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ORIGINAL ARTICLE

Fetal Valproate Syndrome

Hatice Mutlu-Albayrak [a,*], Cahide Bulut [b], Hüseyin Çaksen [a,b]

[a] *Department of Pediatric Genetics, Meram Medical Faculty, Necmettin Erbakan University, Konya, Turkey*
[b] *Department of Pediatric Neurology, Meram Medical Faculty, Necmettin Erbakan University, Konya, Turkey*

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Key Words
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skeletal abnormalities

Background: There have been several reports of congenital malformations in the offspring of mothers who took valproic acid (VPA) during pregnancy as a treatment for epilepsy.
Methods: Herein, we describe four cases with typically similar facial features of fetal valproate syndrome accompanied to minor skeletal abnormalities.
Results: The first case was a 16-month-old girl, presenting with facial dysmorphism, and finger abnormalities. Her mother took VPA (1500 mg/d) up to the 10th gestational week and at a dosage of 1000 mg/d through the pregnancy. The second patient was 5-year-old boy with speech disability, bilateral cryptorchidism, facial dysmorphism, and finger abnormalities whose mother took VPA (1000 mg/d) through pregnancy. The third 19-month-old patient was the brother of the second patient who had facial dysmorphism, bilateral cryptorchidism, and finger abnormalities. His mother also took VPA (1000 mg/d) through pregnancy. The fourth 3-year and 6 month-old boy with minor facial dysmorphism and sternum deformity was exposed to VPA (500 mg/d) *in utero*.
Conclusion: In conclusion, there is a recognizable spectrum of abnormalities in some infants exposed to VPA without dose-depence and the common facial dysmorphic features and minor skeletal abnormalities that may occur within the both low and high dose VPA use.

1. Introduction

The use of valproic acid (VPA) monotherapy in the 1st trimester of pregnancy was associated with significantly increased risks of major and minor malformations, including a 20-fold increase in neural tube defects (NTDs), cleft lip and palate, cardiovascular abnormalities, genitourinary defects, developmental delay, endocrinological disorders, limb defects, and autism, compared with the risk without the use of antiepileptic drugs (AEDs).[1]

VPA causes dose-related teratogenic effects in all species investigated (monkeys, rodents, rabbits); these include

* Corresponding author. Department of Pediatric Genetics, Meram Medical Faculty, Necmettin Erbakan University, Konya, Turkey.
E-mail address: haticemutlu@gmail.com (H. Mutlu-Albayrak).

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skeletal malformations and craniofacial defects. The most common malformations in humans are cardiac and NTDs.[2] Many previous cases and studies focused on the associated major anomalies but overlooked the minor musculoskeletal abnormalities. However, substantial minor skeletal abnormalities were often reported.[3]

The facial features in infants exposed to VPA in infancy were first analyzed in detail by DiLiberti et al.[4] The commonly recognized features are epicanthal folds connecting with an infraorbital crease or groove, a flat nasal bridge, a small nose with anteverted nostrils, a long upper lip with relatively shallow philtrum, a relatively small mouth with downturned angles, and a thin upper vermilion border.[5]

We report four cases with typically similar facial features to VPA exposure *in utero*, accompanied by minor skeletal abnormalities.

2. Case Reports

2.1. Case 1

A 16-month-old girl was referred with limited extension in the fingers of both hands. She was born full-term weighing 3000 g by cesarean section (breech presentation). Her parents did not have consanguineous relations and she was the first child of the family. Her mother was a 22-year-old with a 12-year history of epilepsy. Before becoming pregnant she had been taking 1500 mg of VPA daily (in 3 × 500 mg doses). She discovered her pregnancy at the 10th week of gestation. VPA treatment was set at a dose of 1000 mg daily by an obstetrician from this gestational week and the mother was recommended to use folic acid during pregnancy. She used 1000 mg of VPA (500 mg twice daily) and folic acid (5 mg/d) up to birth. Her seizure disorder was well-controlled.

The patient was able to hold her head steady while sitting at the 4th month and able to sit unsupported at the 7th month. She spoke her first word at the 12th month. On examination, her weight was 11 kg (50th percentile), height was 75 cm (10th percentile) and fronto-occipital head measurement was 45 cm (10th–25th percentile). She had a narrow bifrontal diameter, round face, short neck, full cheeks, telecanthus, broad and low nasal bridge, small nose, long and smooth philtrum, thin upper vermillion border, downturned angles of the mouth, pointed chin, posteriorly rotated ears with attached earlobes (Figures 1A and 1B). Her thumbs were structured proximally. She had a camptodactyly deformity on the right thumb, 3rd and 4th fingers, left 4th and 5th fingers and also overriding on the left 2nd and 4th toes (Figures 1C, 1D and 1E). Her echocardiography revealed no cardiac structural defect. No central nervous system abnormality was identified on magnetic resonance imagining (MRI). No urinary system abnormalities were detected on abdominal ultrasonographic screening. The patient was recommended physical therapy exercises for finger anomalies.

2.2. Cases 2 and 3

Case 2, a 5-year-old boy, was admitted to the Pediatric Neurology Department with a speech disability. He was born by cesarean section (cephalopelvic disproportion) at the 34th gestational week to a 21-year-old mother. His

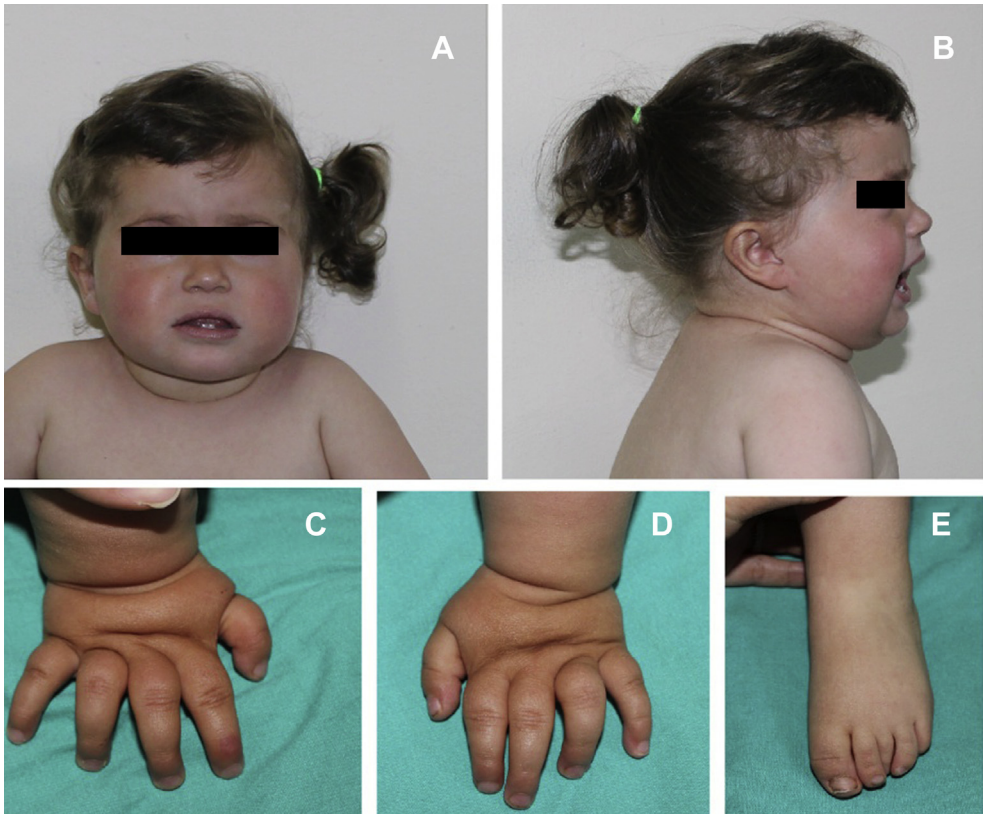

Figure 1 Clinical aspects of Case 1.

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