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Pediatrics

FETAL VALPROATE SYNDROME

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ABSTRACT Valproic acid (VPA) is a teratogenic drug widely used for treatment of seizures and mood disorder. Fetal valproate syndrome (FVS) results from in utero exposure of fetus to VPA. It is characterised by presence of consistent facial dysmorphism, group of minor and major malformations and developmental delay. We report a case of 1 year old boy presented with features of FVS with Arnold chiari I malformation and reviewed literature.

KEYWORDS : Arnold chiari I malformation, fetal valproate syndrome, valproic acid.

Introduction

Valproic acid (VPA) is widely used for treatment of seizures and mood disorders since 1964. First study about teratogenic potential of VPA was published in 1980 [1] and after that many studies have described teratogenic and dysmorphogenic potential of VPA. The term fetal valproate syndrome was coined by DiLiberti et al. in 1984 and he found similar facial phenotype in all 7 children who were exposed to VPA during pregnancy. [2] Association of Arnold chiari I malformation with FVS has not been reported in literature.

Here, we report a 1 year old boy, born to a mother who was treated with VPA throughout pregnancy, presented with facial dysmorphism and cluster of malformations including Arnold chiari I malformation, and reviewed literature.

Case report

One year old male child, who is the first and only child, born out of a nonconsanguineous marriage to a 22 year old female. The child delivered at full term by low segment caesarean section, done for breech presentation and cried immediately after birth. Birth weight was 2 kilograms and neonatal period was uneventful. Mother was suffering from epilepsy and was taking tablet valproic acid 500mg twice a day since last 10 years and also throughout pregnancy.

The child presented with fever and cough. Developmental delay was present. Microcephaly was present and weight for height was less than -3 standard deviation. On examination, we found trigonocephaly with metopic suture ridge palpable, open anterior fontanel (0.5 into 0.5 centimetre), flat facial profile, hypertelorism, epicanthal folds, infraorbital groove, depressed nasal bridge, long and flat philtrum, thin upper lip, broad nose, small mouth and low set ears [Figure 1]. Oral cavity was normal. Loose skin, hypospadias and hypotonia were present. Overlapping of toes was seen in both feet [Figure 2]. Early systolic murmur of grade III/VI was present.

Chest X-ray showed normal lung fields. Skeletal x-rays were normal. Echocardiography revealed patent ductus arteriosus (PDA) and ostium secundum atrial septal defect (ASD). Ultrasonography of abdomen was normal except for left sided non-obstructive renal calculi of size 3 millimetres. Arnold chiari I malformation was seen in magnetic resonance imaging of brain. Karyotyping was normal.

We did diagnosis of foetal valproate syndrome as typical facial dysmorphic features and cluster of malformations were present with confirmed history of ingestion of VPA throughout pregnancy. Patient treated for upper respiratory tract infection and for PDA, device closure was done.

Discussion

Incidence of malformations is more in children born to epileptic mother on antiepileptic drugs than general population. Polytherapy including VPA and VPA more than 1000 milligrams/ day is associated with more malformations than monotherapy or less dose of VPA respectively.[3,4] Recent study revealed that VPA alone, and not association with epilepsy syndrome, is responsible for teratogenecity. [5] Various factors contribute to the teratogenecity of VPA. These include the number of antiepileptic drugs that are co-administered, drug dosage, differences in maternal and/or infant metabolism and the gestational age of the fetus at exposure. [6]

After the review of 69 cases of FVS, Kozma C [7] reported that the clinical features of FVS shows wide spectrum of abnormalities like consistent facial phenotype, multiple systemic and orthopaedic involvement, central nervous system dysfunction, and altered physical growth. The author found that 62% of the patients had musculoskeletal abnormalities, 30% had minor skin defects, 26% had cardiovascular abnormalities, 22% had genital abnormalities, 16% had pulmonary abnormalities and 3% had neural tube defect. Less frequently encountered abnormalities included brain, eye, kidney, and hearing defects. Although 15% of patients had growth retardation, an overgrowth pattern was seen in 9%. [7] The facial features seen in FVS are trigonocephaly, tall forehead with bifrontal narrowing, epicanthic folds, infraorbital groove, medial deficiency of eyebrows, flat nasal bridge, broad nasal root, antiverted nares, shallow philtrum, long upper lip and thin vermillion borders, thick lower lip, small downturned mouth. [8]

Our case had developmental delay, growth retardation, consistent facial dysmorphism, microcephaly, loose skin, hypspadias, hypotonia, congenital heart defect (ASD and PDA) and Arnold chiari I malformation. We found Arnold chiari type I malformation which is not reported in literature as per my knowledge. Association of developmental delay and learning disabilities with FVS is frequently described.[7,8] Joint laxity and hypotonia is observed with all anticonvulsants including VPA. [9]

There is increase in incidence of NTD at around 10 times and congenital heart disease at around 4 times in fetuses exposed to VPA than normal. NTD specifically related to valproate therapy, rather than to other anticonvulsants. [6] NTD can be detected antenatally by maternal alpha fetoprotein level and targeted ultrasonography. To decrease the risk of NTD with VPA, high dose folic acid (4 mg/day) is recommended during pregnancy, starting at least 6 weeks preconception and continuing through the first trimester.[10] In our case, no specific test was done antenatally and mother didn't receive folic acid.

Woman on VPA should plan pregnancy and try to avoid VPA. If not possible, try to give monotherapy, lowest effective dose with frequent drug level monitoring and give high dose folic acid.

Figure 1: Note hypertelorism, epicanthal folds, infraorbital groove, depressed nasal bridge, long and flat philtrum, thin upper lip, broad nose, small mouth and low set ears

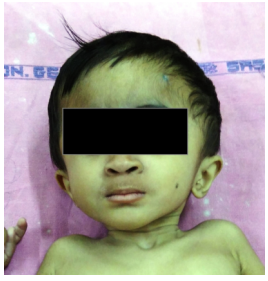
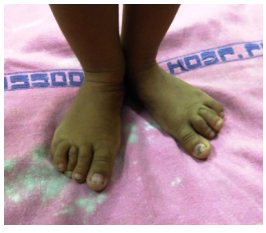


Figure 2: Overlapping of toes



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