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Valproic Acid Embryopathy: Report of Two Siblings With Further Expansion of the Phenotypic Abnormalities and a Review of the Literature

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Fetal Valproate Syndrome (FVS) results from prenatal exposure to valproic acid (VPA). It is characterized by a distinctive facial appearance, a cluster of minor and major anomalies, and central nervous system dysfunction. In this study, two siblings who were exposed to monotherapy with VPA are described with documentation of long-term follow up. Both children had craniofacial findings, multiple systemic and orthopedic abnormalities, an overgrowth pattern, and developmental deficits. The literature from 1978–2000 is reviewed. A total of 69 cases that were solely exposed to VPA with adequate phenotypic description were identified. The clinical manifestations of FVS encompass a wide spectrum of abnormalities including consistent facial phenotype, multiple systemic and orthopedic involvement, central nervous system dysfunction, and altered physical growth. The facial appearance is characterized by a small broad nose, small ears, flat philtrum, a long upper lip with shallow philtrum, and micro/retrognathia. In this review, 62% of the patients had musculoskeletal abnormalities, 30% had minor skin defects, 26% had cardiovascular abnormalities, 22% had genital abnormalities, and 16% had pulmonary abnormalities. Less frequently encountered abnormalities included brain, eye, kidney, and hearing defects. Neural tube defects were seen in 3% of the sample. Twelve percent of affected children died in infancy and 29% of surviving patients had developmental deficits/mental retardation. Although 15% of patients had growth retardation, an overgrowth pattern was seen in 9%. The data from this comprehensive review especially the developmental outcome should be added to the teratogenic risk, that arises in association with the use of VPA during pregnancy.

KEY WORDS: valproic acid; teratogen; multiple congenital anomalies; fetal valproate syndrome; seizure disorders; anticonvulsants

INTRODUCTION

Valproic acid (VPA), an antileptic agent, is indicated for the treatment of simple and complex seizures. In addition, VPA is used in combination with other anticonvulsants in patients with multiple types of seizures, that include absence seizures. Valproic acid, also known as dipropylacetic acid, is primarily metabolized in the liver and readily crosses the placenta. It is present in higher concentrations in the fetus than in the mother. VPA is a popular drug because of its broad range of anticonvulsant effects and relative freedom from sedative and behavioral effects [Clayton-Smith and Donnai, 1995]. Valproic acid was first released in the United States in 1978. The first case report suggesting teratogenicity of VPA in humans was by Dalens et al. [1980]. Since then, there has been an expressed concern regarding the possible teratogenic effects of the drug. In 1982, Jeavons summarized the outcomes of 196 pregnancies exposed to anticonvulsants from 9 countries. There were 39 abnormal pregnancies and in 13 of them, the mothers received monotherapy with VPA. Of those 13 cases, there were 3 cases of neural tube defects (NDTs), 4 cases of heart defects, 3 cases with facial abnormalities, 1 case of cleft lip and palate, and 2 cases with abnormal digits. The author pleaded that the outcome of all pregnancies, while on VPA, be reported to manufactures.

Initially, the teratogenic potential of VPA was difficult to establish because most case reports described children who were exposed to multiple anticonvulsants; therefore making a causal relationship between VPA and its adverse effects on the developing fetus

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questionable. With additional observations in humans, however, a pattern of facial manifestations, multiple systemic involvement, and central nervous system dysfunction has emerged that is distinctly different from those observed after in utero exposure to other anticonvulsant medications. This constellation of minor and major malformations is referred to as the fetal valproate syndrome (FVS) [DiLiberti et al., 1984; Jager-Roman et al., 1986; Winter et al., 1987; Ardinger et al., 1988; Thisted and Ebbesen, 1993]. A particular concern has been the occurrence of neural tube defects in infants exposed to valproate in utero, with the incidence estimated to be 1–2% [Stanley and Chambers, 1982; Robert and Guibaud, 1982; Lindhout and Schmidt, 1986; Robert and Rosa, 1983; Nau et al., 1984; Oakeshott and Hunt, 1989; Lindhout et al., 1992, Omtzigt et al., 1992].

Additional support for the teratogenic aspects of VPA came from animal studies. VPA causes dose-related teratogenic effects in all investigated species so far (monkeys, rodents, rabbits). A marked difference in the teratogenic potency and the types of malformations, however, occurs between species. The species' differences in the drug response are presumably due to both the intrinsic sensitivities of the developing tissues and the differences in exposure of the embryo during the sensitive stages of gestation. VPA causes skeletal malformations and craniofacial defects in all species. Furthermore, VPA causes neural tube defects in humans, mice and hamsters (exencephaly) but not in monkeys, rats or rabbits [Cotariu and Zaidaman, 1991].

The purposes of this paper are twofold. First, it is to describe the facial characteristics, multiple systemic and orthopedic abnormalities, and 10 to 12 years postnatal growth and development follow up studies in two siblings whose mother received VPA monotherapy throughout both pregnancies. Second, it is to review all published cases that were *solely* exposed to VPA prenatally and profile their medical complications in an effort to provide a comprehensive summary of the clinical aspects of FVS and to separate the effect of monotherapy versus polytherapy because a similar pattern of malformations has been reported after prenatal exposure to phenytoin, trimethadione, and other anticonvulsants.

CLINICAL REPORTS

Patient 1

The propositus was delivered vaginally at term to a 26-year-old mother with a history of idiopathic seizures and an otherwise negative family history. Both parents are of average height and head circumference. The mother had taken valproic acid, 500 mg PO/TID, throughout the pregnancy. Her seizures were well-controlled under this regimen. Her valproic acid blood levels ranged from 54 μg/ml to 95 μg/ml (therapeutic range being 33.9–57.0 μg/ml). Fetal movements were hypoactive. Multiple sonograms were performed and no major abnormalities were found. Apgar scores were 7 and 9 at 1 and 5 min respectively. Birth weight was 4.2 kg (95th centile) and length was 55.2 cm (90th centile). The infant had contractures of the second and third fingers as well as subluxation of the left hip. He developed jitteriness on the third hospital day. Serum calcium, glucose and carbon dioxide concentrations were normal. He was discharged on the sixth hospital day. The mother was instructed to stretch her son's fingers and to apply a double set of diapers when changing. At the age of two months the hips were found to be normal. A chest wall cyst was discovered shortly thereafter and was removed surgically. In the first year of life, he had multiple hospitalizations for croup, recurrent otitis media, tracheomalacia, and pneumonia. Developmental history was remarkable for delays in the acquisition of gross motor and speech and language milestones. Independent walking was achieved at the age of 18 months. A laboratory workup including chromosome analysis, chemistry, and serum amino acids was normal.

On physical examination at the age of 3 years, his OFC measured 52.5 cm (98th centile), height 103.5 cm (>97th centile), and weight: 20.5 kg (>95th centile). He had a mild forehead prominence, depressed nasal bridge and hypertelorism. The inner canthal distance measured 3 cm (>75th centile) and the outer canthal distance measured 9.5 cm (>97th centile). The ears were small, each measuring 4.3 cm (>3rd centile), posteriorly rotated with a prominent tragus and heavily folded upper helixes. He had a high arched palate, but no oral clefting. Also noted were ulnar deviations of the fingers of both hands, mild contractures of the terminal phalanges of 2–4th digits, pes planus, a lordotic curvature of the spine, and generalized hypotonia (Fig. 1).

On the Receptive-Expressive Language Scale (REEL), language function was delayed commensurating with a 24–27 month developmental level. Gross motor skills, as assessed on the Bayley Scales of Infant Development, were at the 24.8 month level demonstrating a 1-year delay. Non-verbal cognitive skill abilities were in the borderline to low average range on the Merrill-Palmer Scale. Hearing assessment revealed a mild bilateral conductive hearing loss. On a follow-up at the age of 8.5 years, height was 145 cm (>95th centile), weight was 46.5 kg. (>95th centile), and head circumference was 54 cm (>95th centile). Interval history was significant for recurrent ear infections, that caused moderate conductive hearing loss in the left despite medical and surgical intervention. On developmental testing, he had language-based learning disabilities and a visual perceptual processing disorder. He had borderline to low average cognitive abilities and Attention Deficit Hyperactivity Disorder (ADHD). He showed favorable response to treatment with stimulants.

Patient 2

During her second pregnancy, the mother of Patient 1 continued to take VPA, 500 mg, PO/TID. Her seizure disorder was well-controlled. Her blood valproic acid levels were at 80 μg/ml. Multiple sonograms were performed and no major abnormalities were identified. A male sibling was delivered at term vaginally. Apgar scores were 7 and 8 at 1 and 5 min respectively. He

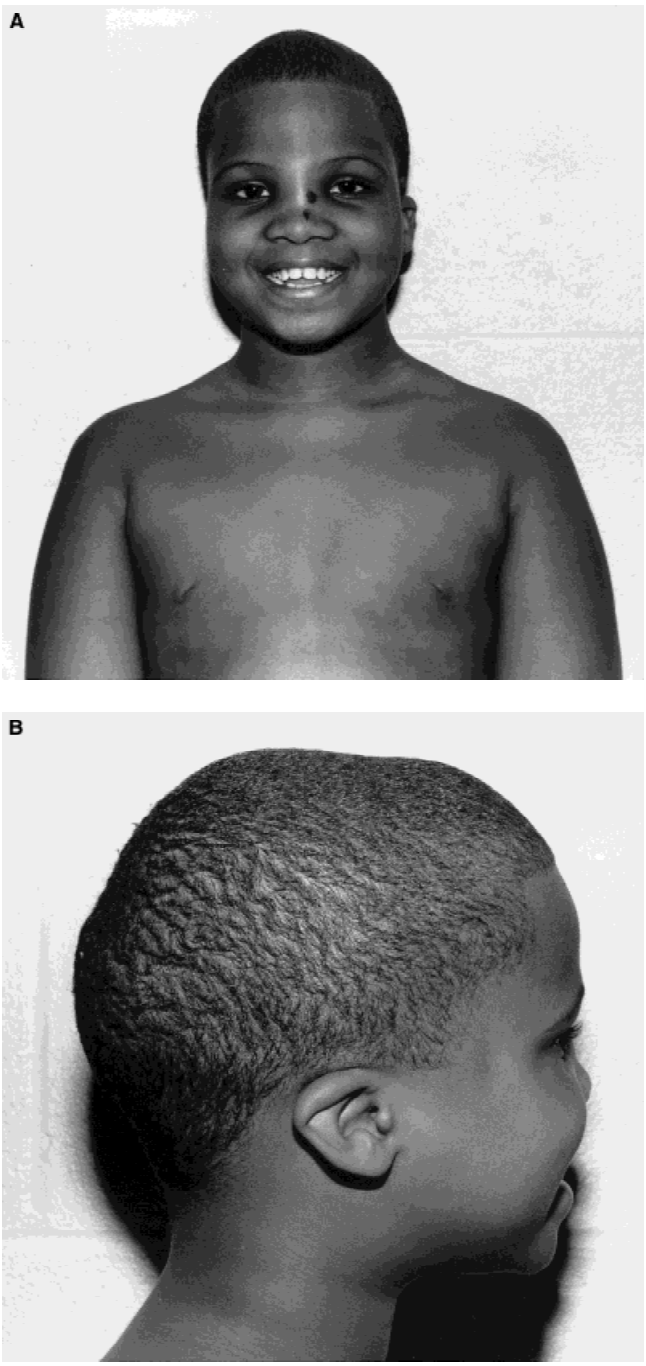

Fig. 1. **A:** Note the prominent forehead, hypertelorism, broad nose, smooth philtrum, and inverted nipples. The dark spots on the nose are abrasions due to a fall. **B:** The ears are small, posteriorly rotated with heavily folded upper helix, and prominent tragus.

weighed 3.4 kg (75th centile), measured 55 cm (90th centile) and his OFC was 37.5 cm (90th centile). In the nursery, he had curved middle toes bilaterally, contractures of the right index finger and the left middle finger, talipes equinovarus of the right foot, and metatarsus adductus of the left foot. Renal ultrasound showed the presence of two small cysts around the collecting system of the right kidney. Laboratory studies, including serum amino acids and chromosomes, were normal.

On evaluation at the age of 8 months, his OFC was 48 cm (95th centile), height 75.5 cm (75th centile), and weight 7.85 kg (75th centile). Multiple nevi each measuring 2–3 mm were noted on the arms and legs. He had skull and facial asymmetry, a wide fontanelle, a depressed nasal bridge and hypertelorism. The inner canthal distance measured 3.5 cm (>97th centile) and the outer canthal distance 9 cm (>97th centile). He had anteverted nostrils, a short smooth philtrum and small ears, each measuring 3.5 cm (<3rd centile) with heavily folded upper helices (Fig. 2). Internipple distance was

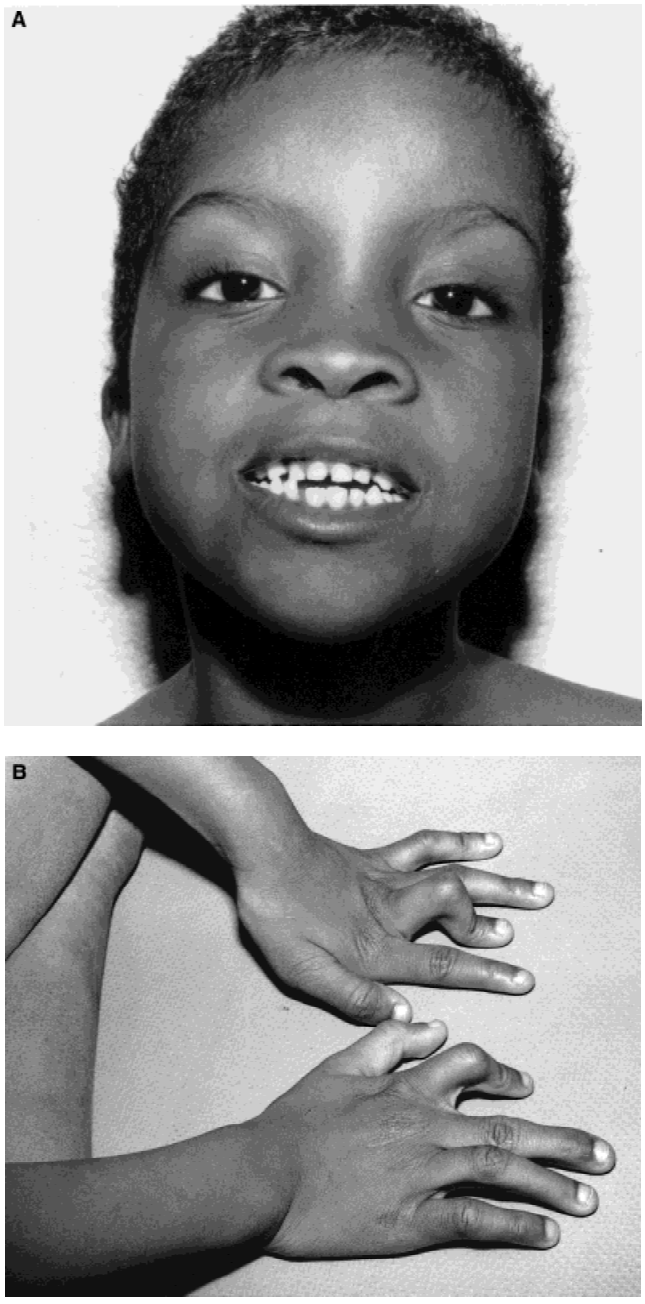

Fig. 2. **A:** Note the facial asymmetry, prominent forehead, hypertelorism, broad nose, smooth philtrum, malocclusion type III and open bite. **B:** Contractures of right index and left middle fingers, mild nail hypoplasia, and wide distant phalanges.

12 cm (90th centile) and an inverted left nipple was present. Diastasis recti was noted. The left testicle was undescended for which an orchiopexy was performed at a later date. He had generalized moderate hypotonia. A computerized axial tomography of the head, CAT scan showed prominence of the ventricles and of the cortical sulci in the frontal region, with cranial asymmetry.

Developmental assessment at the age of 12 months indicated the Mental Index on the Bayley Scales of Infant Development to be 59, with an age equivalent of 9.4 months. The Motor Index on the Bayley Scales of Infant Development was 50, with an age equivalent of 8.1 months.

At the age of 4 years he was administered the REEL language skills were at the 22–24 month developmental level. The Merrill-Palmer Scale of Mental Tests and the Vineland Adaptive Behavior Scales were also completed; cognitive functioning and adaptive skills were at the 3 year, 4 month age level. On follow up at the age of 10 years, his height was 162.5 cm (>98th centile), weight was 50 kg. (>98th centile) and head circumference was 55 cm (>98th centile). He had a large café-au-lait spot on his left axilla measuring 10 × 4 cm and another one on the left shoulder measuring 25 × 18 cm. His facial characteristics included narrow bifrontal diameters, mid face hypoplasia, short upturned nose with a broad flat bridge and a long flat philtrum. His ears were small and cupped. He had a high arched palate. He had pronated feet and moderate generalized hypotonia. His cognitive and adaptive abilities were in the mild to moderate range of mental retardation and his language skills clustered around the 3 year developmental level with significant delay in social communication. On the Wechsler Intelligence Scale for Children-Third Edition (WISC-III), he received a full scale IQ score of 54, a verbal IQ of 50, a performance IQ of 66. His overall fine and gross motor skills were measured at a 5-year developmental level.

DISCUSSION

In an effort to further delineate the phenotypic features of FVS, the English literature was reviewed from 1978–2000 to identify patients with FVS. Cases that did not have adequate phenotypic description were excluded [Stanley and Chambers, 1982; Oakeshott and Hunt, 1989; Lindhout et al., 1992; Omtzigt et al., 1992; Hockey et al., 1996; Case 3] as well as cases that were exposed to VPA and other anticonvulsant treatment [Thomas and Buchanan, 1981; Gomez, 1981; DiLiberti et al., 1984 Cases 2,4,5; Chitayat et al., 1988 Cases 1,2; Ardinger et al., 1988 Cases 9–19; Serville et al., 1989 Christianson et al., 1994 Cases 1,2; Thisted and Ebbesen, 1993 Cases 12–17; Baggot et al., 1999].

In this study, a total of 70 cases including the above two mentioned were identified and their clinical findings are summarized in Table I. In the sample there were 32 males, 19 females, and 19 cases of undetermined gender. As Table I indicated, exposure to VPA prenatally is associated with a wide spectrum of abnormalities including facial abnormalities, multiple systemic involvement, central nervous dysfunction, and altered physical growth.

TABLE I. Systemic Manifestations of the Fetal Valproate Syndrome

	Case 1	Case 2	Total cases (70)	%
Craniofacial abnormalities				
Macrocephaly	+	+	11/70	16
Microcephaly	–	–	9/70	13
High/broad forehead	+	+	17/70	26
Bifrontal narrowing	–	+	12/70	19
Hypertelorism	+	+	19/70	27
Epicanthal folds	–	–	22/70	31
Midface hypoplasia	+	+	14/70	20
Small/broad nose	+	+	39/70	57
Small/abnormal ears	+	+	31/70	46
Long/flat philtrum	+	+	29/70	43
Thin vermillion border	+	+	26/70	37
Micro/retrognathia	–	–	18/70	26
Cleft palate	–	–	3/70	4
Organ malformations				
Skin & appendages	–	–	20/70	29
Brain abnormalities	–	+	7/70	10
Eye abnormalities	–	–	6/70	9
Cardiac abnormalities	–	–	18/70	26
Pulmonary Abnormalities	–	–	11/70	16
Renal Abnormalities	–	+	5/70	7
Genital Abnormalities	–	+	15/70	21
Musculoskeletal System	+	+	44/70	63
Spina Bifida	–	–	2/70	3
Evolution				
Early Death	–	–	8/67*	12
Hypotonia	+	+	7/67	10
Growth Retardation	–	–	10/67	15
Overgrowth Pattern	+	+	6/67	9
Developmental Deficits	+	–	13/67	20
Mental Retardation	–	+	6/67	10
Seizures	–	–	2/67	3

*In the group there were 67 live births, two fetuses, and one stillbirth [Dalens et al., 1980; Clay et al., 1981; Bailey & Pool, 1983 cases 1, 2; Bantz, 1984; DiLiberti et al., 1984 cases 1, 3, 5, 7; Tein et al., 1985; Chessa & Iannetti, 1986; Jager-Roman, 1986 cases 1–14, Huot et al., 1987 cases 1, 2; Massa et al., 1987; Winter et al., 1987 cases 1–3; Ardinger et al., 1988 cases 1–8; Verloes et al., 1990; Buntinx, 1992; Sharony et al., 1993 cases 1, 2; Thisted & Ebbesen, 1993 cases 1–11; Christianson et al., 1994 cases 3, 4; Hubert et al., 1994; Langer et al., 1994; Boussemart et al., 1995; Okada et al., 1995; Hockey et al., 1996 cases 1, 2; Williams & Hersh, 1997; Janas et al., 1998 cases 1–3; Mo & Ladusans, 1998 cases 1, 2].

The most common craniofacial abnormality involves the nose (57%) which is small and broad and has a flattened nasal bridge, followed by abnormal/small ears (46%), a long/flat philtrum (43%), and thin vermillion border (37%). Also noted in decreasing frequency were epicanthal folds (31%), hypertelorism (27%), micro/retrognathia (26%), a high/broad forehead (26%), and bifrontal narrowing (17%). Although the ears are frequently involved, they do not seem to have any specific abnormality. They are usually small, low set, and posteriorly rotated. This consistent facial phenotype is distinctive to prenatal exposure to VPA [DiLiberti et al., 1984, Winters et al., 1987; Ardinger et al., 1988]. In this study, there were 3 cases with cleft palate (4%), a rate 40 times higher than the general population. This is in contrast to a previous study that indicated that monotherapy with VPA is not associated with an increased risk for oral clefts [Martínez-Frías, 1990].

In this review, abnormalities of the musculoskeletal system were the most common systemic abnormalities

found in the majority of patients (63%). Perhaps the reason that this study is highlighting the involvement of the musculoskeletal system is that the discussion of many previous cases and studies focused on the associated major anomalies and overlooked the minor musculoskeletal abnormalities. The musculoskeletal abnormalities are variable ranging from nail hypoplasia to more severe ones such as radial defects and thoracic cage abnormalities (Table II). The most observed musculoskeletal abnormalities consisted of contractions of the small joints and the presence of long overlapping fingers (36%), followed by foot deformity (30%). These abnormalities could be related to abnormal muscle tone in intrauterine life, as well as in postnatal life. Thumb abnormalities (17%) and radial defects (16%) were also noted. Radial reduction defects are a severe type of skeletal defect associated with exposure to VPA prenatally. Ten patients had abdominal wall defects. Although the majority of these defects consisted of inguinal and umbilical hernias, there were 2 cases of omphaloceles [Winter et al., 1987 Case 1; Boussemart et al., 1995].

In laboratory animals, the administration of VPA early in gestation is associated with skeletal defects in all tested species. Treatment of CD-1 pregnant mice with VPA (105-389 mg/kg) produced dose-related skeletal malformations [Brown et al., 1980]. Experiments with mice confirmed the report of dose-dependent teratogenic craniofacial malformations, yolk sac defects, and abnormalities of body [Bruckner et al., 1983]. In the belted Dutch rabbit, high doses of VPA (350/mg) induced costal and vertebral malformations together with hypoplasia or aplasia of the thumb [Petrere et al., 1986]. When rhesus monkey fetuses were exposed to VPA concentrations 10-fold above the usual human therapeutic level, defects of fore and hind limbs were noted as well as craniofacial abnormalities and reduced body weight. The limb abnormalities included shortened digits, absence of the distal radius, shortened fibulae, bowed tibia, and an abnormal knee joint [Mast et al., 1986]. In another study, the skeletal teratogenic response in rats exposed to VPA at different embryonic stages was studied. A significant number of malformed fetuses were observed in all treated groups. The malformations were localized at the axial skeleton level and included alterations of cervical vertebrae, presence of extra lumbar ribs, duplications of thoracic and lumbar segments, and lumbo-sacral abnormalities [Menegola et al., 1998]. It is not clear how VPA induces malformations of the axial segments. A reduction of retinoid acid concentration, a physiologic morphogen during morphogenesis of vertebrate and invertebrate embryos, could be regarded as a possible mechanism of teratogenesis. Similar transformations of axial segments are seen in mice after in utero exposure to retinoic acid. It is postulated that the teratogen interferes with the Hox gene code, that controls the specification of the segment skeleton [Kessel, 1992].

TABLE II. Fetal Valproate Syndrome Musculoskeletal Abnormalities

	Case 1	Case 2	Total cases (70)	%
Abdominal wall defects	–	–	10/70	14
Fingers abnormalities/contractures	+	+	25/70	36
Foot abnormalities	+	+	21/70	30
Thumb abnormalities	–	–	12/70	17
Radial defects	–	–	11/70	16
Nails abnormalities	–	–	7/70	10
Thoracic cage abnormalities	–	–	5/70	7
Large joint abnormalities	+	–	4/70	6

In this study, minor anomalies of the skin and its appendages were frequent and documented in 30% of patients. The most common abnormalities were nipple abnormalities and hemangiomas. There were 2 cases of pigmentary abnormalities. One child had depigmented eyebrows [Dalens et al., 1980] and another one had a very large café-au-lait spot (this report, Case 2). Aplasia cutis congenita of the scalp was seen in one case. This condition is regarded as a cutaneous marker of neural dysraphism and fetal exposure to VPA is known to increase the risk of midline defects and NTDs [Hubert et al., 1994]. Teratogenic agents that can cause aplasia cutis congenita include prenatal exposure to methimazole (antithyroid drugs) as well as intrauterine herpes and varicella infection [Sybert, 1997].

In this review, slightly more than one quarter of patients (26%) with FVS had cardiovascular abnormalities (Table III). The most frequent lesion in decreasing

TABLE III. Fetal Valproate Syndrome Cardiovascular Malformations

Reference	Cardiovascular abnormalities
Dalens, 1980	Levocardia, partial right bundle branch block
Clay et al., 1981	VSD
Bailey et al., 1981	Aortic stenosis
DiLiberti et al., 1984 (Case 6)	Aortic stenosis
Jager-Roman et al., 1986 (Case 1)	Lesion not specified
Jager-Roman et al., 1986 (Case 13)	PDA
Winter et al., 1987 (Case 2)	VSD
Winter et al., 1987 (Case 3)	Pulmonic stenosis
Ardinger et al., 1988 (Case 3)	Lesion not specified
Ardinger et al., 1988 (Case 4)	Lesion not specified
Huot et al., 1987 (Case 2)	Abnormalities of coronary sinus, anomalous left Superior vena cava
Janas et al., 1998 (Case 3)	Coarctation of the aorta, transposition of the great vessels, VSD
Thisted and Ebbegen, 1993 (Case 4)	ASD, VSD
Thisted and Ebbegen, 1993 (Case 10)	Pulmonary stenosis
Thisted and Ebbegen, 1993 (Case 11)	Tetralogy of fallot
Hockey et al., 1996	ASD, PDA
Mo and Ladusans, 1998 (cases 1 & 2)	Anomalous right pulmonary artery, tricuspid regurgitation, abnormal origin of right pulmonary artery, dysplastic pulmonary valve

frequency was VSD, aortic stenosis, pulmonary stenosis, and PDA. These lesions belong to the category of abnormalities resulting from altered embryonic blood flow. The pathogenesis of VPA-induced cardiovascular abnormalities is not well known. VPA is known to be teratogenic to the developing cardiovascular system in several experimental animals, including monkeys, rabbits, rats, hamsters, and mice. Sonoda et al. [1993] investigated the effect of VPA in a mouse model looking into peak sensitivity of gestational day and dose-dependent effect. Cardiovascular abnormalities appeared with the highest incidence when VPA was administered on day 7 of gestation, present in 29% of live fetuses and 86% of litters. Day 7 of gestation in mice corresponds to the 16th day after conception in humans. The cardiovascular abnormalities included VSD, endocardial cushion defect, transposition of the great vessels, double outlet right ventricle, tricuspid atresia, and hypoplastic left heart. In addition, there was significant correlation between the frequency of CVS abnormalities and the VPA dose.

In this review, genital abnormalities were seen in 21% of patients and consisted mainly of hypospadias [Jager-Roman et al., 1986 Cases 1,2,3,11; Winter et al., 1987 Cases 1,3], hypospadias with undescended testicles [Bailey et al., 1983 Case 2; DiLiberti et al., 1984 Case 6; Thisted and Ebbesen, 1993 Case 11; Sharony et al., 1993 Case 2], and undescended testicle [Hockey et al., 1996 Case 1; this report, Case 2]. The genital defect was not specified in 3 cases [Ardinger et al., 1984 Cases 2,3,6]. The mechanism by which VPA causes genital abnormalities is not clear. It is possible that the teratogen interferes with HOX genes, that are necessary for genital development. HOX genes specify developmental boundaries and determine cell fate during morphogenesis [Innis, 1997].

Respiratory tract abnormalities were seen in 16% of patients. The most common abnormality was tracheomalacia that was seen in 6 cases [Ardinger et al., 1988 Cases 1,2,5; Christianson et al., 1994 Cases 3,4; this report, Case 1], followed by lung hypoplasia [Janas et al., 1998 Cases 1–3], severe laryngeal hypoplasia with abnormal lobulation of the right lung [Huot et al., 1989 Case 2], and right oligemic lung [Mo and Ladusans 1998 Case 1]. The etiology of congenital tracheomalacia is unknown. It is frequently seen in patients who have a TE fistula, patients with chondrodysplasias, in premature infants who have been treated with positive pressure ventilation, and in association with extrinsic compression of the trachea by vascular structures. Lung hypoplasia is thought to result from prenatal hypoxic insult, space occupying growth, or lesions that decrease the size of the chest wall [Albers and Wood, 1993]. Although the true incidence of congenital respiratory tract abnormalities is not known, such conditions are not commonly observed malformations and their presence among patients with FVS seems to be a specific teratogenic effect of VPA.

Ocular abnormalities were documented in 9% of patients with FVS. It consisted of esotropia [DiLiberti et al., 1984 Case 6], nystagmus [DiLiberti et al., 1984 Case 9], tear duct anomalies [DiLiberti et al., 1984 Case 4], microphthalmia [Janas et al., 1998 Case 3], bilateral iris defect [Mo and Ladusans et al., 1998 Case 2], bilateral cataract [Thisted and Ebbesen, 1993 Case 10], and corneal opacities [Hockey et al., 1996 Case 3].

Brain abnormalities were seen in 6 patients. Mild atrophy of the brain was noted in 2 cases [Huot et al., 1987 Case 2; Okada et al, 1994]. The brain defect was not specified in 2 cases [Jager-Roman et al., 1985 Case 1; Ardinger et al., 1988 Case 4]. One patient had a septum pellucidum cyst and mild dilatation of the ventricles [Huot et al., 1987 Case 1] and another one had prominent ventricles and cortical sulci in the frontal region accompanied by cranial asymmetry (this report, Case 2). Isolated hydrocephalus was previously noted in two children who were solely exposed to VPA prenatally [Martínez-Frías, 1990].

Renal abnormalities were seen in 7% of patients and consisted of renal hypoplasia [Bailey et al., 1983 Case 1; Verloes et al., 1990], hydronephrosis [Huot et al., 1987 Case 2], cysts around the collecting system (this report, Case 2), and duplication of the calyceal system [Bantz, 1984].

Hearing loss was infrequent and seen in 2 cases [Thisted and Ebbesen, 1993 Case 10; (this report, Case 1].

During pregnancy in humans, VPA intake results in a tenfold increase in the incidence of NTDs compared to the incidence in the general population [Bjerkedal et al., 1982; Robert and Guibaud, 1982; Lindhout and Schmidt, 1986; Omtzigt et al., 1992]. NTDs are among the most common birth defects in humans. Their etiology is heterogeneous and their mode of inheritance falls into the multifactorial model. Studies in genetically susceptible mice with prenatal exposure to VPA predict that human conceptuses with a genetically determined elevated risk for NTDs could be easily tipped into high risk by mild teratogens [Hall et al., 1997]. In an epidemiological study done in the Netherlands between 1971 and 1991, 34 cases of NTDs were identified. Approximately two-thirds of the identified infants had been exposed to VPA, in the majority of cases as a single drug. The study showed that most NTDs caused by prenatal exposure to VPA were severe open defects. In addition, they were frequently complicated by hydrocephalus and other midline defects within and outside the central nervous system [Lindhout et al., 1992].

Several studies showed that NTDs are induced by VPA at significant rates only in humans and mice [Nau et al., 1981]. Additional animal studies showed that multiple doses of VPA on day 9 gestation in mice result in low incidence of spina bifida aperta and a high incidence of spina bifida occulta [Ehlers et al., 1992]. Rats treated with VPA during gestation did not develop NTDs. They seem to be more resistant than mice to VPA-induced teratogenesis; an interspecies effect that has not been very well studied [Alonso-Aperte et al., 1999]. The mechanism by which VPA causes NTDs remains unclear. Folate deficiency has been suggested as a possible mechanism causing NDT in VPA-exposed pregnancies. Animal studies did not, however, support this mechanism. Mice experiments showed that dietary supplementation with large doses of folic acid failed to decrease the embryotoxicity of VPA and to reduce the

incidence of NDTs in exposed litters [Hansen et al., 1995].

In a search for possible protection against neural tube defects, the role of methionine has been investigated. Methionine is an essential amino acid for normal growth and development in mammals. In cultured rat embryos, the neural tubes failed to close in the absence of methionine. In humans, methionine metabolism may be implicated in some cases of NTDs possibly due to a derangement of homocysteine metabolism. Alterations in the methionine cycle are the strongest hypothesis to explain the occurrence of neural tube defects. The effect of methionine on the incidence of VPA-induced NDTs was investigated in a mouse model. The results showed that methionine reduced VPA-induced spina bifida in mice without altering valproic acid kinetics [Ehlers et al., 1996].

In another experiment, the influence of VPA administration during neural tube formation in the rat and its relationship on the methionine cycle was studied. Although VPA exposed rats did not develop NTDs or gross malformations, an increased frequency of malformations in the axial skeleton was seen. In addition, exposed-rats developed impaired methionine synthesis and DNA hypomethylation. It has been suggested that these axial skeletal malformations may be secondary to the action of VPA on the neural plate. Also, it has been hypothesized that VPA affects methionine synthesis through an altered methionine synthase activity, an effect that impairs methionine availability and disrupts the methylation cycle, inducing DNA hypomethylation [Alonso-Aperte et al., 1999].

In this review, the mortality of FVS is not insignificant and death in early infancy was seen in 12% of cases. All of those who died had multiple congenital malformations, especially of the cardiovascular system. Furthermore, follow-up data on surviving patients in this study documented developmental delays in 20% and mental retardation in 10% (Table I). These figures are felt to be an underestimate because a fair number of reported cases of FVS did not give adequate long term follow up with minimal or no information regarding the developmental outcome. Whereas growth retardation was seen in 15% of patients, 9% including the two siblings in this report had an overgrowth pattern. Because patient 2 had an overgrowth pattern and congenital contractures, the possibility of Weaver syndrome was considered in the differential diagnosis. He did not have the typical facial characteristics of Weaver syndrome, however, such as large ears, flat occiput, and micrognathia.

At least 7 sib pairs have been reported [Winter et al., 1987; DiLiberti et al., 1988; Clayton-Smith and Donnai, 1990, Christianson et al., 1994, Janas et al., 1998; this report] . This indicates that the recurrence risk of FVS in subsequent pregnancies with exposure to VPA would be high, possibly owing to intrinsic problems with the metabolism of VPA in the mothers [Clayton-Smith and Donnai, 1990].

The teratogenic effects of VPA are related to the dose in first trimester [Lindhout et al., 1992; Thisted and Ebbsen, 1993] and large daily doses of VPA (>1,000 mg) have a higher risk of causing malformations and NTDs than smaller doses. Furthermore, high daily doses of VPA increase the likelihood of withdrawal symptoms such as irritability, jitteriness, and seizure activities in the neonatal period [Thisted and Ebbesen, 1993 Cases 1,7,9,10; this report, Case 1].

It is important to provide insight into the spectrum of FVS to women of reproductive age who are receiving VPA treatment. All women with epilepsy should be advised that uncontrolled epilepsy is associated with maternal and fetal risk and that the incidence of malformations in their infants following treatment with anticonvulsants is 2–3 times higher than the general newborn population. Moreover, children of mothers with epilepsy without treatment with anticonvulsants tend to have slightly more minor anomalies than control [Zahn, 1998]. The data from this comprehensive review especially the developmental outcome should be added to the teratogenic risk, that arises in association with the use of VPA during pregnancy.

If treatment with VPA cannot be avoided, it is recommended that the least effective dose be used and the division of the daily dose into 3 or 4 equal doses administered throughout the day [Lindhout et al., 1992]. Diet should be fortified with an adequate amount of folate prior and throughout conception [Delgado-Escueta and Janz, 1992]. Fetuses exposed to VPA should undergo detailed prenatal ultrasonographic evaluation to detect any limb or systemic abnormalities. Because maternal serum alpha feto protein may not be elevated in all cases of NTDs in fetuses exposed to VPA, the direct use of amniocentesis and fetal ultrasound examinations are recommended [Omtzight et al., 1992].

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