A male with fetal valproate syndrome and autism

P Gail Williams* MD, Assistant Professor of Pediatrics; **Joseph H Hersh** MD, Professor of Pediatrics; University of Louisville School of Medicine, Child Evaluation Center, Louisville, Kentucky.

**Correspondence to first author at* University of Louisville School of Medicine, Child Evaluation Center, 571 South Floyd Street, Suite 100, Louisville, KY 40202-3828, USA.

Fetal valproate syndrome (FVS) is characterized by minor craniofacial anomalies, major organ malformations, and developmental delay. We report on a patient who has a clinical phenotype compatible with both FVS and autism. The presence of an autistic disorder in a previously reported case of FVS and similar findings in our patient suggest that a relation between this known teratogen and autism may exist.

Autism is a developmental disorder that presents early in life and is defined by deficits in social interaction, communication, and range of play and interests. Although the etiology of autism is unknown, evidence that it is neurobiologic in nature includes a male-to-female ratio of 4:1, recurrence risk of 3% after having an affected child, increased frequency of seizures in affected individuals, mental retardation in approximately 70% of cases, and associated sensorimotor deficits (Gillberg 1987). In a small percentage of children with autism, a variety of other medical conditions have been reported (Bailey et al. 1996). These entities include chromosomal abnormalities (Down and fragile X syndromes), neurocutaneous disorders (tuberous sclerosis), inborn errors of metabolism (phenylketonuria and defects in purine metabolism), teratogen exposure during pregnancy (fetal alcohol syndrome), and infectious diseases (congenital rubella and postnatal herpes virus) (Ciaranello and Ciaranello 1995). However, cases in which autism occurs in conjunction with a medical condition represent only a small percentage of patients (Bailey et al. 1996).

Exposure in utero to valproic acid (VPA), an anticonvulsant, is associated with an increased risk of phenotypic abnormalities of the face (Table 1), developmental disabilities, and occasional major organ abnormalities including respiratory, cardiovascular, gastrointestinal, genitourinary, and skeletal defects (e.g. spina bifida and limb anomalies) (DiLiberti et al. 1984, Clayton-Smith and Donnai 1995). In one previously described case of FVS (Christianson et al. 1994), features of autism also were present. We describe a second patient with FVS and autistic disorder, and suggest that an association between the two conditions may exist.

Case report

A 5 1/2-year-old white boy was referred for neurodevelopmental evaluation secondary to speech and language delays. He was the first child of parents who were 19 (mother) and 25 (father) years old when he was born. The family history was unremarkable and there was no consanguinity. The patient's mother had been taking VPA for 2 or 3 years before her pregnancy, because of dizzy spells, concerns about absence seizures, and abnormal

EEG findings; she continued to take VPA (500 mg 4 times a day) until the end of the fifth month of pregnancy. There was no reported tobacco or alcohol use, and methyl dopa was used to treat hypertension in the last half of the pregnancy. The patient was delivered vaginally at term in an uncomplicated delivery and weighed 3.6 kg (length 49.5 cm; occipitofrontal circumference 37 cm). Phototherapy was required for hyperbilirubinemia; there were no other neonatal complications. In early childhood recurrent otitis media necessitated two sets of bilateral myringotomy tubes. A CT scan of the head at 1 year of age, made because of macrocephaly, revealed no intracranial abnormality.

The patient's gross motor milestones were normal, but his speech and language development were delayed. When he was evaluated at aged 5 1/2 years, his speech consisted of a few single words, two-word combinations, and echolalia. Communication was achieved primarily through gestures. Usually he played alone and did not interact with other children, although he imitated their acts at times. He lined up stuffed animals and engaged in perseverative activities such as opening and closing doors, and washing his hands repetitively. There was insistence on routines connected with bathing and eating. When excited, he bounced up and down and flapped his hands; when angry, he hit himself or banged his head. He covered his ears upon hearing certain sounds.

The boy's height was 110.5 cm (>25th, <50th centile); weight, 18 kg (>25th, <50th centile); and occipitofrontal circumference, 55.5 cm (>95th centile). He had frontal bossing and a high forehead, a flat nasal bridge, a smooth philtrum, and a thin upper lip (Fig. 1). A small midface, mild micrognathia, and a small mouth with tenting of the upper lip were also noted. His eyes were somewhat deep-set with mild bilateral epicanthal folds. His ears were appropriately formed but posteriorly rotated. No heart murmur was heard and the patient had pronated feet. Clinodactyly of the fifth fingers and mild hypoplasia of the fingernails were present. Neurologic examination revealed muscular hypotonia, hyperreflexia, and unsustained ankle clonus. The gait was somewhat awkward. Findings on fragile X chromosome analysis and screening for urine amino acid, organic acid, mucopolysaccharide, and oligosaccharide were normal, as was the EEG.

Psychological evaluation was performed. The Stanford-Binet Intelligence Scale, Form L-M (Terman and Merrill 1973), revealed scattered successes to a 3-year level. The patient obtained a standard score of 65 on the Test of Visual–Motor Integration. He met criteria for a diagnosis of autism in all areas on the Autism Diagnostic Interview (Le Couteur et al. 1989). Audiological evaluation indicated adequate hearing for speech and language purposes, with normal typanograms bilaterally. Speech and language evaluation revealed a communication disorder characterized by significant deficits in receptive and expressive language and in pragmatic aspects of language.

Table I: Facial features seen in fetal valproate syndrome

Trigonocephaly or prominent metopic ridge
Tall forehead with bifrontal narrowing
Epicanthal folds
Infraorbital groove
Midface hypoplasia
Broad or flat nasal bridge
Short nose with anteverted nares
Long, smooth philtrum
Thin vermilion border
Micrognathia
Small, downturned mouth

Discussion

Neurodevelopmental problems are common manifestations in children exposed to VPA in utero. Ardinger et al. (1988) reported developmental delay or neurological abnormalities in 71% of children exposed to VPA alone and in 90% of those on combination therapy, including VPA and another anticonvulsant. No consistent alterations in linear or head growth were evident in children exposed to VPA monotherapy. However, when VPA was used with other anticonvulsants, postnatal growth deficiency and microcephaly were identified in two-thirds of cases.

Although neurodevelopmental problems represent common features of FVS, the nature of the developmental disabilities has not been well categorized. Christianson et al. (1994) reported on the developmental findings in two sibling pairs

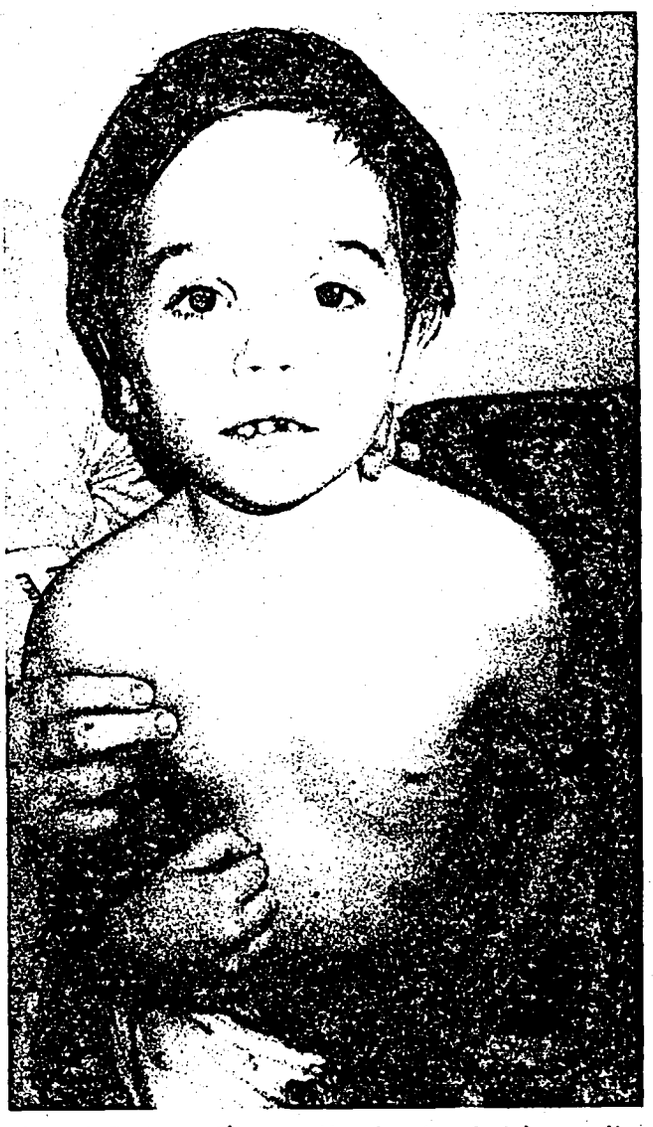

Figure 1: *Patient at 5 1/2 years. Note the minor facial anomalies consistent with fetal valproate syndrome.*

with FVS. Of these four subjects, one boy had mild mental retardation and characteristics of autism, and the three other subjects had variable cognitive impairments, with greater relative deficits in language development. Our patient is the second child with FVS to have features of autism. In our patient, as well as the patient reported by Christianson et al. (1994), no other identifiable risk factors responsible for the development of autism were evident. Therefore it is our feeling that observations both in this case and in the patient described by Christianson et al. (1994) may support the notion that a relation between autism and FVS exists. Additional neurodevelopmental data need to be obtained on children affected with FVS to determine the full spectrum of disabilities and the frequency of autism in this condition.

Accepted for publication 24th January 1997.

References

Ardinger H, Atkin J, Blackston RD, Elsas LJ, Clarren SK, Livingstone S, Flannery DB, Pellock JM, Harrod MJ, Lammer EJ et al. (1988) Verification of the fetal valproate syndrome phenotype. *American Journal of Medical Genetics* **29:** 171–85.

Bailey A, Phillips W, Rutter M. (1996) Autism: towards an integration of clinical, genetic, neuropsychological and neurobiological perspectives. *Journal of Child Psychology and Psychiatry* **37:** 89–126.

Christianson AL, Chesler N, Kromberg JGR. (1994) Fetal valproate syndrome: clinical and neurodevelopmental features in two sibling pairs. *Developmental Medicine and Child Neurology* **36:** 361–9.

Ciaranello A, Ciaranello RD. (1995) The neurobiology of infantile autism. *Annual Review of Neuroscience* **18:** 101–28.

Clayton-Smith J, Donnai D. (1995) Fetal valproate syndrome. *Journal of Medical Genetics* **32:** 724–7.

DiLiberti JH, Farndon PA, Dennis NR, Curry CJR. (1984) The fetal valproate syndrome. *American Journal of Medical Genetics* **19:** 473–81.

Gillberg C. (1987) The neurobiology of infantile autism. *Journal of Child Psychology and Psychiatry* **29:** 257–66.

Le Couteur A, Rutter M, Lord C, Rios P, Robertson S, Holdgrafer M, McLennan J. (1989) Autism diagnostic interview: a standardised investigator-based instrument. *Journal of Autism and Developmental Disorders* **19:** 363–87.

Terman L, Merrill M. (1973) *Stanford-Binet Intelligence Scale Form L-M*. Chicago, IL: Riverdale Publishing Company.