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Congenital Abnormalities in Two Sibs Exposed to Valproic Acid in Utero

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Neural tube, craniofacial, and other congenital abnormalities have been described in infants born to mothers with epilepsy who were treated with valproic acid (VPA) during pregnancy. The pathogenetic relationship between the congenital abnormalities and exposure to VPA is not clear. We describe 3 sibs born to a mother with epilepsy. Only the 2 sibs who were exposed to VPA in utero had certain of the characteristic craniofacial changes described in previous reports of children with similar exposure. In addition, the 2 affected children had other craniofacial and skeletal abnormalities which have not been reported previously as teratogenic sequelae of VPA exposure. Many of the minor anomalies present in the 2 affected patients resemble those observed in rhesus monkeys exposed to VPA in utero. This suggests that the abnormalities observed in the 2 children may have been a consequence of intrauterine exposure to VPA.

Key words: valproic acid, valproate, birth defect, teratogen

INTRODUCTION

Valproic acid (VPA) is effective in preventing a wide range of seizure types and is associated with relatively few cognitive side effects. It has been estimated that 700–1,000 pregnant women in North America receive this drug each year [Morbidity and Mortality Weekly Report, 1982]. Neural tube defects (NTD), and craniofacial, skeletal, cardiovascular, and urogenital abnormalities have been reported in infants born to mothers receiving valproic acid during pregnancy [Morbidity and Mortality Weekly Report, 1982; Lindhout and Schmidt, 1986; DiLiberti et al., 1984; Tein and MacGregor, 1985; Jager-Roman et al., 1986].

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The incidence of birth defects in infants of epileptic women has been reported to be about 2 to 3 times higher than in the general population [British Medical Journal (editorial), 1981]. The contribution of antiepileptic drugs taken during pregnancy to the increased risk of birth defect is not clear. We describe 3 sibs born to a mother with epilepsy. Only the 2 sibs exposed to VPA in utero had minor anomalies. In addition to abnormalities described previously as the "fetal valproate syndrome" [DiLiberti et al., 1984; Tein and MacGregor, 1985; Jager-Roman et al., 1986], the 2 affected children in this report also had minor anomalies which have not been described previously as teratogenic effects of VPA.

CLINICAL REPORTS

Parents

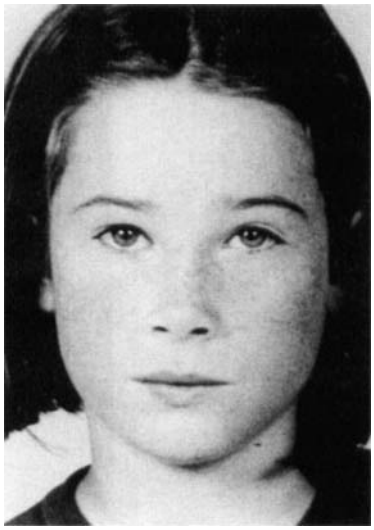
The 3 children had the same non-consanguinous parents. The mother started to have absence seizures at 10 years and tonic-clonic seizures at 14 years. Her early mental development was delayed. Thus, she did not speak until age 3, repeated a grade at school and only completed grade 10. The father had educational difficulties and only completed grade 8.

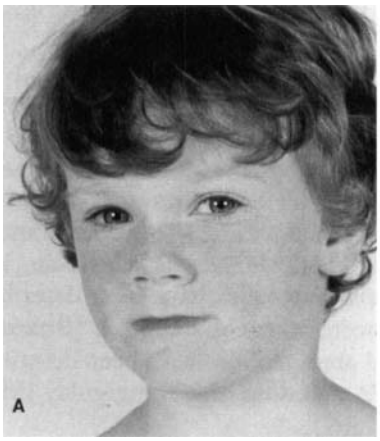
Patient 1

This 10-year-old girl was born at term following a pregnancy during which the mother received 100 mg carbamazepine (CBZ) and 900 mg methsuximide (MT) daily. She did not receive any VPA. At 6 weeks of gestation, the mother took an intentional overdosage of 3,000 mg of CBZ. The mother had no tonic-clonic seizures during the pregnancy but had frequent absence seizures. She was otherwise healthy, received no other medications, and did not drink alcohol or smoke. Labor and delivery were normal. The infant's birthweight was 2,630g (25th centile), and she did well in the neonatal period. This patient now has an attention deficit disorder and is one grade behind at school. On examination at age 10, she has a broad forehead, small pointed nose, and prominent ears (Fig. 1). The mother has a similar appearance.

Patient 2

This 2 1/2-year-old boy (Fig. 2) was born at 37 weeks of gestation. The mother received 500 mg VPA and 400 mg CBZ daily during the pregnancy. She also received up to 3 tablets daily of an analgesic containing acetylsalicylic acid, caffeine, and codeine (282^{R}) for headache during the early months of pregnancy. She was otherwise healthy and did not drink alcohol or smoke. She had no seizures during the pregnancy. The labor and delivery were normal. At birth, the infant weighed 3,240g (50th centile), his length was 50 cm (50th centile) and his head circumference was 35.5 (75th centile). Apgar scores were 9 and 9 at one and 5 minutes, respectively. Neonatally he was normal. On examination at age 2 1/2 years, of age he had an attention deficit disorder and mild expressive language delay. The minor craniofacial anomalies (Fig. 2) included a prominent and broad forehead, eyebrows starting 1 cm lateral to the inner canthal point, depressed nasal bridge, small pointed nose, anteverted nostrils, infraorbital crease, hypoplastic zygomatic arches, small mouth with long upper lip and a narrow upper vermilion, protruding and posteriorly angulated ears, and opalescent teeth. In addition, he had hypoplastic nails and a carrying angle of 0 degrees.





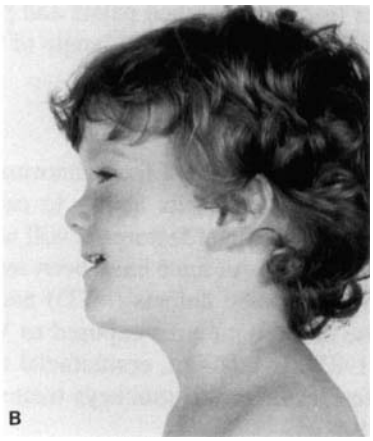


Fig. 2. Patient 2, front **A**; side **B**.

Patient 3

This 8-month-old girl was born at term following a pregnancy during which her mother received 500 mg VPA and 400 mg CBZ each day. The mother had no seizures during the pregnancy and was healthy. She received no other medications and did not drink alcohol or smoke. The labor and delivery were normal, and the Apgar scores were 9 and 9 at one and 5 minutes, respectively. At birth, the child weighed 2,900g (35th centile), her length was 51 cm (75th centile), and her head circumference was 32 cm (3rd centile). Neonatally she was normal. On examination at age 8 months, her development was normal. She had a prominent and broad forehead, eyebrows that started 1 cm lateral to the inner canthal point, depressed nasal bridge, small pointed nose, hypoplastic zygomatic arches, shallow philtrum, small mouth, long

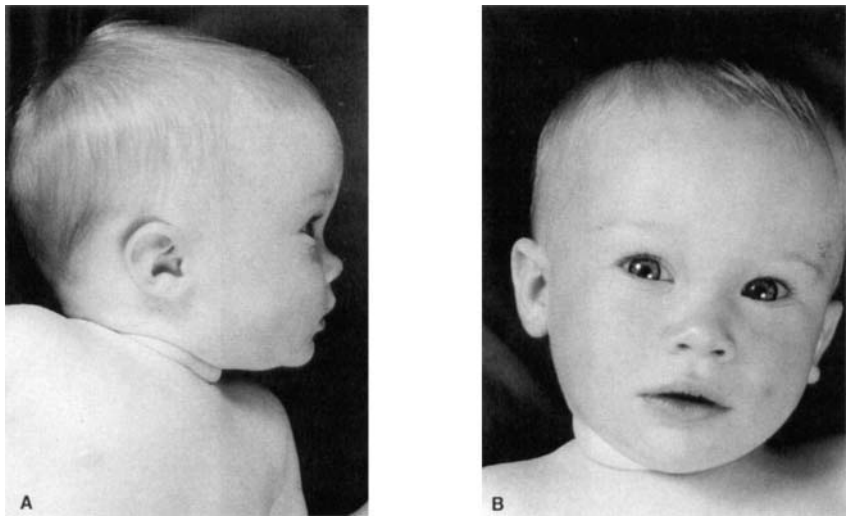


Fig. 3. Patient 3, side **A**; front **B**.

upper lip, highly arched palate and prominent, posteriorly angulated ears (Fig. 3). In addition she had a carrying angle of 0 degrees.

DISCUSSION

The spectrum of fetal abnormalities caused by VPA has not been fully delineated. In particular, its ability to cause specific minor anomalies and, most of all, characteristic facial features is still not clear. Maternal plasma VPA concentrations of 230–250 mg/L in mice have been associated with NTD in the offspring [Nau, 1986]. Both neural tube defects (NTD) and craniofacial anomalies have been described in mouse embryo cultures exposed to VPA at concentrations of 150 mg/L [Bruckner et al., 1983]. In addition, craniofacial and skeletal abnormalities have been described in the fetuses of rhesus monkeys treated with VPA at a dose of 200 mg/g/day [Mast et al., 1986].

Neural tube defects, craniofacial, skeletal, cerebral, cardiovascular, and urogenital abnormalities have been described in infants born to mothers receiving VPA during pregnancy [Morbidity and Mortality Weekly Report, 1982; Lindhout and Schmidt, 1986; DiLiberti et al., 1984; Tein and MacGregor, 1985; Jager-Roman et al., 1986; Winter et al., 1987; Ardinger et al., 1988]. A prospective collaborative study involving 393 infants exposed to VPA in utero has demonstrated a prevalence of NTD of 1.5% [Lindhout and Schmidt, 1986]. Typical minor anomalies have also been attributed to VPA. In a smaller prospective controlled study, the prevalence of minor abnormalities in the 26 infants of mothers who received VPA during pregnancy was 4 times higher than in the 90 infants born to mothers who received other antiepileptic drugs [Jager-Roman et al., 1986; Winter et al., 1987; Ardinger et al., 1988].

The prominent forehead, small nose, anteverted nostrils, long upper lip, shallow philtrum, narrow upper vermilion, posteriorly angulated ears, and hypoplastic nails

which were present in our 2 patients exposed to VPA have been previously described in infants exposed to VPA in utero [DiLiberti et al., 1984; Jager-Roman et al., 1986; Winter et al., 1987; Ardinger et al., 1988]. The presence of these anomalies in the brother and sister exposed to VPA but not in the other sibs also suggests that these anomalies are causally related to VPA. This hypothesis is supported by the demonstration of similar craniofacial and skeletal abnormalities in the fetuses of rhesus monkeys exposed to VPA during pregnancy [Mast et al., 1986]. Bulging forehead, retarded upper lip and nostril formation, apparently low-set and poorly defined ears, and missing or short digits have all been described in these animals [Mast et al., 1986].

In addition to the above abnormalities, which have been described previously, new and characteristic anomalies were present in both of these affected sibs. Thus, both had lateral displacement of the medial origin of the eyebrows, hypoplastic zygomatic arches, and a carrying angle of 0 degrees. In addition, patient 2 had infraorbital creases and hypoplastic teeth, and patient 3 had a highly arched palate. The presence of maxillary hypoplasia, exophthalmos, and abnormal skeletal formation in the forelimbs in the rhesus monkey model suggests that the additional abnormalities described in this report may be related to exposure to VPA in utero [Mast et al., 1986].

The similarity in the minor anomalies described in the 2 sibs exposed to VPA and their absence in the parents and the sib not exposed to VPA suggest that these minor abnormalities are related to the intrauterine exposure to VPA. This suggestion is supported by the presence of certain of these minor anomalies in primates with the fetal VPA syndrome.

REFERENCES

Ardinger HH, Atkin JF, Blackston RD, Elsas LJ, Clarren SK, Livingstone S, Flannery DB, Pellock JM, Harrod MJ, Lammer EJ, Majewski F, Schinzel A, Toriello HV, Hanson JW (1988): Verification of the fetal valproate syndrome phenotype. Am J Med Genet 29:171–185.

British Medical Journal (editorial) (1981): Teratogenic risks of antiepileptic drugs. Br Med J 283:515–516.

Bruckner A, Lee YJ, O'Shea KS, Henneberry RC (1983): Teratogenic effects of valproic acid and diphenylhydantoin on mouse embryos in culture. Teratology 27:29–42.

DiLiberti JH, Farndon PA, Dennis NR, Curry CJR (1984): The fetal valproate syndrome. Am J Med Genet 19:473–481.

Jager-Roman E, Deichl A, Jakob S, Hartmann A, Koch S, Rating D, Steldinger R, Nau H, Helge H (1986): Fetal growth, major malformations and minor anomalies in infants born to women receiving valproic acid. J Pediatr 108:997–1004.

Lindhout D, Schmidt D (1986): In utero exposure to valproate and neural tube defects. Lancet 1:1392–1393.

Mast TJ, Cukierski MA, Nau H, Hendrickx AG (1986): Predicting the human teratogenic potential of the anticonvulsant, valproic acid, from a non-human primate model. Toxicology 39:111–119.

Morbidity and Mortality Weekly Report (1982): Valproic acid and spina bifida: A preliminary report—France. 31:565–566.

Nau H (1986): Transfer of valproic acid and its main active unsaturated metabolite to the gestational tissue: Correlation with neural tube defect formation in the mouse. Teratology 33:21–27.

Tein I, MacGregor DL (1985): Possible valproate teratogenicity. Arch Neurol 42:291–293.

Winter RM, Donnai D, Burn J, Tucker SM (1987): Fetal valproate syndrome: is there a recognisable phenotype? J Med Genet 24:692–695.

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