Late-onset cholestasis of pregnancy: Diagnostic challenges

Accepted 26th February, 2018

ABSTRACT

Cholestasis of pregnancy generally occurs in the third trimester of pregnancy and is connected with disturbances of intrahepatic bile flow. The disease is caused by the increase of bile acid synthesis, stimulated by estrogens and progesterone. Here, we described the course of cholestasis of pregnancy that occurred during the second trimester of pregnancy and seriously exacerbated four weeks after delivery. Clinical course was very severe. Analysis of biopsy material under an electron microscope and genetic studies showing mutations conditioning development of hepatic cholestasis were very helpful in the establishment of diagnosis. Long-term treatment with ursodeoxycholic acid resulted in recovery. The patient was warned about the risk of recurring cholestasis in the case of another pregnancy.

Keywords: Cholestasis, bile acid synthesis, pregnancy, estrogens, progesterone.

INTRODUCTION

Causes of intrahepatic cholestasis of pregnancy are not satisfactorily studied. Bile acids synthesized in hepatocytes act as detergents for food metabolized in the gut and facilitate lipid absorption. Bile acids are synthesized in a classical manner in the liver with participation of cytochrome P450, CYP7A1 (enzyme limiting the rate of synthesis), CYP8B1 and CYP27A1. In an alternative pathway, they are synthesized extrahepatically, while CYP27A1 is the most important enzyme in this pathway. Wherever bile acids are synthesized, they are excreted by the liver and before excretion they are coupled with taurine or glycine, which causes their cytotoxicity (McIlvride et al., 2017).

Bile acid concentration above >40 μmol in blood serum is thought to be toxic. High concentration of estrogens and sulfated metabolites of progesterone in the third trimester of pregnancy stimulates synthesis of bile acids (Dixon et al., 2017). This is probably the cause of cholestasis of pregnancy in the third trimester. The cause of the disease is usually mild, but sometimes women's health is in serious danger; and at other times harmful effect of bile acids on fetus requires earlier induction of labor (Jurate et al., 2017).

Numerous studies show that the disease present in families requires genetic testing. Research has shown a connection with a mutation in ABCB11 genes and sometimes in ABCB4. Such mutations stimulate synthesis and inhibition of secretion of bile acids from hepatocytes (Dixon et al., 2017). Late-onset cholestasis of pregnancy occurs rarely, but its course may be severe and pose direct danger to life (Dixon et al., 2017).

CASE REPORT

A 23-year-old pregnant woman, in her first pregnancy was hospitalized due to severe skin rash and increased concentration of bile acids in the blood. Cholestasis was diagnosed and in the 27th week of pregnancy cesarean section was performed. After the delivery, the patient's condition improved. The patient gave birth to a girl weighing 1,080 g. At five minutes after birth Apgar test of the newborn was done and the child obtained 4 points. The child was intubated due to respiratory failure. The newborn was treated for bronchopulmonary dysplasia, pneumonia, anemia, osteopenia of preterm infants, eating...
disorder, gastro-esophageal reflux and suspected retinopathy of prematurity. On day 125 of life, the child was dismissed from the hospital in good condition.

The woman stated that her brother died 6 months after delivery due to undiagnosed disease of bile ducts and secondary liver failure. Moreover, the patient’s cousin died as a result of chronic liver failure. For the last 3 years, the patient was under ambulatory care due to unspecific liver injury. Periodically, increase of ALT 2 to 3 times above ULN and increased bilirubin concentration were found.

Four (4) weeks after delivery, the patient’s condition worsened. She was admitted to the hospital due to yellow sclera and skin, thickened epidermis, skin rash and mutilations. Increase of ALT five times above ULN, hypoalbuminemia and hyperammonemia increased the concentration of bile acids in the serum (above 300 μmol), hypertriglyceridemia, hyperbilirubinemia and increased ceruloplasmin concentration were found. Based on serologic and biochemical studies, HBV, HCV, HAC, HIV, CMV infections, autoimmune diseases, Wilson’s disease and hemosyderosis were excluded. In an ophthalmological examination, Kayser-Fleischer rings were not observed. No
significant pathologies, except the constriction of gallbladder, were found in imaging examinations: ultrasound and MR cholangiography of the abdomen. Therapy with ursodeoxycholic acid was not effective. Hyperbilirubinemia worsened, while activity of ALP and GGTP increased.

Due to the possibility of autoimmune process, glucocorticosteroids were administered, bringing good results in the beginning. After several days of improvement during the use of methylprednisolone, the patient’s condition worsened, which was connected with increased concentration of bilirubin, bile acids, ALT and ALP activity. Therapy with cholestyramine, because of increased concentration of bile acids was not effective. Arterial hypertension was effectively treated with doxazosin. Liver biopsy was performed 8 weeks after delivery and genetic testing was ordered. The clinical condition of the patient worsened. Because of increased concentration of bilirubin above 22 mg% and bile acids, plasmapheresis was performed thrice (6,000 ml of plasma was exchanged), reaching transient improvement of clinical condition. The patient was qualified for liver transplantation.

In liver biopsy material (evaluation under light and electron microscope), decreased number of glycogen granules and their scattering in the cytoplasm was found in numerous hepatocytes. Moreover, the presence of large, variform mitochondria containing crystalline inclusions, numerous large autophagosomes with damaged cellular organelles, presence of intermediate filaments in the cytoplasm, fibrils concentrated in bundles and increased number of peroxisomes were found. Glycogen rosettes were distributed in a linear fashion in the cytoplasm of some cells and lumen of many bile ducts were closed by bile deposits. The presence of numerous inflammatory cells and collagen bundles in the sinuses and Disse's spaces was demonstrated (Figures 1 and 2).

Sporadically, the presence of collagen fibrils in the spaces of sinuses between hepatocytes was found. In some cells, lysosomes containing small vacuoles and high

Figure 2: Fragment of liver cell with visible cholestasis in intrahepatic bile ducts nucleus (Ch) and individual, scattered glycogen granules in clear cytoplasm (Magnification × 4, 400).
electrons density material that could suggest copper deposits were found. The description suggested Wilson's disease or cholestasis of unknown etiology.

Genetic testing* evaluating a fragment of the coding sequence of ABCB11 gene (exons 4, 9 and 12 with surrounding fragments of intronic sequences were analyzed) demonstrated c.850_855delinsTGAGAATGTTC mutation (another name: p.Val284Ter) in one of alleles of evaluated gene (in heterozygotic setting). Detected mutation was not registered in the database of mutations of the human genome (no data on its frequency or clinical significance). Testing was expanded by diagnosis of exons 2, 3, 5, 7, 8, 10, 11, 13-28. p.Glu135Lys mutation was identified in one of alleles of studied gene (in heterozygotic setting). The mutation is registered in the Human Gene Mutation Database as pathogenic, correlated with intrahepatic cholestasis of pregnancy and its frequency in the general population is 0.002%. Therapy with ursodeoxycholic acid and cholestyramine brought slow improvement. After 6 months of its administration, the patient recovered, skin rash receded, bilirubin and bile acid concentration became normalized.

DESCRIPTION

In the presented case, it is interesting to note that delivery only transiently improved the clinical condition of the patient. After the delivery, there was another exacerbation of pathological process, although normalization of hormonal status is usually observed during this period. Metaanalysis including 207 pregnant women with liver cholestasis treated with ursodeoxycholic acid showed beneficial effect of such therapy for skin rash, decrease of the concentration of bile acids in the serum, ALT activity of the woman and decreased frequency of respiratory pathologies in newborns (Bacq et al., 2012). These results justify the validity of this treatment.

SUMMARY

Prolonged cholestasis of pregnancy may pose a significant diagnostic and therapeutic challenge. In the described case only genetic test and evaluation of liver biopsy sample under electron microscope allowed establishment of diagnosis and selection of treatment. Detection of mutation underlying the disease brought information on the risk of another pregnancy and possible consequences for its course.

REFERENCES


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