A case of fetal valproate syndrome with new features expanding the phenotype

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ABSTRACT

تعرف متلازمة فالبرويت الجنين FVS بوجود تشوهات خلقية وتخلف في تطور الجهاز العصبي ناتج عن تعرض الجنين لعقار الصوديوم فالبرويت، أثناء الشهور الأولى من الحمل. نصف في هذا التقرير حالة طفلة بها تشوهات خلفية متطابقة مع فالبوريت الجنين FVS، بالإضافة إلى وجود قصر في العنق واتساع المسافة بين حلمتي الثدي، وهي تشوهات لم توصف من قبل مع المتلازمة. تعرضت الأم لحادث أدى إلى إصابتها بحالة صرع مما استدعى علاجها بعقار صوديوم فالبوريت (ديباكين) 500mg مرتين في اليوم طوال فترة الحمل. ومن المعروف أن هذا العلاج يسبب تشوهات للجنين في حال تناولته السيدة خلال فترة الحمل، كتشوهات في الأطراف، العامود الفقري، وتخلف في تطور الجهاز العصبي. لذلك نوصي بعدم استخدام علاج الصوديوم فالبوريت خلال فترة الحمل، نظراً لوجود بدائل وعلاجات حديثة. وتعتبر التشوهات، مثل اتساع المسافة بين حلمتي الثدي وقصر العنق ملامح جديدة إضافية لمتلازمة فابرويت الجنين FVS.

Fetal valproate syndrome (FVS) is a well-recognized constellation of dysmorphic features, and neurodevelopmental retardation that results from prenatal exposure to the anticonvulsant valproic acid. In this report, we describe a case with typical features of FVS. A 23-year-old lady with post-traumatic epilepsy controlled by sodium valproate (Depakene) 500 mg twice daily throughout pregnancy as monotherapy, gave birth to a female baby with facial features characteristic of FVS, and severe radial ray reduction. She also had wide-spaced nipples and short neck, features not described before. Sodium valproate, a widely used anticonvulsant and mood regulator, is a well-recognized teratogen that can result in severe limb deformities, craniosynostosis, neural tube defects and neurodevelopmental retardation. Therefore, we recommend that valproic acid must be avoided during pregnancy, as new generation of anticonvulsant drugs have emerged into the market.

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Valproic acid (VPA) was widely used as an anticonvulsant since 1967 in Europe, and in 1978 in the United States to treat epilepsy and various psychiatric disorders such as bipolar disorders. During pregnancy, VPA can cross the placenta and affect the fetus causing a spectrum of malformations referred to as fetal valproate syndrome (FVS), or VPA embryopathy. The first case report suggesting teratogenicity of VPA in human was in 1980.[1] Since then, there had been several reports of FVS, and the phenotype was well described, which encompass a wide spectrum of abnormalities including consistent facial phenotype, multiple systemic and orthopedic involvement, central nervous system dysfunction, and altered physical growth. The facial appearance is characterized by small broad nose, small ears, flat philtrum, a long thin upper lip with shallow philtrum, and micro/retrognathia. Our case presents the typical facial phenotype, severe radial ray reduction, metopic synostosis, and trigonocephaly, features similar to Baller-Gerold syndrome.[2] Our case also has wide-spaced nipples, a feature not described with FVS. We are reporting this case to add to the previously published cases of FVS, and to increase awareness of the teratogenic effect of VPA, and hence, must be avoided during pregnancy.

Case Report. The propositus, a 13 month-old-female was delivered normally as preterm 31 weeks gestation. Her parents were first cousins. The mother,

a 23-year-old was involved in a road traffic accident that resulted in post traumatic epilepsy, for which she was placed on sodium valproate (Depakene) 750 mg twice per day. After 6 years of primary infertility, she conceived, and the dose of sodium valproate was reduced to 500 mg twice a day. She was kept on this dose throughout pregnancy, and no other anticonvulsants were used. She was on folic acid 1 mg per day for one year before pregnancy, which was gradually increased to 5 mg per day during pregnancy, and iron supplement was started in the last trimester. She had no seizures during pregnancy, and there was no relevant family history. The baby was delivered at 31 weeks gestation with a birth weight of 1400 gm (25th centile), length of 42 cm (50th centile), occipitofrontal circumference of 23 cm (below 5th centile). She developed respiratory distress syndrome for which she was ventilated for a short period. She was found to have upper limbs deformities with absent right radius, and was transferred to our hospital as a case of thrombocytopenia absent radius (TAR) syndrome. Examination revealed dysmorphic features (**Figure 1**) consisting of ridging over metopic suture, midface hypoplasia, infraorbital groove, broad nose with flat nasal bridge, anteverted nares, abnormally folded right ear, flat long philtrum, thin upper lip, retrognathia, short neck, wide-spaced nipples. Upper limb deformities consists of absent right radius, floating hypoplastic right thumb, slender fingers, bent left hand with long overlapping fingers. The neurological examination was appropriate for her age. The laboratory investigations revealed normal hematological indices, in particular repeatedly normal platelet counts. Chromosome analysis showed normal female karyotype. The skeletal survey (**Figure 2**) showed rudimentary right radius, bowed ulna, absent first carpal bone with a floating thumb, and clinodactyly of index and little fingers. The left hand showed abnormal position of phalanges of the thumb, clinodactyly of third, fourth, and fifth fingers.

Figure 1 - Distinctive features at **a**) age 2 months, note characteristic facial appearance and wide-spaced nipples **b**) age 14 months, note thin upper lip and full lower lip and prominent forehead

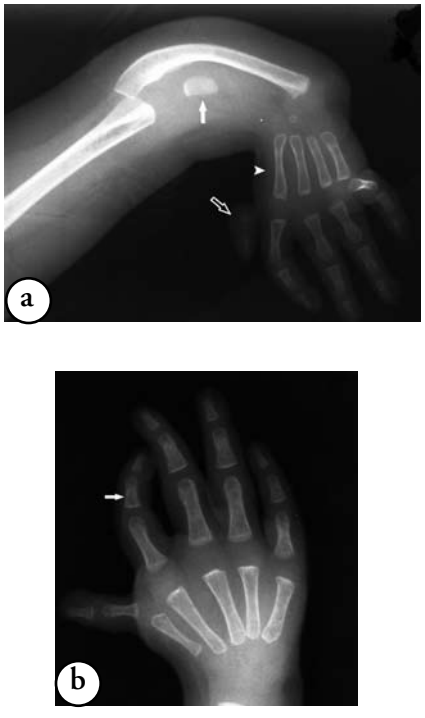

Figure 2 - X-ray of the **a**) right upper limb showing club hand, radial aplasia (solid arrow) and floating thumb (open arrow) absent first carpal bone (arrow head) **b**) left hand showing clinodactyly (arrow).

Discussion. The first case report suggesting teratogenicity of VPA in humans was in 1980.[1] A consistent facial phenotype in infants exposed to VPA was first described by DiLiberti et al.[3] This phenotype is known as valproate embryopathy. The phenotype was expanded to include: tall forehead, depressed nasal bridge, hypertelorism, epicanthic folds, long smooth philtrum, small mouth with thin upper lip and full lower lip, low set posteriorly rotated ears, and overlapping toes. Other features reported included polydactyly, clinodactyly, hypospadias, and cryptorchidism. Radial ray reduction was reported as a severe type of skeletal defect associated with VPA exposure.[4-10] Rodriguez-Pinilla et al[11] conducted a case control study on the relationship between prenatal exposure to VPA, and

Table 1 - Features reported with fetal valproate syndrome.

Features	Kozma's study[12] (%)	Present study
Craniofacial abnormalities		
Macrocephaly	16	Absent
Microcephaly	13	Present
High/broad forehead	26	Present
Bifrontal narrowing	19	Absent
Hypertelorism	27	Present
Epicanthal folds	31	Present
Midface hypoplasia	20	Present
Small/broad nose	57	Present
Small abnormal ears	46	Present
Long flat philtrum	43	Present
Thin vermillion border	37	Present
Micro/retrognathia	26	Present
Cleft palate	4	Absent
Organ malformations		
Skin and appendages	29	Absent
Brain abnormalities	10	Present
Eye abnormalities	9	Absent
Cardiac abnormalities	26	Absent
Pulmonary abnormalities	16	Absent
Renal abnormalities	7	Absent
Genital abnormalities	21	Absent
Musculoskeletal system	63	Present
Spina bifida	3	Absent
Evolution		
Early death	12	Absent
Hypotonia	10	Absent
Growth retardation	15	Absent
Overgrowth pattern	9	Absent
Developmental deficits	20	Absent
Mental retardation	10	
Seizures	3	Absent
New features		
Wide-spaced nipples	Absent	Present
Short neck	Absent	Present

the presence of limb deficiencies in newborn infants. Of the total of malformed infants exposed to VPA, 38.8% (21/57) presented with congenital limb defects of different types, and 3 of them had limb deficiencies. According to the study, the estimated risk for women treated with VPA of having a baby with limb deficiencies is approximately 0.42%. Kozma[12] reported 2 siblings with VPA embryopathy, and reviewed the literature from 1978-2000. She identified a total of 70 cases that were exposed to VPA with adequate clinical description. She found that 62% of the patients had musculoskeletal abnormalities, 30% had minor skin defects, 26% had cardiovascular abnormalities, 22% had genital abnormalities, and 16% had pulmonary abnormalities. Neural tube defects (NTDs) were seen in 3% of the subjects, 15% had growth retardation, while overgrowth pattern was seen in 9%, and developmental deficit was found in 29%. Our case exhibited the characteristic facial phenotype, and severe radial reduction. She also had short neck and wide-spaced nipples, features that were not described in previous cases (**Table 1**).

The most common major congenital malformations associated with FVS include NTDs, congenital heart defects, cleft lip and palate, genitourinary malformations, and radial ray defects, and the other less frequent associated anomalies include abdominal wall defects, tracheomalacia, strabismus, arachnodactyly, and overlapping fingers.[13] The risk factors for the teratogenicity of sodium valproate include the number of drugs that are co-administrated, the dosage of drug, the differences in maternal and/or infant metabolism, the fetal gestational age at exposure, and the hereditary susceptibility.[14] Sodium valproate appears to be associated with lower lumbar, or sacral spina bifida in humans.[13] The prevalence of spina bifida with FVS is approximately 1-2%, a 10-20 fold increase in NTDs.[15] The spina bifida in FVS is often skin covered, and the maternal serum α-fetoprotein (AFP) level is often normal.[13]

The teratogenic effect of VPA is well documented in both animal models and humans.[16-20] As in our case, it can result in major malformations like limb reduction, and metopic synostosis beside NTDs, and psychomotor retardation. As new anticonvulsant drugs were introduced to the market, we recommend that sodium valproate must be avoided during pregnancy, and that pregnancy in epileptic women on anticonvulsant therapy should be planned, and both obstetrician and neurologist should be consulted. Wide-spaced nipples and short neck are new features expanding the FVS phenotype.

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