Mutations of FIC1 (ATPase class 1 type 8B [ATP8B1]) gene that encodes a P type ATPase, which is believed to play a role in the enterohepatic circulation of bile acids, have been identified in PFIC1 and BRIC (19). ATP8B1mutations were also demonstrated in patients with ICP in some recent studies (20, 21). PFIC2 exists as a

result of a defect in canalicular bile acid transport pump caused by mutations in the bile salt export pump gene (BSEP) (22). It is also called as ABCB11 because it is ATP binding cassette subfamily B member 11, and it is responsible for the bile salt efflux system of the hepatocytes. BSEP is also demonstrated to be inhibited in pregnancy by the influence of high circulating levels of estrogens (23). Single nucleotide polymorphisms in BSEP are shown to be associated with ICP in Finland, and BSEP is suggested to be a susceptible gene in obstetric cholestasis according to these results (24). The multidrug resistance 3 (MDR3) gene encodes the MDR3 protein which is a member of ATP binding cassette family of transporters and also called as ABCB4. PFIC3 is characterized by a defect in the biliary secretion of phospholipids and this causes liver damage. MDR3 is responsible for PFIC3. GGT is highly elevated in this MDR3 defect different from BSEP and FIC1 defects. Mutations of **the** ABCB4 gene encoding the hepatobiliary phospholipids transporter have been identified in a small proportion of patients with ICP (25, 26). Different groups reported additional mutations in MDR3 gene associated with the presence of ICP, and more than 10 different MDR3 gene mutations have been identified in recent data. ABCB4 variants were found to represent genetic risk factors for the severe form of ICP (26–28). ICP-specific variants in MDR3 and BSEP were observed by Pauli-Magnus and colleagues (29) who found that the percentage of MDR3 variants in ICP was twice as strong as BSEP. MDR3, BSEP and FIC1, all seem to be responsible for the genetic etiology of ICP but these three genes were not demonstrated in Finnish ICP families. This suggests that there are still some unknown genes underlying ICP (30).

UDCA is the only therapy that has been proven to be effective in alleviating pruritus and in restoring the abnormal profiles of bile acids and sulfated steroids, serum, and other body fluids toward normal levels. UDCA seems to have no obvious adverse effects on the fetus, but experience is insufficient to draw conclusions regarding teratogenicity and prevention of adverse effects (31–33). In one study, women with ICP and serum bile acids > 40 μmol/L were allocated to UDCA (1 g/d for 3 weeks); UDCA had significant effects on pruritus, bile acids, ALT and bilirubin, but not on fetal complications (33).

In our case, UDCA improved the clinical features of the patient as pruritus and serum levels of hepatic enzymes decreased.

The management of ICP is dictated by the increased risks of fetal distress, spontaneous preterm delivery, and sudden fetal death and these risks rise progressively up to delivery, regardless of serum levels of bile acids and ALT. Close monitoring of these markers is essential but does not prevent sudden fetal distress, so labor should be induced as soon as fetal lung maturity is established. Also, clinicians must be aware of the possibility of the sudden onset of eclampsia at any time during pregnancy. The aim of the present case report is also to point out the possibility of genetic factors that could be responsible for the concomitant occurrence of eclampsia patients with and ICP.

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