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

Received May 12, 2015; received in revised form Oct 3, 2015; accepted Jan 22, 2016
Available online 17 June 2016

Key Words
facial dysmorphism; fetal valproate syndrome; minor birth defects; 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.

Copyright © 2016, Taiwan Pediatric Association. Published by Elsevier Taiwan LLC. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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...
skeletal malformations and craniofacial defects. The most common malformations in humans are cardiac and NTDs.\textsuperscript{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.\textsuperscript{3}

The facial features in infants exposed to VPA in infancy were first analyzed in detail by DiLiberti et al.\textsuperscript{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.\textsuperscript{5}

We report four cases with typically similar facial features to VPA exposure \textit{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 x 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 vermilion 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

\textbf{Figure 1} \hspace{1cm} Clinical aspects of Case 1.
mother had epilepsy and had used VPA since her 1st decade. She started to use folic acid (5 mg daily) supplementation from the 4th week of preconception to the 3rd trimester and continued taking VPA (1000 mg twice daily) throughout the pregnancy. At the 2nd trimester, intra-abdominal acid was visualized on the fetal ultrasonography. After delivery the patient was hospitalized with respiratory insufficiency and nonimmune hydrops fetalis. No evidence was found in terms of congenital cytomegalovirus, herpes virus and toxoplasma virus infections. Cardiac examination and echocardiography screening were normal. At Postnatal Day 21 he was discharged in healthy condition. He was able to hold his head steady at the 8th-9th month and walked at the 18th month. At 2 years old he started to speak one or two words but never gained the ability to make sentences. He was operated on due to bilateral cryptorchidism at the age of 12 months. On examination, his weight was 21 kg (50th-75th percentile), height was 120 cm (90th-97th percentile), and fronto-occipital head measurement was 48.5 cm (<3rd percentile). He had telecanthus, flaring eyebrows, a broad nasal ridge, short nose, midface hypoplasia, full cheeks, long and smooth philtrum, downturned corners of the mouth, low-set ears, pointed chin, pectus excavatum, bilateral mega-halluces, and hypoplasia of the 5th toes with cutaneous syndactyly on the left 4th-5th toes. His left 2nd, 3rd and 4th toes were laterally angulated and the right 4th toe was medially angulated (Figures 3B and 3C). Small joint contractures were not observed on the hands. No additional abnormalities were demonstrated on cranial MRI and abdominal ultrasonography.

2.3. Case 4

A 3.5-year-old boy was referred to the Pediatric Genetics Clinic because of dysmorphic face and sternum deformity. He was born by cesarean section (polyhydroamnios) at the 38th gestational week to a 25-year-old mother as her second
child. The mother was epileptic and had used VPA for 15 years. She was taking VPA (500 mg daily, controlled release formulation) when she became pregnant. She continued to take VPA at the same dosage throughout the pregnancy. She started to use folic acid (5 mg daily) supplementation until the 8th week but did not use it regularly. The mother took VPA (500 mg daily) during her first pregnancy and had a healthy baby. The patient could walk and speak by 2–3 years. On examination his weight was 12 kg (10th percentile), height was 106 cm (50th percentile), and fronto-occipital head measurement was 45 cm (< 3rd percentile). He had upswept frontal hair, a high forehead, narrow bifrontal diameter, broad nasal bridge, short nose, anteverted nares, a long and smooth philtrum, thin upper vermillion border, downturned angles of the mouth, clefting on the lower right central incisor and pectus excavatum (Figure 4). An ostium secundum atrial septal defect was detected by echocardiography screening. No additional anomalies were depicted on cranial MRI and renal ultrasonography.

3. Discussion

VPA has been associated with a variety of major and minor malformations, including a 20-fold increase in NTD, cleft lip and palate, cardiovascular abnormalities, genitourinary defects, developmental delay, endocrinological disorders, limb defects, and autism. On account of the observed teratogenic effects of high-dosage (>1000 mg) VPA exposure in utero, VPA was offered at a dose not exceeding 1000 mg and with folate supplementation for the prevention of NTD in most cases. Although a number of cohort studies of women exposed to VPA in pregnancy showed an association with a range of malformations, individually these studies had limited power to detect excess risks of specific congenital malformations and overlooked the minor abnormalities. Many studies have indicated that women taking VPA during pregnancy had a twofold to 16-fold greater chance of having a child with a major congenital malformation, with dose-dependent characteristics. The rate of major congenital malformations up to 1 year with VPA < 700 mg daily was 24%, for 700–1500 mg it was 50%, and for >1500 mg it was 24%. The most common were cardiac malformations and NTDs. Almost all reported dose-related series were of major congenital malformations. In Case 1 the child had no major congenital malformation, having been exposed to maximum dose VPA (1500 mg/d) up to the 10th gestational week. Case 2 had bilateral cryptorchidism. Case 3 (1000 mg/d VPA throughout the pregnancy) had a ventricular septal defect in addition to bilateral cryptorchidism. Case 4 (500 mg/d VPA) had a small secundum atrial septal defect, detected in utero (Table 1).

Most available studies identified that abnormalities of the musculoskeletal system were the most common systemic abnormalities associated with the use of VPA in pregnancy. These abnormalities are variable, including the following: contractions of the small joints and the presence of long overlapping fingers (36%), followed by foot deformity (30%), thoracic cage abnormalities (7%), and nail abnormalities (10%). Skeletal deformities have also been observed in animal models. The most frequent malformations were fusion, agenesis and duplication of vertebrae, fusion or agenesis of ribs, fusion and asymmetry of sternebrae, and extra sternebrae. There were flexion contractures of fingers and toe overlapping in Case 1; pectus excavatum, left 5th finger clinodactyly, bilateral toe angulation deformities in Case 2; bilateral 5th toe hypoplasia and toe angulation deformities in Case 3; and pectus excavatum in Case 4. Kozma reported two siblings exposed...
<table>
<thead>
<tr>
<th>Case</th>
<th>Age (sex)</th>
<th>Valproate dose (exposure time)</th>
<th>Brain abnormalities</th>
<th>Cardiac abnormalities</th>
<th>Urogenital abnormalities</th>
<th>Musculoskeletal system abnormalities</th>
<th>Developmental delay</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Our cases</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case 1</td>
<td>16 mo (female)</td>
<td>1500 mg (preconception to 10th wk gestation) / 1000 mg (10th wk gestation to delivery)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Small hand joint contractures and toe overlapping</td>
<td>—</td>
</tr>
<tr>
<td>Case 2</td>
<td>5 y (male)</td>
<td>1000 mg (throughout pregnancy)</td>
<td>—</td>
<td>—</td>
<td>Bilateral cryptorchidism</td>
<td>Pectus excavatum, left 5th finger clinodactyly, bilateral toe angulation deformities</td>
<td>Speech delay</td>
</tr>
<tr>
<td>Case 3</td>
<td>19 mo (male)</td>
<td>1000 mg (throughout pregnancy)</td>
<td>—</td>
<td>Ventricular septal defect</td>
<td>Bilateral cryptorchidism</td>
<td>Bilateral 5th toe hypoplasia and toe angulation deformities</td>
<td>—</td>
</tr>
<tr>
<td>Case 4</td>
<td>3.5 y (male)</td>
<td>500 mg (throughout pregnancy)</td>
<td>—</td>
<td>Secundum atrial septal defect</td>
<td>—</td>
<td>Pectus excavatum</td>
<td>Gross motor delay</td>
</tr>
<tr>
<td>Winter et al 1987</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case 5</td>
<td>2 mo (male)</td>
<td>1600 mg (throughout pregnancy)</td>
<td>N/A</td>
<td>N/A</td>
<td>Hypospadias</td>
<td>Pectus excavatum, polydactyly of the right 5th finger and clinodactyly of the left 5th finger with mild talipes</td>
<td>N/A</td>
</tr>
<tr>
<td>Case 6</td>
<td>1d (male)</td>
<td>2400 mg (throughout pregnancy)</td>
<td>N/A</td>
<td>Ventricular septal defect</td>
<td>N/A</td>
<td>2nd and 4th toes of both feet overrode the 3rd toes</td>
<td>N/A</td>
</tr>
<tr>
<td>Case 7</td>
<td>3 mo (male)</td>
<td>2400 mg (throughout pregnancy)</td>
<td>N/A</td>
<td>Pulmonary stenosis</td>
<td>N/A</td>
<td>The 5th toes of both feet were proximally placed and overlapped the 4th toes</td>
<td>Gross motor delay</td>
</tr>
<tr>
<td>Kozma 2001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case 8</td>
<td>3 y (male)</td>
<td>1500 mg (throughout pregnancy)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Ulnar deviations of the fingers of both hands, mild contractures of the terminal phalanges of 2nd to 4th digits, pes planus, a lordotic curvature of the spine, curved middle toes bilaterally, contractures of the right index finger and the left middle finger, talipes equinovarus of the right foot, and metatarsus adductus of the left foot</td>
<td>Gross motor delay</td>
</tr>
<tr>
<td>Case 9</td>
<td>8 mo (male)</td>
<td>1500 mg (throughout pregnancy)</td>
<td>Prominence of the ventricles and of the cortical sulci in the frontal region, with cranial asymmetry.</td>
<td>—</td>
<td>—</td>
<td>The left testicle was undescended, two small cysts around the collecting system of the right kidney</td>
<td>Gross motor delay</td>
</tr>
</tbody>
</table>
to VPA 1500 mg/d, with contractures of the small joints and spinal and foot deformity without significant major malformation (Table 1). Schorry et al\textsuperscript{15} reported five siblings with finger and nail abnormalities, where each one was exposed to VPA of minimum 500 mg/d and maximum 2000 mg/d. Winter et al\textsuperscript{16} reported three cases with sternum and finger abnormalities accompanied by cardiac malformation, who were exposed to VPA doses between 1600 mg and 2400 mg/d \textit{in utero}.

VPA was also identified as a potential risk for developmental delay, cognitive impairment, attention deficit hyperactivity disorder, and autism, exceeding the risks for other AEDs.\textsuperscript{17,18} Although variation in study designs, outcomes, and cognitive tests precluded synthesis of these data into meta-analyses, all researchers reported developmental delays and cognitive deficits that were associated with VPA use in pregnancy. The most prominent effect was on verbal intelligence quotient. The Ankara Developmental Screening Inventory was applied to all cases. Case 2 suffered from delay of speech development and Case 4 had significant motor delay; however, there was no gross motor delay in Case 1 or 3. A common feature of all our cases was the presence of minor facial dysmorphism. All cases were microcephalic except for Case 1. Telecanthus (3/4), low nasal bridge with short nose (4/4), long smooth philtrum with a thin vermilion border (4/4), and downturned angles of the mouth (4/4) were the most common facial dysmorphic features (Table 2). It should be noted that the feature of downturned angles of the mouth was infrequently specified in the literature on similar cases. As all our cases had the typical facial appearance of fetal valproate syndrome (FVS), it was clear that this developed when the fetus was exposed to between 500 mg/d and 1000 mg/d.

The teratogenicity of an exposure is also influenced by both the maternal and fetal genotypes.\textsuperscript{1} However, most women with epilepsy have healthy children. While some infants exposed to an anticonvulsant drug \textit{in utero} had abnormalities, others did not. Genetic differences in the fetal response to medications probably play a role. The risk of recurrence of FVS in a subsequent pregnancy exposed to VPA would therefore appear to be high, possibly due to inherent problems with the metabolism of VPA in the mothers concerned. A hypothesis that links a reduced level of expression of placental drug transporters and AEDs prescribed during pregnancy with birth defects and neurodevelopment impairments in later childhood opens potential avenues for further research.\textsuperscript{19} Naturally-occurring genetic variations causing differences in the expression of transport proteins are likely to be an important cause of interindividual variability in pharmacokinetics and pharmacodynamics of many drugs. The effects that polymorphisms have on placental expression of these transporters undoubtedly contribute to fetal susceptibility. The “common ground” of the four mothers in the study was their long-term use of VPA (>10 years). As well as a genetic fetal susceptibility, previously introduced somatic epigenetic mutations have also been suggested for long-term drug usage. Previous studies demonstrated that VPA, a direct inhibitor of histone deacetylase, could induce histone hyperacetylation and other epigenetic changes such as histone methylation and DNA demethylation.\textsuperscript{20} Malm et al\textsuperscript{21} described three families in which the occurrence of FVS in all the siblings strongly suggested hereditary susceptibility to
References regarding the publication of this paper.

The authors declare that there are no conflicts of interest and high-dose VPA use. Minor skeletal abnormalities could occur with both low-exposed to VPA. Though minor anomalies were not widely dependent spectrum of abnormalities in some infants were minor malformations in Cases 2 and 3.

In conclusion, there is a recognizable nondose-dependent spectrum of abnormalities in some infants exposed to VPA. Though minor anomalies were not widely reported in a large number of antiepileptic drug teratology investigations, common facial dysmorphic features and minor skeletal abnormalities could occur with both low- and high-dose VPA use.

Conflicts of interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

References