Prenatal Exposure to Methamphetamine Presenting as Neonatal Cholestasis

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Introduction: Methamphetamine has been recognized as a common cause of acute toxic hepatitis in adults with clinical and histologic features indistinguishable from acute viral hepatitis. Clinical presentation of methamphetamine hepatotoxicity ranges from mild acute hepatitis with prompt recovery to fulminant hepatic failure. The pathophysiology of this hepatotoxicity is not well elucidated. Prenatal exposure to methamphetamine has been linked to intrauterine growth retardation and variety of withdrawal symptoms. Neonatal cholestasis is rare but serious problem that indicates hepatobiliary dysfunction and has several categories of etiologies. These include infectious, metabolic, endocrine, toxic, structural, familial, and autoimmune disorders. Cholestatic hepatitis is a recognized complication of exposure to some drugs including carbamazepine and trimethoprim-sulfamethoxazole.

Case: A 35-week preterm, appropriate for gestational age, white girl was born to a 39-year-old mother who had no prenatal care. The mother's urine drug screen revealed methamphetamine. The baby passed pale meconium and her subsequent stools were hypopigmented. A detailed work up was done and was unremarkable except for hepatobiliary scintigraphy, with no activity noted in the small bowel on delayed imaging. An operative cholangiogram and liver biopsy were performed. The cholangiogram revealed patent bile ducts. Liver biopsy was consistent with acute viral or toxic hepatitis. Gradual drop of bilirubin was noted. With negative extensive work up for other etiology, known hepatotoxicity of methamphetamine, early onset of cholestasis that improved without specific therapy, it is strongly suspected that prenatal exposure to methamphetamine is the most likely culprit in this patient.

Discussion: This is the first recorded case of neonatal cholestasis related to prenatal exposure to methamphetamine. Methamphetamine is considered the fastest-growing illicit drug in United States. Hence, prenatal exposure to methamphetamine is expected to rise. Healthcare providers should become aware of the possibility of methamphetamine effect on the fetal liver. Raising awareness of the expectant mothers through the healthcare profession may reduce the risk of this condition.

Key Words: methamphetamine, neonatal cholestasis, prenatal drug exposure

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Neonatal cholestasis is an uncommon but potentially serious problem that indicates hepatobiliary dysfunction and has several recognized etiologies. These include infectious, metabolic, endocrine, toxic, structural, familial, and autoimmune causes. At least one third of all cases are still attributed to "idiopathic" neonatal hepatitis after a thorough work up.[1] The idiopathic category is now being used much less frequently because of the advances in the understanding of the molecular basis of several cholestasis syndromes.[2]

Methamphetamine has been recognized as a common cause of acute toxic hepatitis in adults[3] with clinical and histologic features almost identical to acute viral hepatitis.[4,5] There are reports of fulminant hepatic failure after its use.[6,7]

Methamphetamine abuse is a growing problem in several urban and rural parts of the United States. The recreational use of methamphetamine has been recognized at alarming proportion even in young adults.[8,9] Prenatal exposure to methamphetamines has been reported to result in intrauterine growth retardation and variety of withdrawal symptoms.[10,11] There are some reports on the effects of prenatal exposures on the developing brain of infants and young children.[12]

CASE REPORT

A 35-week preterm, appropriate for gestational age, white girl was born to a 39-year-old mother had no prenatal care and had pregnancy-induced hypertension. On admission to the hospital, the mother's urine drug screen revealed methamphetamines. The mother had premature rupture of membranes for 1 to 2 weeks with intermittent leaking of meconium-stained amniotic fluid followed by onset of preterm labor. Owing to breach presentation and meconium-stained fluid, emergency cesarian section was performed. Apgar scores were 5 at 1 minute and 9 at 5 minutes and birth weight was 2335 g. After initial stabilization and admission to the neonatal intensive care unit, the baby was noted to pass a pale meconium and all her subsequent stools were hypo-pigmented or acholic. There was no respiratory distress, dysmorphic features, hepatosplenomegaly or symptoms, and signs of methamphetamine withdrawal. The baby received intravenous Ampicillin and Gentamicin until sepsis was ruled out. She tolerated full enteral feeding by day 3. Jaundice and elevated liver enzymes developed by the second day of life.

Pediatric gastrointestinal service was consulted and a detailed work up was done to identify the possible etiology. This included normal abdominal ultrasound examination, serum amino acid screen, urine organic acid screen, blood and urine cultures, rapid plasma reagin test, Coombs test, serum ferritin and total iron-binding capacity, urine bile acid metabolites, and normal newborn metabolic state

screening for galactosemia, genetic mutations for cystic fibrosis, T4, and thyroid-stimulating hormone. Her α-1 antitrypsin level was 105 (respiratory rate: 100 to 210) and Pi phenotype was M2Z, not usually associated with liver disease. Laboratory evaluation was remarkable for elevated liver enzymes (aspartate aminotransferase 143, alanine aminotransferase 50, total bilirubin 8.9 with direct bilirubin 3.9, γ-glutamyl transferase 614, alkaline phosphatase 141, and triglycerides 316). Chemistry profile revealed initial metabolic acidosis (bicarbonate 15), moderate anemia (hemoglobin 11.4 g/dL), and both her urine and meconium drug screen revealed amphetamine metabolites. After 1 week on oral Phenobarbital 5 mg/kg/d, the baby had abnormal hepatobiliary scintigraphy (hydroxy imino-diacetic acid scan) with no isotope activity detected in the small bowel on the 24 hours delayed imaging. She has then undergone an operative cholangiogram and open liver biopsy. The operative cholangiogram revealed normally patent extra hepatic bile ducts.

The liver biopsy (Fig. 1) revealed marked intralobular cholestasis with significant acute and chronic portal and intralobular inflammation, including eosinophils. Degenerative hepatocellular changes and focal necrosis were also noted. Portal bile ducts were normal in appearance and number. Glycogen was noted within the hepatocytes but it was abolished by diastase digestion. These features were consistent with acute hepatitis picture, commonly seen in acute viral hepatitis. The liver biopsy was sent for additional evaluation in a regional center by consultant hepatic pathologist with considerable expertise in pediatric liver diseases. Additional immunohistochemical stains were performed. The consultant hepatic pathologist concurred with the acute hepatitis features and suggested the possibility of toxic or drug-induced hepatic injury. Immunohistochemical stain revealed no HBsAg, HB core Ag, cytomegalovirus, CD1a, and α-1 antitrypsin. Histologic examination of the placenta was unremarkable with no evidence of viral infection or features of intrauterine infections.

Although the biopsy had features consistent with acute viral hepatitis, there was no evidence of viral infection on several studies (hepatitis A, C, culture for enteroviruses, TORCH titers, and HIV screen). Hepatitis B surface antigen was detected in the baby's serum at 7 days of age. However, she had no detectable HBV on immunostain of the liver biopsy and the mother had no hepatitis B surface antigen and had normal liver enzymes. As the baby received recombinant hepatitis B vaccination in the first day of life, HB surface antigenemia was most likely secondary to her recent immunization. Transient HB surface antigenemia in newborns has been previously reported after immunization and may persist up to 3 to 4 weeks after the vaccine.[13,14]

The baby was treated with ursodeoxycholic acid, fat-soluble vitamins supplements and was fed a high medium chain triglycerides oil-containing formula. The cholestasis gradually improved (bilirubin dropped to 3.6 total and 2.8 direct by day 21). The liver enzymes have also improved but did not normalize by day 21. The synthetic liver function has remained normal. She had appropriate weight gain and was discharged in custody of her father, while the mother underwent rehabilitation for drug abuse. Follow-up in the pediatric gastrointestinal clinic at 3 months of age revealed completely normal liver enzymes and bilirubin with appropriate weight gain.

With biopsy features consistent with drug-induced or acute toxic hepatitis, negative extensive work up for viral infections or other etiology, the early onset of cholestasis followed by gradual improvement of the liver and general condition without specific therapy, and the known hepatotoxic effects of methamphetamine in adults, it is strongly suspected that prenatal exposure to methamphetamine is the most likely culprit in the pathogenesis of this baby's acute hepatitis and neonatal cholestasis.

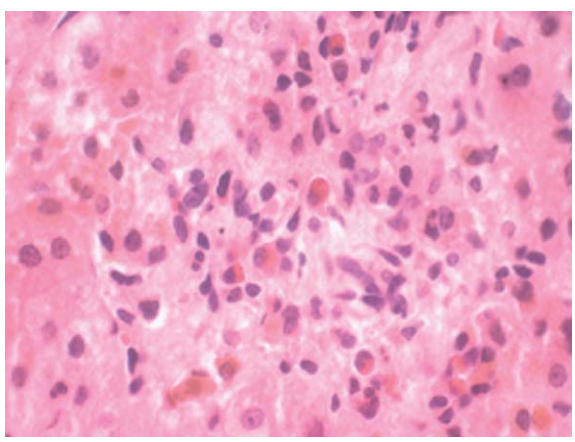

FIGURE 1. Hematoxylin and eosin photomicrograph of the liver biopsy showing intrahepatic cholestasis, intralobular inflammation, and hepatocellular damage.

DISCUSSION

Ten percent of American adults abuse drugs at some point in their lives, including 2.6% who become dependent on drugs, according to a recent federal report.[15] Methamphetamine is a powerfully addictive stimulant, that is generally considered the fastest-growing illicit drug in the United States.[8] Unlike imported recreational drugs such as heroin and cocaine, methamphetamine can be manufactured locally from commonly available household ingredients according to simple recipes readily available to young adults.[8] Methamphetamine users and producers are frequently the same. These characteristics of methamphetamine production and use may create conditions for a crisis of medical and social complications.[8,9] Hence, prenatal exposure to methamphetamines is only expected to rise in many communities in urban and rural United States.

There is a great variability of the clinical presentations of methamphetamine-associated hepatotoxicity, ranging from mild acute hepatitis with complete recovery in few weeks, to a fulminating hepatic failure with possible fatal outcome. Chronic exposure has also been linked to accelerated hepatic fibrosis.[16] Histologic features of methamphetamine-associated hepatotoxicity include lobular hepatitis with cholestasis, acute confluent necrosis, ballooning degeneration in centrilobular zones with little, or no inflammatory changes involving the portal tracts.[17] The pathophysiologic mechanism of this hepatotoxicity is not well elucidated. Various hypotheses were postulated including immunoallergic-type hypersensitivity, apoptosis phenomenon, vitamin E deficiency and the role of the occasionally concomitant malignant hyperthermia, with or without ischemia.[18,19] The

metabolites of methamphetamine and also individual genetic susceptibility to idiosyncratic hepatotoxicity have also been suggested. The hepatotoxicity of methamphetamines does not seem to be dose dependent nor related to cumulated duration of exposure.[18] There are no parameters which could predict the course and severity of methamphetamine-induced hepatopathy. Brncic and colleagues[20] propose a possible association of a specific HLA phenotype to methamphetamine-induced hepatotoxicty.

Cholestatic hepatitis has been recognized as a complication of prenatal or postnatal exposure to certain medications, including carbamazepine and trimethoprim-sulfamethoxazole.[21,22]

To the best of our knowledge, this is the first reported case of neonatal cholestasis related to prenatal exposure to methamphetamine. There are better recognized fetal and neonatal complications to prenatal exposure to methamphetamine, therefore, another confounding factor or a "second hit" effect in this case may need to be considered.

Although not usually associated with liver disease, α-1 antitrypsin Pi M2Z and preterm labor may have played a role in this baby's liver susceptibility to maternal illicit drug use.

Universal vaccination of the newborn against hepatitis B may result in transient antigenemia with HBsAg. Caution in interpreting the result of this test to screen for hepatitis B is therefore recommended. HBV DNA titer in this setting or repeating HBsAg more than 4 weeks after immunization would be more reliable.

In addition to the well-recognized risks for intrauterine growth retardation, withdrawal symptoms, and concerns about long-term neurodevelopment outcome,[10–12] physicians and other healthcare providers should become aware of the possibility of its effects on the developing liver of the unborn baby as highlighted by this case. Long-term hepatic outcome and prognosis in our patient is not definitively established but it appeared to have promptly resolved. Raising awareness of the expectant mothers through the healthcare profession and, hopefully, the popular media may reduce the risk of this condition.

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