

Fetal valproate syndrome and autism: additional evidence of an association

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Autism has been described in association with a variety of medical and genetic conditions. We previously reported on a patient whose clinical phenotype was compatible with both fetal valproate syndrome (FVS) and autism. Here we present five additional patients with FVS and autism. In all five of our patients, there was evidence of cognitive deficits, manifestations of autism, and typical phenotypic characteristics of FVS. The association between this known teratogen and autism has both clinical and research implications.

Autism is a clinically diagnosed developmental disorder, occurring in at least 1/1000 individuals and characterized by pervasive deficits in social interaction, communication, and range of interests and activities. Evidence for the neurobiologic basis of autism is extensive and includes a recurrence risk 30 to 70 times that of the general population, increased frequency of seizures and mental retardation*, and sensorimotor deficits seen commonly in affected individuals (Ciaranello and Ciaranello 1995). Approximately 10% to 15% of those with autism have associated medical conditions (Bailey et al. 1996, Barton and Volkmar 1998). These entities include chromosomal abnormalities (Down and fragile X syndromes), neurocutaneous disorders (tuberous sclerosis), inborn errors of metabolism (phenylketonuria and defects in purine metabolism), infectious diseases (congenital rubella, *Haemophilus influenzae* meningitis), and teratogen exposure during pregnancy i.e. fetal alcohol syndrome (Gillberg 1987).

Valproic acid (VPA) is a recognized teratogen originally found to be associated with an increased risk for a low myelomeningocele lesion, following its use in the first trimester for maternal epilepsy (Robert 1983). Subsequently, fetal valproate syndrome (FVS) was recognized as a clinical entity characterized by phenotypic abnormalities of the face, developmental disabilities, and occasional major organ abnormalities involving respiratory, cardiovascular, gastrointestinal, genitourinary and skeletal systems (DiLiberti et al. 1984, Clayton-Smith and Donnai 1995). Two previous case reports

*US usage. UK usage: learning disability.

Table I: Case report data

<i>Diagnostic features</i>	<i>Patient 1</i>	<i>Patient 2</i>	<i>Patient 3</i>	<i>Patient 4</i>	<i>Patient 5</i>
Age at dual diagnosis (y:mo)	6:11	3:6	6:6	4:1	9:10
Family history					
Maternal	Seizures, mitral valve prolapse, depression	Seizures, depression	Seizures, migraines	Absence seizures, academic deficits	Generalized seizure disorder; three previous miscarriages
Paternal	Hypertension, cancer	Negative	Negative	Unknown	Cleft lip and palate
Pre- and perinatal history					
Medications	VPA 500 mg tid	VPA 250 mg qid Carbamazepine Folic acid	VPA 300mg qd during 1st trimester; 2500 mg qid remainder of pregnancy, Carbamazepine 600 mg bid	VPA 500 mg tid	VPA 500 mg tid
Alcohol	No	No	No	No	No
Tobacco	No	No	No	No	No
Maternal seizures during pregnancy	No	Several seizures	No	No	No
Complications of pregnancy	Vaginal spotting 1st trimester	Oligohydramnios, anemia	None	Lack of prenatal care (mother age 12), 30 week gestation	Preterm contractions at 6 mo
Delivery	Vaginal	Caesarean section due to breech, oligohydramnios	Vaginal	Vaginal	Vaginal
Birthweight	2.2 kg	3.67 kg	2.9 kg	1.86 kg	3.06 kg
Neonatal features	Talipes equinovarus, hypospadias	Hypotonia	Hypospadias, penile torsion	Dysmorphic features, inguinal hernias	Dysmorphic features
Medical history	Chronic otitis media, bilateral myringotomy tubes ×4, asthma, gastroesophageal reflux, hypospadias repair, amblyopia, surgical release of heelcords	Environmental allergies, sinusitis	Feeding problems, gastroesophageal reflux, poor weight gain in infancy, chronic otitis media, myringotomy tubes, asthma to present	Hernia repair; enterococcal sepsis, 2 months; generalized tonic-clonic seizures, 2 months to 2 years; asthma 18 months	Tracheomalacia, subglottic stenosis, multiple hospitalizations for stridor (airway management), chronic otitis media, multiple sets of myringotomy tubes, left exotropia requiring surgery
Growth parameters ^a	Ht 75–90th centile; Wt, OFC 50–75th centile	Ht 25–50th centile, Wt 75th centile, OFC 95th centile	Wt >95th centile, OFC 25th centile	Ht, Wt, OFC 50th centile	Ht, Wt, OFC 95th centile
Physical examination	Hypertelorism, small nose, flat nasal bridge, thin upper lip, downturned corners of mouth, posteriorly rotated ears, bridged palmar creases, mildly dysplastic nails, minimal residual talipes equinovarus, no murmur	Frontal bossing, bitemporal narrowing, hypertelorism, short and flat nose, simplified philtrum, posteriorly rotated ears, I-II/VI systolic ejection murmur, hypoplastic nails	Trigonocephaly, midface hypoplasia, broad nasal bridge, short columella, bulbous nasal tip, thin upper lip, posteriorly rotated and cupped ears, ankyloglossia, inverted nipples, no murmur	Hypertelorism, mild epicanthal folds, posteriorly rotated ears, broad nasal bridge, anteverted nares, thin lips, long philtrum, inverted nipples, camptodactyly, proximally placed left thumb, no murmur	Frontal bossing, broad forehead, epicanthal folds, slight downslant palpebral fissures, small ears, short nose with mildly anteverted nares, slightly thin vermilion border of upper lip, inverted nipples moderate laxity of PIP joints, underdeveloped palmar creases, no murmur
Neurologic examination	Hypotonia, wide-based, stiff-legged gait	Hypotonia, brisk symmetric DTRs, flat-footed gait	Low-normal muscle tone, slightly increased muscle mass	Mildly decreased muscle tone	Mild immaturities; gross and fine motor incoordination, low muscle tone in trunk and extremities
DSM-IV criteria for autism	Yes	Yes	Yes	Yes	Yes

presented patients with features of both FVS and autism (Christianson 1994, Williams and Hersh 1997). We present five additional patients who meet clinical criteria for both FVS and autism, and discuss the clinical and research implications of this association.

Case reports

Pertinent information regarding the five patients with FVS and autism is summarized in Table I. VPA was used alone during pregnancy in two of the patients and in combination with another anticonvulsant in three patients. While these children were seen at different institutions, each had an intensive neurodevelopmental evaluation that involved a pediatrician with expertise in autism. Diagnosis of autism was based on markedly impaired development in social interaction and communication and significantly restricted range of activities and interests. Each child met the criteria for autism specified in the

DSM-IV (American Psychiatric Association 1994). As can be seen from the table, behavioral characteristics and communication data are consistent with the diagnosis.

The diagnosis of FVS was made by a clinical geneticist in each case. Listed in the table are relevant physical and neurodevelopmental findings that support the diagnosis, as well as pertinent medical history and diagnostic testing. None of our patients had evidence of growth deficiency or microcephaly, consistent with previous studies which have indicated no specific pattern of pre- or postnatal growth with exposure to VPA alone; however, postnatal growth deficiency and microcephaly have been described in up to two-thirds of individuals exposed to VPA in combination with other anticonvulsants (Ardinger et al. 1988). Patient 1 had a mild cardiovascular abnormality; cardiovascular lesions of varying types have been described in 20% to 50% of individuals with VPS (Ardinger et al. 1988). Another of our patients had significant respiratory

Table I: continued

<i>Diagnostic features</i>	<i>Patient 1</i>	<i>Patient 2</i>	<i>Patient 3</i>	<i>Patient 4</i>	<i>Patient 5</i>
Developmental profile					
Psychological ^b	Leiter: SS=61; VMI-SS=83	Bayley: scatter to age-appropriate; DPII: self-help 26 mo, Social 18 mo, Communication 12 mo	Leiter: SS=66 Vineland: Comprehension=44	CDI: adaptive score 2–2.5 years, Diff: SS=44	WISC-III Perf IQ 100, Verbal IQ 81, Woodcock–Johnson: average academic skills
Speech and language	Communication disorder (language skills 17–30 mo)	Communication disorder (few single words, echolalia)	Communication disorder (six spontaneous words, echolalia)	Communication disorder (rote utterances)	Deficits in receptive, expressive and pragmatic language
Audiologic evaluation	Mild bilateral conductive loss	Normal hearing	Mild conductive loss left, normal hearing right	Mild high frequency hearing loss	Mild conductive loss left ear, moderate conductive loss right ear
Behavior characteristics	Lined up trains, watched spinning objects, only parallel play, withdrew in crowded settings	Repetitive activities, rolled cars while watching wheels, no interactive play	Decreased eye contact, lined up objects, decreased imaginative play, aggressive, head banging, hand flapping	Decreased eye contact, restricted play, hand flapping and other stereotypies, limited social smile, fascinated by lights, bothered by noise	Poor eye contact, difficulty adapting to changes, no imaginative play, poor peer interactive (parallel but no interactive play), fascination with spinning objects, laughs or talks to self
Other diagnostic studies	Normal: chromosome analysis, renal ultrasound, brain MRI, fragile X DNA, urine metabolic screen. Abnormal: EEG – generalized high amplitude spike and slow wave activity. ECG: narrowing of descending aorta, tricuspid regurgitation	Normal: chromosome analysis, fragile X DNA, TSH, urine metabolic screen, CT of head, ECG, echocardiogram	Normal: chromosome analysis, TSH, lead level, fragile X DNA, urine organic and amino acid screen, very long chain fatty acids, brain MRI, isoelectric focusing of plasma transferrin; FISH for 15q deletion, duplication	No additional studies. VPS diagnosed by clinical geneticist at 3 days of age	Normal: brain MRI, chromosome analysis, TSH. Abnormal: Bone age (advanced)

^a Ht, height; Wt, weight; OFC, occipitofrontal circumference.

^b Psychological tests: Leiter, Leiter International Performance Scale (Reid and Miller 1995); Bayley, Bayley Scales of Infant Development (Bayley 1993); CDI, Child Developmental Inventory (Ireton 1992); WISC-III, Wechsler Intelligence Scale for Children, 3rd edn (Wechsler 1991); VMI, Developmental Test of Visual Motor Integration, 4th edition (Beery 1997); Vineland, Vineland Adaptive Behaviour Scales (Sparrow et al. 1984); DPII, Developmental Profile II (Alpern et al. 1984); Diff, Differential Ability Scales (Elliott 1990); Woodcock–Johnson, Woodcock–Johnson Psycho-educational Battery, Revised (Woodcock and Johnson 1989); SS, standard score.

tract abnormalities (tracheomalacia, subglottic stenosis).

A sixth patient for whom there is only limited data was seen for one visit by the clinical geneticist. This child also appeared to meet criteria for FVS and autism spectrum disorder, but did not undergo a developmental evaluation. He presented at 3 years 6 months of age due to concerns about speech delays and deficits in social interaction. His mother took phenytoin and 1500 mg of valproic acid daily during pregnancy. Behaviorally, the child had no imaginative play and had only recently become interested in the activities of other children; he also had rituals and insistence on routine. On physical examination, height and weight were at the 75th and 90th centiles, respectively; occipitofrontal circumference was between the 10th and 25th centiles. Facial features included a high forehead, arched eyebrows, broad nasal bridge, anteverted nares, long smooth philtrum, thin upper lip, micrognathia, and ears with folded helices and prominent lobes; joints were hyperextensible and neurologic examination was unremarkable. Fragile X DNA analysis and urine organic and amino acid screens were normal. MRI of the brain revealed a Chiari 1 malformation. Hearing and vision were within normal limits.

Discussion

While it is clear that fetal exposure to VPA commonly produces neurodevelopmental problems, the nature of these problems has not been well described in large series. Ardinger et al. (1988) described 19 children with FVS and reported neurologic abnormalities or developmental delay in five out of seven children exposed to VPA alone and 10 out of 11 of those exposed to combination anticonvulsant therapy. Christianson et al. (1994) reported on two sibling pairs with FVS: one boy had mild mental retardation and characteristics of autism, and the other three patients had variable cognitive impairments with greater relative deficits in language development. Laegreid et al. (1993) reported seven children exposed to VPA *in utero*, all of whom had dysmorphism and neurologic abnormalities. Of the five exposed to VPA monotherapy, three demonstrated minimal developmental delays, one had uneven development with greatest deficits in gross motor and speech development, and the other exhibited mild mental retardation with autistic traits. Of the two other children, who were exposed to both VPA and diazepam, one had severe psychomotor retardation, was non-verbal, and had autistic traits.

In all five of our patients, there was evidence of cognitive deficits, manifestations of autism, and typical phenotypic characteristics of FVS. Valproic acid was used alone or in combination with other anticonvulsants during each pregnancy and was considered to be the primary risk factor causing the neurodevelopmental problems.

The association between autism and FVS is of particular interest given recent animal studies and autopsy results of the human brain in individuals with autism. *In utero* thalidomide exposure is associated with a high incidence of autism (Stromland et al. 1994). The autopsied brain of an individual with thalidomide exposure and autism yielded evidence of injury at the time of neural tube closure involving brain stem nuclei, with near complete absence of the facial nucleus and superior olive, and shortening of the brainstem between the trapezoid body and inferior olive (Rodier et al. 1996). Similar brain lesions were produced when rat embryos were exposed to VPA, resulting in progressive reductions in the number of motor neurons and secondary reductions in posterior

cerebellar Purkinje cells, but leaving other regions of the brain relatively unaffected (Rodier et al. 1996). Previous autopsy studies of human brains of patients with autism have documented reduction of Purkinje cells in the posterior and inferior cerebellar hemispheres (Bauman and Kemper 1994).

This brainstem neuropathology is similar to that found in *Hoxa-1* knockout mice, raising the possibility that these changes may have resulted from a defect in the *Hoxa-1* gene (Rodier et al. 1997). *Hoxa-1* genes are activated during an early embryonic stage in mice during which the single layered blastula acquires additional germ layers and becomes the gastrula. Expression spreads from the posterior primitive streak anteriorly in mesoderm and ectoderm. *Hoxa-1* genes are regulated by retinoids by means of retinoic acid response elements (RAREs). RARE mutations in mice produce abnormalities in the cranial nerves and portions of the rhombomere similar to, but not as severe as, abnormalities seen in *Hoxa-1* knockout mice (Dupé et al. 1997). This provides evidence that some aspects of *Hoxa-1* function come under the direct control of endogenous retinoids. Either an increase or decrease in retinoid levels can result in malformations (Fex et al. 1995).

Several studies in humans have demonstrated that VPA alters serum levels of retinol. Nau et al. (1995) reported increased levels of retinol with VPA use alone, and decreased levels of retinol metabolites with VPA in combination with other anticonvulsants. Fex et al. (1995) demonstrated that VPA lowers serum levels of retinol metabolites. Therefore, we speculate that VPA disturbs the balance of retinoids, leading to impaired regulation of *Hoxa-1* gene expression in the neuronal organization of the developing rhombomeres of the hindbrain.

Further delineation of the cognitive and behavioral profile seen with VPS and the frequency with which autism is associated with this condition is needed. The five current patients and one previous patient presented by the authors (Williams and Hersh 1997) provide supportive evidence of an association between autism and FVS. A prospective, controlled study of women taking VPA during pregnancy with long term follow-up of their children would provide information about the frequency with which FVS occurs and the prevalence of autism spectrum disorders within this population, regardless of whether phenotypic features of FVS are present. In addition, further anatomic and molecular studies on autopsy specimens of individuals with FVS may result in a better understanding of the pathogenic mechanisms leading to the development of autism.

It is clear that children with FVS are at increased risk for developmental disabilities and deserve close developmental monitoring. The association between autism and FVS has clinical implications which include screening these children at or before 18 months with specific questions and observations on social, communication, and play skills, e.g. Checklist for Autism in Toddlers (Baron-Cohen et al. 1992). If deficits are identified, these children would certainly benefit from additional evaluation involving more detailed parent interview and observation schemata for diagnostic purposes, e.g. Autism Diagnostic Observation Schedule (Lord et al. 1989). Interdisciplinary teams including medicine, psychology, speech pathology, occupational therapy, and education could then devise individualized intervention strategies and address developmental concerns without delay.

Disclaimer

The opinions and assertions contained herein are the views of the authors and are not to be construed as official or as reflecting the views of the United States Department of Defense.

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