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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

A rare case of alpha-methyldopa-induced hepatitis in pregnancy

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SUMMARY

Introduction There are three groups of disorders during pregnancy: disorders specific for pregnancy that resolve spontaneously or soon after delivery, acute hepatic disorders coinciding with pregnancy, and chronic disorders. Drug-induced liver disease prevails among women and it is estimated to be a leading cause of acute liver injury. Drug-induced hepatitis is rare in pregnancy with only a few cases reported in literature. Alpha-methyldopa is one of the commonly used drugs in pregnancy that could cause hepatotoxicity with different clinical presentations and possible adverse effects on normal course of pregnancy.

Case outline We reported a rare case of hepatotoxicity caused by alpha-methyldopa in 26 gestational weeks pregnancy in a 35-year-old patient admitted because of jaundice and elevated liver function tests. She had been using antihypertensive drug, alpha-methyldopa, from 12th gestational week, and no other medication or supplementation was recorded. Ultrasound of the abdomen excluded obstruction or any other abnormalities. Autoimmune panel was done. Biochemical analyses were indicative of toxic acute liver injury caused by alpha-methyldopa according to values of transaminase. After 13 days, patient was discharged recovered from the hospital.

Conclusion Diagnosis of alpha-methyldopa hepatotoxicity is challenging since the low incidence, unpredictability, diverse symptomatology and absence of specific biomarkers. That is why timely diagnosis is crucial for the well-being of both future mother and child.

Keywords: drug-induced hepatitis; alpha-methyldopa; hypertension in pregnancy; hepatotoxicity

INTRODUCTION

Hepatic disorders during pregnancy are divided into three groups: disorders specific for pregnancy that resolve spontaneously or soon after delivery, acute hepatic disorders coinciding with pregnancy such as acute viral hepatitis, and chronic disorders – chronic viral hepatitis or cirrhosis [1]. Drug-induced hepatotoxicity is an acute or chronic liver injury caused by medications, herbs or dietary supplements with incidence under 15 per 100,000 in general population [2]. Although drug-induced liver disease prevails among women and is estimated to be a leading cause of acute liver injury, drug-induced hepatitis is rare in pregnancy with only a few cases reported in the literature [2, 3]. Alpha-methyldopa is one of the commonly used drugs in pregnancy that could cause hepatotoxicity with different clinical presentations [4]. Diagnosis is difficult due to its rarity and diverse symptomatology. Physiological changes in pregnancy and pregnancy-induced hepatic disorders make the diagnosis even more challenging.

Hence, the aim of this paper is to report a rare case of hepatotoxicity caused by alpha-methyldopa in pregnancy, pointing out possible adverse effects of antihypertensive treatment affecting normal course of pregnancy.

CASE REPORT

A 35-year-old patient was admitted to the Clinic for Gynecology and Obstetrics at 26 weeks of gestation because of jaundice and elevated liver function tests. The patient complained of jaundice, dark urine, and pale stools starting the day before admission. No fever, pruritus, or any other symptom were reported. She had been using antihypertensive drug, alpha-methyldopa in the dose of 3 × 250 mg from 12th gestational week, no other medication or supplementation was recorded. Besides that, a normal course of pregnancy has been established. Her personal medical history was positive for chronic hypertension and she had one vaginal delivery three years previously. Upon admission, clinical examination and laboratory tests were done. Physical examination showed only skin and scleral icterus. Palpation of abdomen was without tenderness, rigidity, or guarding. No organomegaly was palpated. No leg oedema or varicosities. Vital signs were within normal range for pregnancy. Obstetrical ultrasound indicated vital singleton pregnancy with adequate amniotic fluid and normal placental insertion. Fetal biometry corresponded for 24 weeks of gestation. Laboratory findings were: leukocytes 12.8 × 10^9/L (normal range 4.0–10.0), lymphocytes 6.40% (20.00–45.00), monocytes 1.60% (4.00–8.00), hemoglobin 121

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g/L, platelet count 273 × 10ˆ9/L, C-reactive protein 22.4 mg/L (0.0–5.0). Prothrombin time was 15.8s, INR 1.48 (0.80–1.20), D-dimer 3.17 mg/L in fibrinogen-equivalent units (<0.50). Liver tests were as following: aspartate transaminase (AST) 1123 U/L (0–37), alanine aminotransferase (ALT) 833 U/L (40–120), total bilirubin 217,4 umol/L (0.0–20.5), direct bilirubin 111.0 umol/L (0.0–3.4), albumin 32 g/L (34–55), alkaline phosphatase 198 U/L (40–120), gamma-glutamyl transferase 40 U/L (0–38), lactate dehydrogenase 757 U/L (220–460). Serological tests for HIV, hepatitis A, B, and C, Epstein–Barr virus (EBV) and cytomegalovirus were negative. Ultrasound of the abdomen excluded obstruction or any other abnormality as cause of present state. During hospitalization, the patient was closely monitored and followed by expert perinatologist, cardiologist, and gastroenterologist. Alpha-methyldopa was suspended and nifedipine was introduced for blood pressure control. Due to further deterioration of liver function tests after two days in hospital the emergency Caesarean section was preformed when female premature neonate weighing 640 grams was born with Apgar score 2 in the first minute and 3 in the fifth minute.

Further evaluation of patient included autoimmune panel to exclude autoimmune liver disease (antinuclear antibody, antineutrophil cytoplasmic antibody, antimitochondrial antibody, anti-liver kidney microsomal antibody, anti-smooth muscle antibody). All tests were negative. Values of ceruloplasmin, blood and urine copper, urinary porphobilinogen, alpha-1 antitrypsin were within normal range. An abdominal magnetic resonance was performed, as well as magnetic resonance cholangiopancreatography, indicating liver steatosis and a 9 mm cyst in the tail of pancreas without any communication with duct of Wirsung. Liver function tests were serially monitored and the decrease was observed. Ten days after alpha methyldopa cessation values of AST was 137 U/L (0–37), ALT 221 U/L (40–120), total bilirubin 61.4 umol/L (0.0–20.5), direct bilirubin 30.6 umol/L (0.0–3.4).

The diagnosis of drug-induced hepatotoxicity was made by exclusion. Biochemical analysis were indicative of toxic acute liver injury caused by alpha-methyldopa according to values of transaminase (AST > ALT) and lactate dehydrogenase (LDH) and ALT ratio (LDH : ALT < 1.5). Since the values of transaminases and bilirubin continued to fall, the patient was discharged after 13 days.

We confirm that we have read the journal's position on issues involving ethical publication and affirm that this work is consistent with those guidelines. The written consent for publication of this article has been obtained from the patient.

DISCUSSION

A rare case of hepatotoxicity as an adverse effect of oral antihypertensive therapy in pregnancy is presented. Alpha-methyldopa is widely used drug for hypertension disorder in pregnancy that lowers blood pressure acting as central inhibitory alpha-adrenergic receptor [5]. Hepatotoxicity with alpha-methyldopa is idiosyncratic, unpredictable and according to literature starts 1–20 weeks after introduction of the drug [4, 5]. It is estimated that liver disease complicates 3% of pregnancies [6]. It is important to distinguish whether liver disease is pregnancy related or not [1]. Thorough evaluation is important to distinguish physiological changes in pregnancy, acute liver injury and wide spectrum of pregnancy-induced hepatic disorders such as hyperemesis gravidarum, acute fatty liver, intrahepatic cholestasis of pregnancy and hemolysis, elevated liver enzymes and low platelets (HELLP) syndrome. Pregnancy related disorders such as preeclampsia, eclampsia, and HELLP syndrome should not be misdiagnosed. Wide panel of hematological and biochemical analysis is obtained to help diagnostics. Blood tests including ALT, ALP, bilirubin, and albumin detect acute liver injury [4]. Transaminase values above 1000 U/L are indicate of hepatocellular injury which occurs in viral hepatitis, ischemic or drug-induced liver injury [5]. Our patient's liver function tests were indicative of hepatocellular injury.

Differential diagnosis includes infections such as viral hepatitis, cytomegalovirus and Epstein–Barr virus, but also autoimmune hepatitis, hypoxic hepatopathy, biliary tract obstruction, Wilson disease, hemochromatosis and Alpha-1-antitrypsin deficiency [4]. Diagnosis is mostly made by exclusion so thorough work-up is mandatory. In this case, serology and autoimmune panel were done accordingly, excluding viral and autoimmune disease. Multidisciplinary team was consulted to exclude various differential diagnosis. Imaging methods proved to be very useful. If drug induced liver injury is suspected, an abdominal ultrasound should be performed [4]. Additional imaging depends on clinical presentation. We performed ultrasound of abdomen and magnetic resonance cholangiopancreatography to exclude biliary tract obstruction.

Timely diagnosis with close monitoring is crucial because liver injury is potentially fatal both for mother and for child. Luckily, most patients recover after drug cessation, as was here the case. Our patient recovered liver function and was discharged after 13 days. Fatal outcome is also possible with only one case described in literature [7]. Because of the diversity of clinical presentation, consultations of multidisciplinary team could contribute to faster diagnosis and enable adequate therapy and follow-up.

Diagnosis of alpha-methyldopa hepatotoxicity is challenging since the low incidence, unpredictability, diverse symptomatology and absence of specific biomarkers. Clinical presentation varies from asymptomatic to foudroyant and possible fatal outcome and could lead to adverse perinatal outcome. Thus, timely diagnosis is important for patient's recovery in order to avoid neonatal morbidity and mortality.

Conflict of interest: None declared.

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Редак случај хепатитиса у трудноћи изазваног алфа-метилдопом

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САЖЕТАК

Увод Поремећаји функције јетре током трудноће су подељени у три групе: поремећаји специфични за трудноћу који спонтано пролазе током трудноће или одмах после порођаја, акутна оштећења јетре која коегзистирају са трудноћом и хронична оштећења. Оштећења јетре узрокована лековима се чешће јављају код жена и водећи су узрок акутног оштећења јетре. Оштећења јетре која су узрокована лековима се ретко јављају у току трудноће; свега је неколико случајева забележених у литератури. Алфа-метилдопа је један од најчешће коришћених лекова током трудноће који би могао да изазове хепатотоксичност са различитим клиничким сликама и могућим негативним утицајем на ток трудноће.

Приказ болесника Представљен је редак случај хепатотоксичности, који је узрокован алфа-метилдопом у трудноћи старој 26 гестацијских недеља код болеснице старости 35 година, која је примљена због жутице и повећаних лабораторијских вредности параметара функције јетре. Болесница је била на антихипертензивној терапији алфа-метилдопом од 12. недеље гестације, без документованог коришћења других лекова или суплементације. Ултразвук абдомена је искључио постојање оклузије или друге патологије у абдомену. Аутоимуна обољења су такође искључена. Биохемијске анализе су указале на акутно токсично оштећење јетре. Тринаест дана по обустављању терапије болесница је отпуштена опорављена из болнице.

Закључак Дијагноза хепатотоксичности проузроковане алфа-метилдопом је изазовна имајући у виду ниску инциденцију, непредвидљивост, различиту симптоматологију и одсуство специфичних биомаркера. Управо због тога је правовремена дијагноза круцијална за добробит и будуће мајке и плода.

Кључне речи: хепатитис узрокован лековима; алфа-метилдопа; хипертензија у трудноћи; хепатотоксичност