Introduction

Antiepileptic drugs (AEDs) received during pregnancy have potential adverse effects on foetal development. In the United States alone, over 25,000 children have a history of in-utero AED exposure each year (1), which increases the risk of major congenital malformations in the foetus from 3.3% to 7.7% (2, 3). Cardiovascular malformations, neural tube defects, cleft palate and urogenital abnormalities are among the congenital abnormalities that can develop secondary to in-utero AED exposure. Multicystic dysplastic kidney, hydronephrosis, ureteropelvic junction stenosis and hypospadias are the abnormalities of the urinary system that are reported to be associated with maternal AED use during pregnancy (2, 3). Cardiac malformations associated with antenatal exposure to an AED have been reported to have a prevalence of 7.8% in infants of mothers with epilepsy (4) and include ventricular septal defect, atrial septal defect, tetralogy of Fallot, patent ductus arteriosus, pulmonary stenosis, tricuspid regurgitation and transposition of great arteries (2-4).

Carbamazepine (CBZ) is among the most commonly used AEDs during pregnancy. Major congenital malformations reported to be associated with CBZ use in the cohort studies are several cardiovascular malformations, spina bifida, cleft lip with or without cleft palate, hypospadias, inguinal hernia, diaphragmatic hernia, hypertrophic pyloric stenosis, ectopic and hypoplastic thyroid (2-4).

This report describes the case of a newborn exposed in utero to CBZ during pregnancy and who was born with a cardiac malformation. The infant was referred due to cardiac murmur in the second week of his life. The mother had not received folic acid supplementation. Transthoracic echocardiography revealed bicuspid aortic valve, mild aortic stenosis, patent foramen ovale and the renal ultrasound revealed mild left hydronephrosis. Follow-up echocardiography performed 14 weeks later showed increased severity of aortic stenosis and percutaneous balloon aortic valvuloplasty was performed. To our knowledge, there is only one case report in the literature mentioning the association of a bicuspid aortic valve with oxcarbazepine exposure, which is a structural derivative of carbamazepine. However, there are no reports for association with carbamazepine itself. Bicuspid aorta and aortic stenosis may be among the cardiac malformations that result from the teratogenic effect of carbamazepine. (J Turk Ger Gynecol Assoc 2014; 15: 259-61)

Key words: Aortic stenosis, bicuspid aortic valve, carbamazepine, pregnancy

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Case Presentation

A 14 day-old male infant born from a mother using AED during pregnancy was referred to the paediatric cardiology department due to cardiac murmur. He was born in the 39th gestational week vaginally to an epileptic mother who had been treated with carbamazepine throughout her pregnancy. He was referred due to cardiac murmur in the second week of his life. The mother had not received folic acid supplementation. Transthoracic echocardiography revealed bicuspid aortic valve, mild aortic stenosis, patent foramen ovale and the renal ultrasound revealed mild left hydronephrosis. Follow-up echocardiography performed 14 weeks later showed increased severity of aortic stenosis and percutaneous balloon aortic valvuloplasty was performed. To our knowledge, there is only one case report in the literature mentioning the association of a bicuspid aortic valve with oxcarbazepine exposure, which is a structural derivative of carbamazepine. However, there are no reports for association with carbamazepine itself. Bicuspid aorta and aortic stenosis may be among the cardiac malformations that result from the teratogenic effect of carbamazepine. (J Turk Ger Gynecol Assoc 2014; 15: 259-61)
mother had no epileptic seizures throughout the pregnancy. At 39 weeks of gestation, she delivered a male infant with spontaneous vaginal delivery with a 1st and 5th minute Apgar score of 8 and 10, respectively. The infant’s birth weight was 3050 grams, head circumference was 34.5 cm, and height was 50 cm, all of which were appropriate for the gestational age at delivery. Physical examination revealed systolic ejection murmur (grade III/VI) at the upper right sternal border and laryngomalacia. There were no additional abnormalities. The phenotype of the infant was not suggestive of known genetic syndromes. Transthoracic echocardiography showed a bicuspid aortic valve (BAV) (functionally bicuspid), mild aortic stenosis, patent foramen ovale, and patent ductus arteriosus. There were no other cardiac lesions. Renal ultrasound revealed mild left hydronephrosis without evidence of posterior urethral valve. Blood count, electrolytes, renal function tests, liver enzymes, thyroid hormones and cranial ultrasound were normal. Repeat echocardiography performed in the 14th week of life showed an increased severity of aortic stenosis. Doppler ultrasound revealed severe aortic stenosis with a mean gradient of 70 mmHg (Figure 1). Aortography showed aortic stenosis with BAV (Figure 2). Upon these findings, percutaneous balloon aortic valvuloplasty was performed with a 9 mm BAV catheter. Peak systolic gradient of aortic valve decreased from 86 mmHg before the procedure to 33 mmHg after the procedure. Echocardiographic follow-up at 6 months showed spontaneous closure of the patent foramen ovale, a small patent ductus arteriosus, BAV, mild aortic stenosis (peak gradient 36 mmHg) and mild aortic regurgitation (Figure 3). Paediatric assessment revealed normal growth and development. Written informed consent was obtained from the parents for this study.

Discussion

Some studies have proposed that the mother’s epilepsy plays an important role in development of foetal malformations (4). However, recent studies have suggested that AED therapy is the main cause of neural tube and cardiac defects. Their association with other birth defects is not clear. Moreover, the congenital malformation rate increases during the first trimester of pregnancy (2, 4, 5). Folic acid supplementation in the periconceptional period is shown to be associated with a reduced risk of congenital malformations, especially of neural tube defects, heart defects, cleft palate and limb defects (2, 5, 6). On the other hand, there is no evidence to suggest that additional folic acid supplementation decreases the risk of congenital malformations associated with in-utero AED exposure (4, 7). During pregnancy, AEDs should be used at the lowest possible dose that is compatible with the maternal disease. The dose of the AEDs should be reduced beginning from the periconceptional period to the first 8 weeks of gestation to avoid any unwanted effect on organogenesis (2, 8). CBZ at doses greater than 400 mg per day increase the risk of congenital anomalies (8). Besides the dose of the AEDs, the risk of major congenital malformations is also affected by other variables such as parental history of congenital anomalies. Moreover, cardiovascular malformations were significantly more frequent in premature infants of mothers with epilepsy (4). The mother in the present case had not only used a high dose of CBZ, but had also not used folic acid supplementation, which might be one of the possible causes of the congenital malformation seen in this infant. However, BAV seen in our case could also be an isolated finding which was not associated with drug exposure since BAV is the most common cardiac lesion seen in the newborn population.
Carbamazepine shows its antiepileptic effect by blocking voltage-gated sodium channels and stabilizing neuroexcitatory tissues. It has been suggested that CBZ is relatively safer than other AEDs during pregnancy (3). Cohort studies evaluating the teratogenic effects of CBZ have shown a significantly increased risk only for spina bifida (2, 3). Cardiovascular malformations associated with in-utero CBZ exposure include ventricular septal defect, hypoplastic left ventricle, transposition of the great arteries and anomalous pulmonary venous return (2-4, 9). Akar et al. (10) have reported a case of foetal CBZ syndrome presenting with facial dysmorphism, skeletal abnormalities, congenital heart defect, renal agenesis, anal atresia, ambiguous genitalia, and right hemihypoplasia of the entire body. Rolnitsky et al. (11) reported an infant with congenital abnormalities (BAV, mild aortic stenosis, patent ductus arteriosus, patent foramen ovale, and severe unilateral hydronephrosis due to ureteropelvic junction stenosis), hyponatraemia, and a withdrawal syndrome following in-utero oxcarbazepine exposure. There is another case report which mentions an association of aortic stenosis with antenatal use of oxcarbazepine (2). The infant also developed hyponatremia and a withdrawal syndrome, which has not been reported in infants exposed to CBZ during pregnancy.

To the best of our knowledge, BAV that may be associated with exposure to CBZ during pregnancy has not been previously described. BAV includes a spectrum ranging from critical aortic stenosis to an asymptomatic finding which is not associated with aortic stenosis or regurgitation. In the present case, severe aortic stenosis developed during follow-up, and valvuloplasty was performed. There was no hyponatremia or neonatal withdrawal syndrome. With the present clinical findings, known genetic syndromes associated with abnormalities of the vascular system such as Marfan disease, Turner, Loews-Dietz, Williams and other syndromes were excluded. We presented a case of BAV and severe aortic stenosis in an infant who had a history of in-utero CBZ exposure. Although it could be just a coincidence of an isolated BAV with an in-utero drug exposure, this possible association should be kept in mind by obstetricians and paediatricians during follow-up of infants exposed to AEDs during pregnancy. In appropriate cases, the AEDs should be reduced to the lowest possible dose beginning from the preconception period and supplementation of folic acid should be considered.

**Ethics Committee Approval:** N/A.

**Informed Consent:** Written informed consent was obtained from patients’ parents who participated in this study.

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