Residência Pediátrica
Publicação Oficial da Sociedade Brasileira de Pediatria

Submitted on: 04/06/2018
Approved on: 05/26/2018

CASE REPORT

Neonatal cholestatic hepatitis associated with maternal use of carbamazepine during pregnancy end breast feeding

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Keywords:
Carbamazepine,
Cholestasis,
Intrahepatic,
Breast Feeding,
Pregnancy,
Jaundice,
Neonatal.

Abstract

This case reports a male newborn who developed neonatal jaundice after the first 20 hours of life due to exposure to carbamazepine during pregnancy and breastfeed. Other causes were excluded after several imaging and laboratory tests. Jaundice ceased weeks after the exclusion of breastfeeding, with normalization of liver enzymes and bilirubin levels.

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Residência Pediátrica 2018;8(3):131-133. DOI: 10.25060/residpediatr-2018.v8n3-05

INTRODUCTION

After migraine, epilepsy is the second most common chronic neurological condition in pregnant women. With proper prenatal care, careful monitoring during pregnancy, and folic acid supplementation, the incidence of maternal and fetal complications can be reduced.[1,2]

Most data on fetal risk from the use of anticonvulsants are obtained from case reports and studies involving epileptic patients. Carbamazepine (CBZ) crosses the placental barrier and is also excreted in breast milk, with the fetal concentration being 50%–80% of that detected in the mother. The use of this drug is associated with a two to three times increased risk of fetal deformations, especially spina bifida, whose occurrence increases when the drug is used in the first two trimesters. The incidence of this disease in the general population is 0.5%–1% while this medication is being used.[3,4,5] This psychopharmaceutical can also cause cleft palate, anal atresia, meningomyelocele, ambiguous genitalia, and the condition known as "anticonvulsant face," which is characterized by midface hypoplasia, short nose, anteverted nostrils, and long upper lip.[4]

Newborns exposed to CBZ may have reversible vitamin K deficiency, altered coagulation, and cerebral hemorrhage with irreversible neurological damage. Also described are transitory changes in liver function with elevated levels of conjugated bilirubin and gamma-glutamyltransferase (gamma-GT), low birth weight, and intrauterine growth retardation.

A few case reports have shown that infants developed cholestatic hepatitis, hyperbilirubinemia, and elevated gamma-GT level; these changes were transitory and ceased when breastfeeding was interrupted. Consequently, with CBZ may be considered an anticonvulsant of choice during breastfeeding, albeit there is rigorous monitoring of the nursing mother.[4,6]

CLINCAL CASE REPORT

A full-term newborn male was delivered via cesarean section at a gestational age (GA) of 38 and 1/7 weeks, calculated according to the date of last menstruation and 39 weeks according to ultrasound (US), which was appropriate for gestational age. Birth weight was 3485 g, Apgar score was 9/10, and blood type was B+. The mother was 30 years old, secundigravida, and attended eight prenatal consultations; maternal blood type was O–. Blood test results showed negative serology for HIV, VDRL, and hepatitis B and C; immunity to rubella and cytomegalovirus; susceptibility to toxoplasmosis; and unknown for Guillain–Barré syndrome. She started using CBZ 800 mg/day at 11 weeks of pregnancy to treat epilepsy. The newborn developed early neonatal jaundice at 20 h of life and presented ABO and Rh incompatibility with negative direct antiglobulin (Coombs') test; he was treated with phototherapy (Bilitron). Despite demonstrating signs of hemolysis, with 5.4% reticulocytes, the level of unconjugated bilirubin dropped while that of conjugated bilirubin continuously increased, reaching a value of 8.7 mg/dL. This was associated with increased gamma-GT (maximum 429 U/L) and slightly elevated liver enzyme (AST/GPT) levels as the case progressed (Tables 1 and 2), without signs of choluria or acholic stools. An abdominal US was performed to rule out biliary atresia; blood samples were obtained for TORCH and trans-infectious hepatic testing; and cranial computed tomography (CT) detected no calcifications. The test results ruled out neonatal sepsis or metabolic disorders that could justify the condition; the Guthrie test was conducted to rule out phenylketonuria, congenital hypothyroidism, sickle cell disease, cystic fibrosis, biotinidase deficiency, and congenital adrenal hyperplasia. This led to the hypothesis of medication-induced cholestatic hepatitis related to maternal CBZ use during pregnancy and breastfeeding, and thus, breastfeeding was suspended. The newborn's condition improved, andthe jaundice gradually improved, with bilirubin and hepatic enzyme levels returning to normal after 16 weeks of follow-up.

DISCUSSION

CBZ use leads to liver damage in adults and children, but there are few reports of neonatal cholestatic hepatitis associated with maternal exposure to the drug during pregnancy and breastfeeding, with CBZ considered safe up to that point. Few case reports or studies have reported CBZ-induced cholestatic hepatitis at birth because early diagnosis is difficult.

Table 1. Evolution of total bilirubin levels and fractions.

	24/Apr	27/Apr	02/May	23/May	06/Jun	04/Jul	17/Aug
BT (mg/dL)	11.80	12.90	9.40	4.30	1.5	0.2	0.2
BD (mg/dL)	2.70	8.70	7.40	3.70	1.2	0.1	0.1
BI (mg/dL)	9.10	4.20	2.00	0.60	0.3	0.1	0.1

Table 2. Evolution of hepatic enzymes.

	25/Apr	30/Apr	02/May	23/May	06/Jul	04/Jul	17/Aug
TGO	45 U/L	79 U/L	98 U/L	72 U/L	72 U/L	43 U/L	
40 U/L TGP	8 U/L	30 U/L	44 U/L	66 U/L	88 U/L	72 U/L	
50 U/L GGT	292 U/L	429 U/L	421 U/L	383 U/L	323 U/L	254 U/L	59 U/L
FA	235 U/L	303 U/L	348 U/L	505 U/L	445 U/L	406 U/L	481 U/L

The following are characteristics of this hepatic dysfunction: early appearance of predominantly conjugated hyperbilirubinemia and discrepancy between normal or slightly elevated liver enzyme and elevated gamma-GT levels. During the course of the clinical investigation, gamma-GT level gradually decreased and remained below normal levels even after the normalization of conjugated hyperbilirubinemia; the case spontaneously resolved after breastfeeding was discotinued.

Because of the difficult diagnosis, we began to investigate maternal use of medications during pregnancy and breastfeeding. This was when the mother reported that with guidance from the gynecology service that provides prenatal care, she had taken CBZ at the dose mentioned above since the beginning of pregnancy because she had been epileptic since adolescence. She also reported that prior to her pregnancy, she had taken phenytoin and that she was advised to switch to CBZ because it was safe for use during pregnancy.

With this information and knowing that CBZ crosses the placental barrier and is excreted through breast milk, we finally arrived at a diagnosis of CBZ-induced cholestatic hepatitis.

CONCLUSION

As CBZ crosses the placental barrier and is excreted in breastmilk, medical professionals should be attentive to adverse effects in infants exposed to the medication during pregnancy or breastfed by mothers who take this drug, considering the risks and benefits of breastfeeding in patients who develop cholestatic hepatitis. Although the patient improved spontaneously after the cessation of breastfeeding and did not suffer any aftereffects, this condition may expose the patient to unnecessary diagnostic procedures, prolong hospitalization, and cause emotional stress in the family.

A close evaluation of the case described above shows that although cases such as these are rare and make excellent progress after diagnosis, all pregnant women using CBZ should be closely monitored, even after childbirth; breastfeeding should not be discontinued if the infant does not present any symptoms, and the mothers should be directed to look out for jaundice during this period, which allows the medication to be safely used.

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