Withdrawal syndrome and hypomagnesaemia and in a newborn exposed to valproic acid and carbamazepine during pregnancy

Mehmet Satar¹, Kadir Ortaköylü², İnci Batun², Hacer Y. Yıldızdaş¹, Ferda Özlü¹, Hüsnü Demir³, Ali Kemal Topaloğlu⁴

¹Division of Neonatology, Department of Pediatrics, Çukurova University School of Medicine, Adana, Turkey

²Department of Pediatrics, Çukurova University School of Medicine, Adana, Turkey

³Division of Pediatric Cardiology, Department of Pediatrics, Çukurova University School of Medicine, Adana, Turkey

⁴Division of Pediatric Endocrinology, Department of Pediatrics, Çukurova University School of Medicine, Adana, Turkey

Abstract

The usage of drugs during pregnancy affect the fetus and the newborn. In this report, we present findings from a newborn baby, whose mother was epileptic, and was under the treatment of valproic acid and carbamazepine during pregnancy. We have found symptoms of withdrawal syndrome, hyponatremia and feeding problem, which was most probably related to exposure to the mentioned drugs. We have also diagnosed hypomagnesaemia and atrial septal defect 4 milimeters in diameter. There are already many reports about the side effects of valproic acid and carbamazepine usage during pregnancy. To the best of our knowledge, hypomagnesaemia has not yet been reported as a side effect. We think that hypomagnesaemia is also related to the usage of antiepileptics. (Turk Pediatri Ars 2016; 51: 114-6)

Keywords: Carbamazepine, hypomagnesaemia, newborn, pregnancy, valproic acid withdrawal syndrome

Introduction

The primary mechanism of action of carbamazepine which is an antiepileptic drug is inhibition of voltage-gated sodium channels. In this way, hyperactive nerve membranes are stabilized and recurrent neuronal discharge is inhibited. In addition, carbamazepine stimulates antidiuretic hormone (ADH) release and increases reabsorption of water (1). When it is used by epileptic mothers during pregnancy, it leads to accumulation in the fetal tissues by crossing the placenta. In babies exposed to carbamazepine in the prenatal period, dysmorphic facial appearance, craniofacial and cardiac abnormalities, spina bifida, intrauterine growth retardation, nausea, vomiting, feeding problems and withdrawal symptoms in the neonatal period have been reported (2, 3).

It is thought that the main mechanism of action of valproic acid which is another antiepileptic drug is related

with strengthening of the GABAergic pathways. It has been reported to lead to facial dysmorphism and multiple malformations in the extremities in case of intrauterine exposure. In addition, it may lead to neural tube defects including meningomyelocele and spina bifida (4).

Here, a newborn patient who was exposed to carbamazepine and valproic acid throughout pregnancy and had hypomagnesaemia and atrial septal defect in addition to withdrawal symptoms has been presented because of observation of findings which have not been reported before.

Case

In the prenatal history, it was learned that the mother had epilepsy for about seven years, used carbamazepine for five years, valproic acid was added to treatment when the number of seizures increased and she had been us-

ing carbamazepine and valproic acid in combination for the last two years. Throughout pregnancy, she used carbamazepine 2x400 mg (Tegretol 400 mg tablet) and valproic acid (500 mg in the morning and 750 mg in the evening) (Convulex 500 mg tablet). It was learned that the mother attended neurology and gynecology outpatient visits regularly throughout her pregnancy. In monthly carbamazepine and valproic acid measurements, the highest valproic acid level was found to be 74.5 mmol/mL and the lowest level was found to be 41.5 mmol/mL. The carbamazepine levels were measured to be in the therapeutic range.

The patient was delivered by cesarean section in the 39th gestational week from the second pregnancy of a 24-year old mother who had epilepsy and a 28-year old healthy father. The birth weight was found to be 3 540 g, the birth height was found to be 47 cm and the head circumference was found to be 34 cm. The baby did not cry at birth and was cyanotic. The apical heart beat was below 100/min. Following continuous positive pressure ventilation for 30 seconds the apical heart beat become >100/min. The Apgar scores at the first and fifth minutes were found to be 6 and 7, respectively.

The baby was internalized in the Neonatal Intensive Care Unit after delivery. His physical examination findings were as follows: body temperature: 36.5°C, pulse rate: 142/min, respiratory rate: 68/min., blood pressure: 68/34 (48) mmHg. His general status was poor and he had groaning, retractions and tremors. The lung sounds were found to be coarse. The cardiac sounds were rhythmic and a 2/6°C systolic murmur was heard. He had a normal male external genital appearance. His right testicle was palpable, but his left testicle was non-palpable.

The capillary blood gas values were as follows: pH= 7.2, pCO₂= 67 mmHg, HCO₃= 20.6 mmol/L, BE= -1.6 mmol/L, Na= 143 mmol/L, K= 4.9 mmol/L, iCa= 1.57 mmol/L, blood glucose= 58 mg/dL, Hct= %43. His complete blood count at admission was normal. Nasal CPAP (continuous positive airway pressure) was initiated. Neonatal withdrawal scale (Finnegan scale) was applied with 12-hour intervals starting from the first day (5). Midazolam was administered intravenously at a dose of 0.1 mg/kg, because the patient had marked tremors. Total parenteral nutrition was initiated, because he could not be fed orally. In the follow-up, the carbondioxide levels decreased in the first 24 hours. When the blood gas values were found to be normal on the second day, nasal CPAP was discontinued. In the follow-up of electrolytes,

sodium levels were found to be decreased on the second day of life. The sodium levels gradually decreased to 129 mmol/L (139-134-131-130-129 mmol/L). The amount of sodium given with parenteral fluid was increased. Additional 5 mEq/kg Na was given for three days and the sodium levels were found to be normal from the fifth day. The biochemical tests measured on the second day were as follows: BUN= 16 mg/dL, creatinine: 0.80 mg/dL, AST= 35 U/L, ALT= 9 U/L, Na= 131 mmol/L K= 4.3 mmol/L Ca= 7.9 mg/dL Mg= 1.72mg/dL (normal range: 1.8-2.5 mg/dL). Magnesium at a dose of 50 mg/kg was given for three days to the baby who was found to have a low magnesium value. The patient's valproic acid and carbamazepine blood levels were found to be below the therapeutic range. The score which was 11 on the first day decreased to 8 on the 2nd-3rd days and to 3 on the following days. Withdrawal symptoms were not found after one week. Oral feeding was initiated from the fourth day. On echocardiography, a small secundum ASD (4 mm), patent foramen ovale and "shelf" in the aortic isthmus were observed. On abdominal ultrasonography, hydro-nephrosis was not observed and mild pelvicalical thickening was found. The baby who was fed orally and had balanced vital findings was discharged on the 14th day with recommendations to be followed up with outpatient visits. Written informed consent was obtained from the patient's family.

Discussion

Many drugs used by the mother during pregnancy affect the fetus. It has been reported that antiepileptics among the drugs which should be used in serious health problems including epilepsy lead to problems in the fetus and in the neonatal period (2-4). Here, the withdrawal symptoms observed in a newborn baby of a mother who used valproic acid and carbamazepine throughout her pregnancy and additional findings which are thought to be related with these drugs have been presented.

While experimental studies and case reports in this area usually address babies of mothers who use a single antiepileptic drug, the findings of a baby whose mother used two antiepileptic drugs in combination throughout her pregnancy have been presented here. The findings described in this patient have been discussed in the light of the literature.

Dysmorphic facial appearance, cranial defects, cardiac anomalies, spina bifida, intrauterine growth retardation, nausea, vomiting, feeding problems, hyponatremia and

withdrawal symptoms in the neonatal period have been reported in babies exposed to carbamazepine in the prenatal period (6). Withdrawal syndrome findings, feeding problem, hyponatremia and ASD as a cardiac anomaly were found also in our patient. Tremors which started in the first hours after delivery in relation with withdrawal syndrome, became prominent in the first three days and disappeared in one week were observed.

Dysmorphic face, various congenital anomalies, neurodevelopmental disorders and withdrawal syndrome findings have been reported in babies exposed to valproic acid in the prenatal period (7-9). In our patient, no anomaly except for cardiac anomaly was observed. Recurrent hypoglycemia attacks in addition to cyanosis and retractions in the first days after delivery were reported in the baby of a mother who used valproic acid and phenytoin during pregnancy (10). Respiratory distress was found in the first hours following delivery and marked hypoglycemia was not found in our patient.

In addition, hypomagnesemia was found in our patient. It was noted that this finding was not observed in the cases reported previously. Absence of diabetes or toxemia in the mother which could lead to hypomagnesemia in the baby, absence of intrauterine growth retardation, premature delivery or polysthemia and improvement of hypomagnesemia with short-term treatment suggested that hypomagnesemia in this baby might be related with the antiepileptic drugs used by the mother.

Here, the findings observed during the neonatal period in a baby whose mother used carbamazepine and valproic acid throughout her pregnancy have been presented. It was thought that tremors observed in the baby, respiratory distress observed in the first hours after delivery, hypomagnesemia and cardiac anomaly were related with carbamazepine and valproic acid used during pregnancy. The finding of hypomagnesemia which was not described before was notable in this baby.

Informed Consent: Written informed consent was obtained from patients.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - M.S.; Design - K.O., İ.B.; Supervision - M.S.; Funding - M.S., H.Y.Y., F.Ö.; Data Collection and/or Processing - K.O., İ.B., H.D.; Analysis and/or Interpretation - M.S., A.K.T.; Literature Review - M.S., K.O., İ.B.; Writing - M.S., K.O.; Critical Review - H.Y.Y., F.Ö., A.K.T.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

References

1. Ambrósio AF, da-Silva PS, Carvalho CM, et al. Mechanisms of action of carbamazepine and its derivatives, oxcarbazepine, BIA 2-093, and BIA 2-024. *Neurochemical Research* 2002; 27: 121-30. [\[CrossRef\]](#)
2. Mølgaard-Nielsen D, Hviid A. Newer-generation antiepileptic drugs and the risk of major birth defects. *JAMA* 2011; 305: 1996-2002. [\[CrossRef\]](#)
3. Elshama SS, Osman HE, El-Kenawy Ael-M, et al. Teratogenic effect of carbamazepine use during pregnancy in the mice. *Pak J Pharm Sci* 2015; 28: 201-2
4. Chandane PG, Shah I. Fetal valproate syndrome. *Indian J Hum Genet* 2014; 20: 187-8 [\[CrossRef\]](#)
5. Zimmermann-Baer U, Nötzli U, Rentsch K, et al. Finnegan neonatal abstinence scoring system: normal values for first 3 days and weeks 5-6 in non-addicted infants. *Addiction* 2010; 105, 524-8. [\[CrossRef\]](#)
6. Karataş Z, Karataş A, Özlü T, et al. Bicuspid aortic valve and severe aortic stenosis in a newborn exposed to carbamazepine during pregnancy. *J Turk Ger Gynecol Assoc* 2014; 15: 259-61. [\[CrossRef\]](#)
7. Bromley R, Weston J, Adab N, et al. Treatment for epilepsy in pregnancy: neurodevelopmental outcomes in the child. *Cochrane Database Syst Rev* 2014; 10: CD010236. [\[CrossRef\]](#)
8. Rodríguez-Pinilla E, Mejías C, Prieto-Merino D, et al. Risk of hypospadias in newborn infants exposed to valproic acid during the first trimester of pregnancy: a case-control study in Spain. *Drug Saf* 2008; 31: 537-43. [\[CrossRef\]](#)
9. Jentink J, Loane MA, Dolk H, et al. Valproic acid monotherapy in pregnancy and major congenital malformations. *N Engl J Med* 2010; 362: 2185-93. [\[CrossRef\]](#)
10. Çoban D, Kurtoglu S, Akın MA, Akçakuş M, Güneş T. Neonatal episodic hypoglycemia: a finding of valproic acid withdrawal. *J Clin Res Pediatr Endocrinol* 2010; 2: 92-4. [\[CrossRef\]](#)