Fetal valproate syndrome

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Introduction

Multiple factors contribute to the increased risk of congenital malformation in babies born to epileptic mothers among which teratogenic effects of anticonvulsants tops the list. Fetal valproate syndrome (FVS) is a rare disorder due to antenatal exposure to sodium valproate, a widely used antiepileptic drug and mood stabiliser. It was licensed for use in 1978 and the first adverse report of fetus exposed to this drug was published in 1980[1].Till today there are only a handful of cases of FVS presenting with typical dysmorphogenic features. Here we report a 3 month old infant with dysmorphism, trigonocephaly, limb defects, hypospadias and congenital cardiac anomaly consistent with FVS.

Case report

A 3 month old infant was admitted with craniofacial and limb defects. He was a preterm, appropriate for gestational age baby born to non-consanguineous parents. He had trigonocephaly, broad nasal bridge, anteverted nares, low set and malformed pinna, cleft palate, bilateral absent radii in x-rays of upper limbs, absent thumb and hypospadias (Figures 1 and 2).

Figure 1: Three month old infant

Echocardiography revealed a small atrial septal defect (ASD). Ultrasound scans of brain and abdomen were normal. There was no history suggestive of intrauterine infection. Baby had a normal vaginal delivery and there was no history of birth asphyxia. The mother was on sodium valproate for epilepsy for seven years and it was continued throughout pregnancy at a dose of 900mg/day. There was no history of diabetes mellitus, hypertension or any other chronic illness. With the maternal history of intake of sodium valproate and dysmorphic features typical of fetal valproate syndrome, a diagnosis of FVS was made.

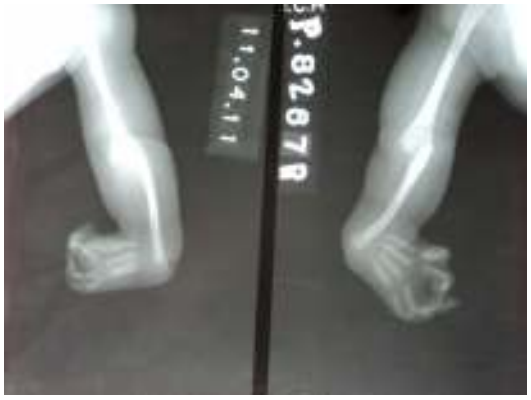

Figure 2: Bilateral absent radii in x-ray of upper limbs

Discussion

Sodium valproate is a widely used antiepileptic drug and is also increasingly used for managing bipolar and other affective disorders. It is thought to act either by inhibiting GABA metabolism or by a direct effect on mitochondria, impairing cellular energy metabolism[2]. It is 80-90% bound to plasma proteins. Valproate therapy can lead to hepatotoxicity.

Various factors contribute to the teratogenecity of valproic acid. These include the number of drugs that are co-administered, drug dosage, differences in maternal and/or infant metabolism and the gestational age of the fetus at exposure. Valproic acid crosses the placenta and is present in a higher concentration in the fetus than in the mother[3,4]. Various congenital malformations are associated with FVS. There is a 6 to 7 time increase of malformations in babies of mothers exposed to valproate. The most frequent major congenital malformations are neural tube defects, congenital heart defects, oral clefts, genital abnormalities and limb defects. Other less frequent abnormalities

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include inguinal and umbilical hernias, supernumerary nipple, postaxial polydactyly, bifid ribs and preaxial defect of feet[5,6]. Zinc deficiency has been suggested as a possible cause of neural tube defects associated with valproate exposure as sodium valproate readily binds to zinc[7].

The patients have typical facial features which tend to evolve with age. 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, anteverted nares, shallow philtrum, long upper lip and thin vermillion borders, thick lower lip and small downturned mouth[3].

Congenital heart defects have been reported in several patients with FVS and the incidence is estimated to be around 4 times that seen in general population[3]. Aortic valve stenosis, interrupted aortic arch, secundum ASD, pulmonary atresia without ventricular septal defect (VSD), perimembranous VSD and hypoplastic left heart syndrome are known to occur[5]. Our case had ostium secundum ASD.

Prenatal diagnosis is focused on the detection of neural tube defects (NTDs). Estimation of maternal serum alpha fetoprotein (AFP) can be used as a screening test for the presence of open NTDs. Prenatal evaluation must include targeted ultrasound examination particularly of the caudal spine for skin covered lesion even when AFP levels are normal. Women taking valproic acid should be counselled and strongly encouraged to plan their pregnancies, so that periconceptional high dose folic acid i.e. 5 mg/day can be taken[7]. Whenever the use of antiepileptic drugs is inevitable during pregnancy, they should be administered as monotherapy, in the lowest possible dose with constant monitoring of serum concentration of antiepileptic drugs.

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