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Fetal valproate syndrome

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The antiepileptic drug valproic acid (VPA) is an established human teratogen, that induces minor craniofacial anomalies and major organ malformations in human fetuses exposed to the drug during early pregnancy.

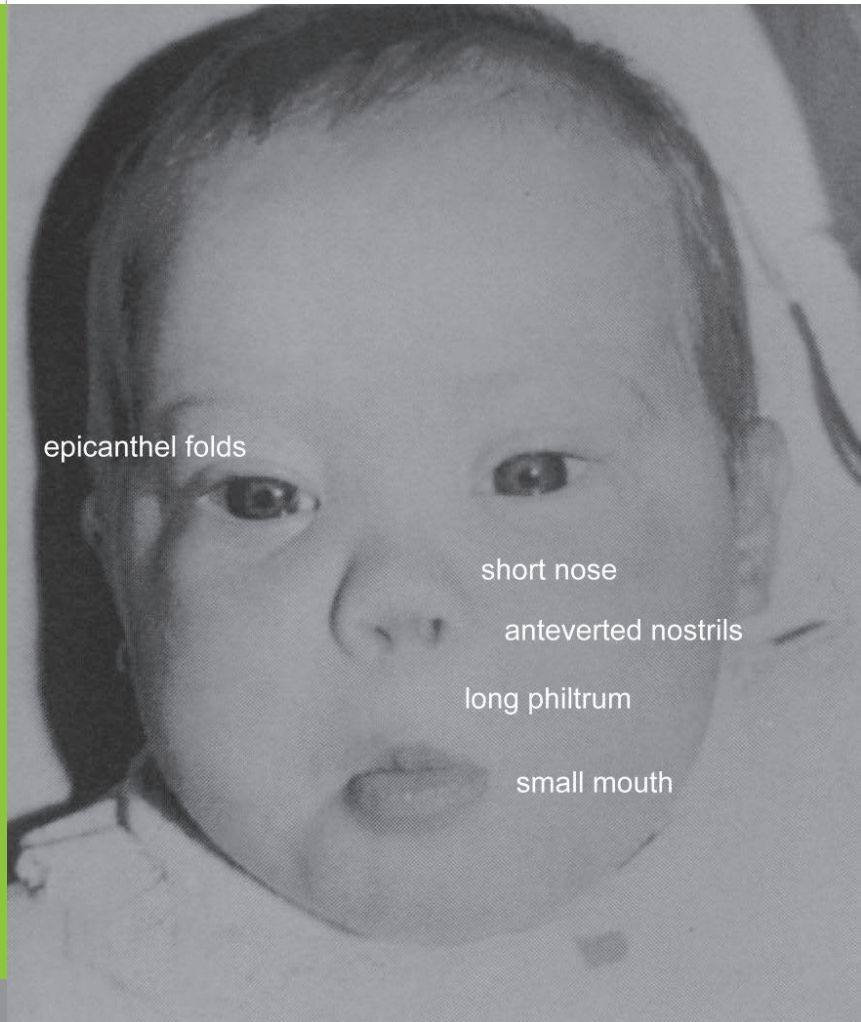
Both parents of the patient originated from Sri Lanka. The father's past medical history was unremarkable. The mother was a 24-year-old G1, who had been taking VPA and phenobarbital since 8 years of age to treat partial complex seizures associated with a left frontal hamartoma. She continued to take VPA (1000 mg - 500 mg) and phenobarbital (100 mg once daily) throughout her pregnancy. Folate was instituted after the sixth week of gestation. The last seizure occurred during the third trimester.

This male term infant (39 5/7 weeks), had a birth weight of 3220 g (P10-50), a birth length of 49 cm (P10-50), and an occipitofrontal head circumference of 34.5 cm (P50). Craniofacial abnormalities were noted: wide anterior fontanelle, hypertelorism, depressed nasal bridge, low-set ears, retrognathia and cleft palate. In addition, there were wide-spaced nipples.

Ultrasound examinations excluded concomitant anomalies of the central nervous system, the heart (except for a small atrial septal defect), the urogenital system and the skeletal system.

BACKGROUND

CASE REPORT



7-month-old girl with fetal valproate syndrome

VPA is a very effective anticonvulsant agent widely used in the management of various forms of epilepsy. VPA exposure in utero is associated with an increased risk of phenotypic anomalies of the face, major organ malformations (1-2% incidence of neural tube defect) and developmental disabilities. The patterns of the neurodevelopmental delay include behavioral problems with hyperactivity or poor concentration, autistic features, learning difficulties and speech delay.

The mechanism of teratogenicity remains unclear, but it has been hypothesized that VPA interferes with the folate cycle and therefore, with methionine/methylation.

Patients should be counseled that the risk of adverse maternal and neonatal outcome from recurrent seizures during pregnancy is greater than the risk of teratogenicity due to VPA. If the use of VPA during pregnancy is unavoidable, administration of the lowest daily dosage as monotherapy, divided into three to four doses is recommended to reduce the teratogenic risk. Recently it has been reported that infants exposed to VPA in utero have a significantly elevated risk of hypoglycemia, and that withdrawal symptoms are often observed.

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