

## Original articles

## A clinical study of 57 children with fetal anticonvulsant syndromes

S J Moore, P Turnpenny, A Quinn, S Glover, D J Lloyd, T Montgomery, J C S Dean

## Abstract

**Background**—Anticonvulsants taken in pregnancy are associated with an increased risk of malformations and developmental delay in the children. To evaluate the pattern of abnormalities associated with prenatal anticonvulsant exposure further, we undertook a clinical study of 57 children with fetal anticonvulsant syndromes.

**Methods**—Fifty two children were ascertained through the Fetal Anticonvulsant Syndrome Association and five were referred to the Aberdeen Medical Genetics Service. Pregnancy and medical history were obtained through a standardised questionnaire and interview and the children were examined.

**Results**—Thirty four (60%) were exposed in utero to valproate alone, four (7%) to carbamazepine alone, four (7%) to phenytoin alone, and 15 (26%) to more than one anticonvulsant. Forty six (81%) reported behavioural problems, 22 (39%) with hyperactivity or poor concentration of whom four (7%) had a diagnosis of attention deficit and hyperactivity disorder. Thirty four (60%) reported two or more autistic features, of whom four had a diagnosis of autism and two of Asperger's syndrome. Forty four (77%) had learning difficulties, 46 (81%) had speech delay, 34 (60%) had gross motor delay, and 24 (42%) had fine motor delay. Nineteen (33%) had glue ear and 40 (70%) had joint laxity involving all sizes of joints. Of 46 who had formal ophthalmic evaluation, 16 (34%) had myopia. **Conclusions**—Speech delay, joint laxity, glue ear, and myopia are common in the fetal anticonvulsant syndromes and autistic features and hyperactivity form part of the behavioural phenotype.

(*J Med Genet* 2000;37:489–497)

Keywords: fetal anticonvulsant syndrome; fetal valproate syndrome; teratogen; birth defects

Seizure disorders are the most frequent major neurological complication in pregnancy, affecting 0.4 to 0.8% of pregnant women.<sup>1</sup> Children exposed in utero to anticonvulsants have an increased risk of malformation, estimated at

between two to seven times greater than the general population risk.<sup>2–7</sup> The risk of developmental delay and behavioural disorder is less certain.<sup>8–9</sup> Characteristic dysmorphic features and malformations have been described with fetal exposure to phenytoin, valproate, and carbamazepine.<sup>6–9–16</sup> Although distinctive phenotypes are described for the different anticonvulsants, there is an overlap in both facial dysmorphic features and malformations.

The facial features of the fetal valproate syndrome include epicanthic folds, an infraorbital groove, medial deficiency of the eyebrows, flat nasal bridge, short nose with anteverted nares, smooth or shallow philtrum, a long thin upper lip, a thick lower lip, and a small, downturned mouth.<sup>6</sup> Fetal phenytoin is said to be associated with hypertelorism, broad nasal bridge, short nose, and facial hirsutism, while the fetal carbamazepine face includes epicanthic folds, short nose, long philtrum, and upward slanting palpebral fissures.<sup>10–11</sup> It has also been noted that untreated maternal epilepsy is associated with minor dysmorphic features in the child, such as high forehead, frontal bossing, and epicanthus.<sup>12</sup>

A wide spectrum of malformations has been reported in association with all the fetal anticonvulsant syndromes. Spina bifida is associated particularly with exposure to valproate or carbamazepine in utero,<sup>17–19</sup> hypoplastic nails with phenytoin and carbamazepine,<sup>10–11</sup> and cardiac malformations can result from exposure to any of these three anticonvulsants.<sup>2–11–16</sup>

The aim of this study was to further understanding of the clinical and behavioural phenotype of the fetal anticonvulsant syndromes. Awareness of the spectrum of features associated with in utero exposure to these drugs will assist in counselling epileptic women planning a pregnancy and in the diagnosis of affected offspring.

## Methods

Mothers completed a medical and family history questionnaire before attending a special clinic where standardised interview and assessment was carried out by three clinical geneticists (SM, PT, JD). Data were confirmed by the general practitioner in 30 cases. The questionnaire included a section which asked about eight behavioural traits in the children; the

Department of Medical Genetics, Medical School, Foresterhill, Aberdeen AB25 2ZD, UK  
S J Moore  
J C S Dean

Department of Medical Genetics, Royal Devon and Exeter Hospital, Barrack Road, Exeter, Devon, UK  
P Turnpenny

Department of Ophthalmology, Royal Devon and Exeter Hospital, Barrack Road, Exeter, Devon, UK  
A Quinn  
S Glover

Department of Neonatal Medicine, Aberdeen Maternity Hospital, Foresterhill, Aberdeen, UK  
D J Lloyd

Department of Human Genetics, University of Newcastle upon Tyne, 19 Claremont Street, Newcastle upon Tyne, UK  
T Montgomery

Correspondence to:  
Dr Dean, j.dean@abdn.ac.uk

Revised version received  
6 January 2000  
Accepted for publication 11  
January 2000

mothers' responses were discussed at the clinical interview. Assessment of joint laxity was based on a modification by Beighton *et al*<sup>20</sup> of the technique described by Carter and Wilkinson. Blood was taken from the children and their parents for karyotype, fragile X mutation test, and analysis for the common mutation in the methylene tetrahydrofolate reductase (MTHFR) gene. An association with maternal MTHFR mutation was found which has been reported elsewhere.<sup>21</sup> To confirm the diagnosis of a fetal anticonvulsant syndrome in each of our patients, we arranged for two external clinical experts (DL, TM) to review the clinical photographs and histories. Those patients for whom doubt was expressed by two or more of the authors were excluded. Forty six patients had a full ophthalmic examination by an ophthalmologist (AQ, SG) including refraction and orthoptic assessment. The study was approved by the local Research Ethics Committees.

## Results

### STUDY POPULATION

Fifty nine children ascertained through the National Fetal Anticonvulsant Syndrome (FACS) Association (a parents' support group) were examined and 52 were diagnosed as affected. A further five children were identified from Aberdeen Genetic Clinic records. The 57 affected cases came from 38 families; 32 were male and 25 female. The ages ranged from 0.33 to 16.42 years, mean age 6.48 years (SD 2.76). In 51, karyotypes were analysed and were normal. In 48 cases who gave blood for DNA studies, fragile X mutation testing was normal. Three children who declined to give a blood sample had affected sibs in this study whose fragile X mutation test was normal. The mother of a further male case also had a normal result.

Thirty seven mothers had a diagnosis of epilepsy; in 31 the cause was idiopathic, four were thought to be the result of head injury, one owing to tuberous sclerosis, and one following meningitis. One mother was prescribed carbamazepine for neuralgia.

There was a history of epilepsy in 15 families, four involving a first degree relative (to the mother, including the case with tuberous sclerosis). In six families, epilepsy affected a second degree relative and in five a more distant relative. A history of learning difficulties occurred in four families and of speech delay in three families. In one family with learning difficulties and one with speech delay, the history was compatible with an inherited predisposition, but the children in this study from both families had normal karyotypes and fragile X mutation tests and had clinical findings different from those reported in their relatives.

### ANTICONVULSANT EXPOSURE

Anticonvulsants taken by the mothers during pregnancy are shown in table 1. Forty six children (80%) were exposed to valproate and, of these, 34 (60%) were exposed to valproate monotherapy. Phenytoin or carbamazepine

Table 1 Anticonvulsant exposure

Anticonvulsant	No of pregnancies (total 57)
Valproate alone	34 (60%)
Carbamazepine alone	4 (7%)
Phenytoin alone	4 (7%)
Valproate+carbamazepine	3 (5%)
Valproate+phenytoin	2 (3.5%)
Valproate+carbamazepine+clobazam	2 (3.5%)
Carbamazepine+clobazam+phenytoin	2 (3.5%)
Valproate+vigabatrin	2 (3.5%)
Valproate+clobazam	2 (3.5%)
Phenytoin+phenobarbitone	1 (1.8%)
Valproate+gabapentin	1 (1.8%)

monotherapy was each taken in only four pregnancies (7%). Fifteen children (26%) were exposed to polypharmacy.

In all cases, anticonvulsants were taken in the first trimester. In 51 cases, anticonvulsants were taken throughout the pregnancy.

### PREGNANCY AND BIRTH HISTORY

During pregnancy, seizures increased in frequency in 20 cases, decreased in four, and remained the same in 20. In 24 pregnancies there were no seizures. This information was recorded for 51 pregnancies.

Alcohol consumption was very low or absent in all pregnancies. In 12 pregnancies, the mother smoked between 20 and 210 cigarettes per week.

First trimester intrauterine bleeding occurred in six cases, hypertension in eight, and gestational diabetes requiring insulin therapy in two (in which the mother was taking valproate plus vigabatrin).

There were seven preterm deliveries, out of 46 in which gestation was known. Emergency caesarian section was performed in 10, of which five had been exposed to phenytoin alone or in combination with other anticonvulsants. An elective caesarian section was performed in four pregnancies and ventouse or forceps delivery in five.

The mean birth weight was 3156 g (SD 709) for boys and 3006 g (SD 476) for girls. This information was recorded in 50 cases. Five birth weights (8.8%) fell below the 9th centile and five were above the 91st centile.

### NEONATAL WITHDRAWAL

Symptoms of neonatal withdrawal occurred in 11 cases (19%). Four required nasogastric feeding, three of whom were described as floppy babies. Six were jittery (at 13, 24, and 48 hours), of whom two had seizures (one was attributed to hypoglycaemia).

### MALFORMATIONS AND MEDICAL PROBLEMS

Most of the malformations recorded (table 2) have been previously reported in fetal anticonvulsant syndromes. Previously unrecognised findings include glue ear (33%) and joint laxity (70%). No malformations of the external auditory meatus were found and there was no history of middle ear malformation being detected at tympanotomy. Upper airway anomalies including subglottic stenosis and laryngeal polyp were seen in one child exposed to carbamazepine (in this case there was no

Table 2 Congenital malformations and medical problems

Malformation/medical problem	No of children	Anticonvulsant exposure, mg (weeks of gestation)
Neural tube defect		
Lumbosacral meningocele	1	V 1000(0–5),800(5–40)
Arnold-Chiari malformation type 1	1	V 1200(1–17),1500(17–26),2000(26–40)
Congenital heart disease		
Septal defects	3 (1 VSD, 2 unspecified)	V 2000(0–40)+Vig 1000(0–40) V 5000(0–40)+C 2000(0–40)+Clob V 2000(0–10),3000(10–40)+C 4000(10–40) C 400
Aortic root dilatation and thick mitral valve as a neonate	1	
Genitourinary		
Cryptorchidism	4	V 1500(0–40). V 1500(0–40).V 1500(0–40). V 1000(0–40)
Hypospadias	2	V 1500(0–40). V 3000(0–40)+C 600(0–40)
Pelvoureteric junction obstruction	1	V 1000(0–5),800(5–40).
Extremities		
Nail hypoplasia	12	6 V, 2 C+P+Clob, 2 P, 1 C, 1 V+Clob
Digit hypoplasia	4	3 V, 1 P
Polydactyly	2 (preaxial)	V 1000(0–40). V 1500(0–40)
Syndactyly	2 (3/4 and 2/3)	V 1000(0–40). V 600(0–26).1200(26–40)+Clob
Upper airway		
Narrow/high palate	9	4 V, 2 C+P+Clob, 1 P, 1 P+Phenobarb. 1 V+Clob
Subglottic stenosis	2	V 1500(0–40). C 600(0–6)
Bifid uvula	2	P 200(0–40). C 600(0–6)
Polyp on vocal cord	1	C 600(0–6)
Eyes (see text)		
Brown syndrome	1	V 700(0–40)
Congenital cataracts	1	V 800(0–40)
Teeth		
Small	3 (1 peg-like)	V 1700(0–40). V 1000(0–40). V 200(0–10), 400–1200(35–40)
Notched	1	V 1000(0–40).
Late eruption (18 months)	1	V 2000(0–10),3000(10–40)+C4000(10–40).
Mottling and discolouration	1	V1000(0–22)+P200(23–26).
Joints		
Laxity	40	24 V, 4 P, 2 C, 3 V+C, 2 V+ Clob, 2 V+Vig, 2 V+C+Clob, 1 V+Gaba.
Talipes equinovarus	7	6 V, 1 C+V+Clob.
Congenital dislocation of the hips	1	C 400.
Contractures of fingers (1 also had elbow contractures)	3	P 300(0–40)+Phenobarb 60(0–40). V 1500(0–40). V 1500(0–40).
Hernias	5 (2 bilateral, 1 unilateral inguinal, 2 unknown)	4 V, 1 C.
Diastasis recti	1	V 1200(0–40)
Skin		
Haemangiomata	4 (trunk, thigh, eyelid)	3 V, 1 V+P.
Brown naevus	1	V 2000(0–40)+Clob 20(8–40).
Glue ear	19 (18 grommets)	15 V, 1 V+Vig, 1 V+Clob, 1 V+C, 1 P.

V = valproate, C = carbamazepine, P = phenytoin, Vig = vigabatrin, Clob = clobazam, Phenobarb = phenobarbitone, Gaba = gabapentin.

history of ventilation, whereas the other case of subglottic stenosis may be the result of prolonged ventilation). No cases of cleft palate were seen. Ocular abnormalities were common. Myopia was present in 34% of those undergoing ophthalmic examination (16/46), astigmatism in 24% (11/46), and strabismus in 17% (8/46). Four further patients reported previous strabismus surgery, of whom two were normal on examination and two declined ophthalmic evaluation. Another patient had Brown syndrome (restriction of upward movement of the eye in the adducted position, sometimes associated with an anatomical abnormality such as shortening of the superior oblique tendon sheath). Dental abnormalities and delayed eruption were reported in six cases (10%).

#### FACIAL DYSMORPHOLOGY

Fig 1A shows a young child with the typical facial appearance of fetal valproate syndrome. With age, the nose in fetal valproate syndrome lengthens and the nasal tip becomes broader or flatter (fig 1B, C). Although the number of children exposed to carbamazepine or phenytoin alone in this study was small, we noted that the mouth tends to be wider and the eyelashes more prominent in this group than in the fetal valproate group. In the older child (more than 3 years old) with fetal carbamazepine syn-

drome, the nose becomes narrower than with the other two drugs, the columella grows to give an appearance of hypoplastic nasal alae, and the chin is small and angular (fig 2). Fetal phenytoin features in the older child include a longer nose with a prominent root and bulbous tip (fig 3). The facial features of fetal phenytoin and fetal carbamazepine become harder to recognise in the older child than fetal valproate syndrome.

#### DEVELOPMENT

Forty four children (77% of the study group) had developmental delay or learning difficulties. Of the 38 children of school age, 28 (74%) were either attending special school or receiving learning support at mainstream school. Many of those at special school had major behavioural difficulties with autistic features. Only 10 were coping in mainstream education without support, of whom three were in their first year at primary school. Forty one of 53 children over 2 years of age (77%) required speech therapy. In 37 cases for whom details were available, 17 had expressive speech delay alone, 19 had expressive and receptive delay, and one had receptive delay alone. Gross motor delay (defined as not sitting by 10 months, not walking by 18 months, or requiring physiotherapy (24 cases)) affected 32 (56%), with

16/41 not sitting by 10 months, 25/54 not walking by 15 months, 20/54 not walking by 18 months, and 4/51 not walking at 24 months. Twenty five (44%) children experienced coordination difficulties, manifesting as difficulty using cutlery over 5 years of age, difficulty riding a bike over 6 years, or requiring occupational therapy (13 cases).

#### BEHAVIOURAL PHENOTYPE

One or more aberrant behaviours (table 3) were reported in 46/57 children (81%). Seven had no behavioural problem (of whom two were infants). Only four patients had neither

developmental delay nor behavioural problems. Hyperactivity or concentration deficit or both were reported in 22/57 cases (39%), of whom four had a diagnosis of attention deficit and hyperactivity disorder and two were on methylphenidate. Four children had a diagnosis of autism, two of whom were exposed to sodium valproate alone, one to sodium valproate and phenytoin, and one to carbamazepine and diazepam (this last child also had attention deficit and hyperactivity disorder). Two further children had a diagnosis of Asperger's syndrome, one exposed to valproate alone, and one to valproate, phenytoin, and a



**Figure 1** Children exposed to valproate alone. (A) A boy aged 22 months. Note epicanthic folds, infraorbital grooves, long, shallow philtrum, and thin upper lip. (B) A girl aged 3 years 10 months, older sister of (A). Note medial deficiency of eyebrows, infraorbital grooves, short nose with anteverted nares, long, shallow philtrum, and thin upper lip. (C) A girl, aged 11 years 4 months. Note thin eyebrows, medial deficiency of eyebrows, flattened nasal tip, shallow philtrum, and thin upper lip.

benzodiazepine. In total, 9/57 (16%) had a formally diagnosed behavioural disorder.

#### RECURRENCE RISK

In the 33 families for whom we have adequate data (from personal clinical examination or from hospital records and clinical photographs), there were 54 affected and 17 unaffected children. Using Weinberg's "proband" method to allow for incomplete ascertainment, the ratio of affected to unaffected sibs is 21:17 or 1.2:1.<sup>22</sup> This is equivalent to a 55% recurrence risk.

#### Discussion

Many studies of fetal effects of maternal anticonvulsant therapy have been based on assessments of children at birth or in the first year of life.<sup>18 23 24</sup> Although there are good prospective data on the frequency of congenital malformations, the frequency of later medical problems, learning difficulties, and behavioural problems is much less robust and is based on small studies often investigating specific problems.<sup>8 10 25 26</sup> Case reports and some retrospective studies have suggested a wider spectrum of difficulties and we undertook this



**Figure 2** Children exposed to carbamazepine alone. (A) A girl aged 9 months. Note telecanthus, short nose with anteverted nares, and long, shallow philtrum. (B) A boy aged 4 years. Note medial deficiency of eyebrows, prominent columella with hypoplastic nasal alae, smooth philtrum, and thin upper lip. (C) The same girl as in (A) aged 6 years. Note medial deficiency of eyebrows, mild hypoplasia of the nasal alae, shallow philtrum, and thin upper lip.



Figure 3 Child exposed to phenytoin alone at different ages. (A) Aged 18 months, note telecanthus, short nose with flat nasal bridge and anteverted nares, long, shallow philtrum, and thin upper lip. (B) Same child aged 15 years 3 months. Note that the nose has grown to a more normal appearance. The nasal root is prominent. The philtrum remains shallow and the upper lip thin.

Table 3 Behavioural phenotype

Behavioural trait	No of children
Poor social interaction	30 (53%)
Poor communication skills	28 (49%)
Short attention span	26 (46%)
Insistence on routines	25 (44%)
Hand flapping	14 (25%)
Gaze avoidance	15 (26%)
Aggressive or violent	11 (19%)
No sense of danger	3 (5%)
Total patients	57

study to contribute to knowledge of the longer term consequences of intrauterine anticonvulsant exposure. It should be recognised that our study is retrospective and therefore does not define the incidence of the problems we discuss. It does, however, give a wider description of the long term effects which may provide a clinical foundation for future research into the reasons why some children exposed to anticonvulsants have disordered development while others do not.

#### OBSTETRIC FINDINGS

Although early studies suggested an association between phenytoin exposure and prenatal growth deficiency,<sup>10</sup> this has not been confirmed. Later studies suggested no increased frequency of prematurity or low birth weight in infants exposed to anticonvulsants in utero<sup>5,24</sup> and our findings confirm this. In our study, delivery by emergency caesarian section was associated with exposure to phenytoin. Previous studies have reported a caesarian section rate (emergency and elective) of around 30% following phenytoin use, comparable to that seen with carbamazepine.<sup>8,27</sup> The association seen in our study may be because of small numbers (five of nine pregnancies exposed to

phenytoin delivered by emergency caesarian section).

#### MALFORMATIONS AND MEDICAL PROBLEMS

As in previous reports,<sup>2,3,16,18,24,28</sup> there was a trend towards more severe malformations with exposure to valproate doses of 1000 mg or higher in the first trimester or polypharmacy or both. Cardiac septal defects occurred in three children exposed to at least two anticonvulsants in utero. However, the fact that several children had malformations and developmental delay following exposure to relatively low doses of anticonvulsant suggests that other factors including genetic predisposition may contribute to the risk to the fetus. The occurrence of seizures in pregnancy did not correlate with the rate of malformations, in contrast to the findings of other authors.<sup>23</sup>

Although many of the malformations seen were those expected in the fetal anticonvulsant syndromes, glue ear and joint laxity were unexpectedly common. Thirty two percent of the patients had glue ear requiring grommets compared with 5% in the general population,<sup>29</sup> suggesting that there may be a teratogenic effect of the anticonvulsants on the development of the middle ear. No specific malformations were seen, but Eustacian tube narrowing or dysfunction was not formally evaluated. Receptive language delay did not correlate with the occurrence of glue ear, so hearing difficulty was not the cause of the language delay.

Joint laxity was a frequent clinical finding, involving all sizes of joints and not restricted to a particular anticonvulsant. Inguinal hernia and congenital dislocation of the hip have been previously reported in children exposed to valproate, phenytoin, and carbamazepine in

utero.<sup>24</sup> In our study group, joint laxity was associated in some cases with chest asymmetry, genu valgum, pes planus, and diastasis recti suggesting that there may be a more general connective tissue disorder associated with anticonvulsant exposure. This may contribute to the frequent finding of "hypotonia" in affected infants. One patient, exposed to carbamazepine, had marked joint laxity, aortic dilatation, and mitral valve thickening as an infant. The aortic dilatation has resolved and the valve thickening has not required treatment, but the association of these cardiac findings with joint laxity in this context may be important for the assessment of future patients.

There have been few previous reports of ophthalmic abnormalities in the fetal anticonvulsant syndromes, although strabismus is often present in published photographs of patients.<sup>10-11</sup> In specific reports, optic nerve hypoplasia has been associated with exposure to phenytoin<sup>30</sup> and anophthalmos, microphthalmos, and optic disc coloboma with carbamazepine.<sup>31</sup> Myopia, astigmatism, and strabismus were particularly common in our patients, who were mainly exposed to sodium valproate. The ophthalmic findings will be described in detail elsewhere.

#### FACIAL DYSMORPHOLOGY

Published photographs of cases of fetal valproate, fetal carbamazepine, and fetal phenytoin syndromes appear to have some features in common, such as a smooth or shallow philtrum and thin upper lip.<sup>6-10-11</sup> This similarity was also evident in our patients who were exposed to monotherapy with these drugs (figs 1, 2, and 3), particularly in early childhood (less than 2 years of age). Similar features give rise to the facial gestalt of fetal alcohol syndrome, of which the characteristic facial findings are short palpebral fissures, smooth philtrum, and a thin upper lip.<sup>32</sup> Epicanthic folds, microcephaly, and hypoplastic nails are also seen,<sup>33</sup> which can occur in the fetal anticonvulsant syndromes. There may be a "fetal teratogen face" arising from exposure to substances which affect the central nervous system and which includes epicanthic folds, short palpebral fissures, smooth philtrum, and thin upper lip. These features were seen with similar frequency in children exposed to any of the anticonvulsants (table 4) in this study. Other

facial features may be associated with specific teratogens, for example, a high, broad forehead, infraorbital grooves, broad nasal root with short nose, anteverted nares, and long philtrum were seen more commonly in valproate exposure (table 4, fig 1A, B). Telecanthus was more prominent with carbamazepine and phenytoin exposure (fig 2A and 3A). With age, the nose in fetal valproate syndrome lengthens, and the tip flattens. The shallow philtrum, thin upper lip, and medial deficiency of the eyebrows persist (fig 1C). A characteristic nose including prominent columella and hypoplastic nasal alae was noted in older children exposed to carbamazepine (fig 2B, C) while the shallow philtrum and thin upper lip seen in infancy are retained. In fetal phenytoin syndrome, although a shallow philtrum, thin upper lip, short nose, flattened nasal bridge, and anteverted nares may be seen in infancy, the nose in the older child may appear of normal length with a prominent nasal root (fig 3A, B). Only the shallow philtrum and thin upper lip persist. Other authors have noted that infraorbital groove does not appear to be a feature of fetal phenytoin syndrome.<sup>9</sup>

#### DEVELOPMENT

Developmental delay has been documented previously in the fetal anticonvulsant syndromes, although the prevalence is uncertain, as the follow up periods in the large prospective studies have been too short to address this issue.<sup>24-34</sup> The high proportion of cases with developmental delay in our study (77%) is unlikely to be because of their age at assessment (6.48 years) alone. Eighty percent of our cases were exposed to sodium valproate and in a previous retrospective study,<sup>14</sup> 5/7 (71%) children exposed to sodium valproate alone in utero and 10/11 (91%) exposed to valproate and another anticonvulsant were developmentally delayed. Sodium valproate may be more toxic to the developing brain than some anticonvulsants,<sup>35</sup> but it should be noted that the methods of case ascertainment are likely to have biased the previous study<sup>14</sup> and ours in favour of developmentally delayed children. In another retrospective study of congenital malformations in fetal anticonvulsant syndromes, only three patients out of a cohort of 151 (1.9%) exposed to multiple anticonvulsants in utero were found to have developmental delay.<sup>23</sup> All three were dysmorphic and a further 11 (7.3%) had malformations that might be attributable to anticonvulsant exposure. In a second cohort of 172 patients exposed to less polypharmacy, 13 had malformations (7.6%) but the incidence of developmental delay was not recorded. In both cohorts, children were evaluated before 5 months of age, too early to obtain accurate information about the prevalence of developmental delay.

More reliable risk information should come from prospective studies. One early American prospective study, mostly of children exposed to phenytoin with or without barbiturates, showed an increased risk of developmental delay (7%) with phenytoin, although this

Table 4 Facial dysmorphic features

Feature	Exposed to valproate only (total 34)	Valproate+other anticonvulsant (total 12)	Anticonvulsant other than valproate (total 10)
Broad forehead	19 (56%)	5 (42%)	3 (30%)
High forehead	12 (35%)	2 (17%)	0
Medial deficiency of eyebrow	11 (32%)	3 (25%)	6 (60%)
Epicanthic folds	6 (18%)	1 (8%)	2 (20%)
Infraorbital grooves	20 (59%)	7 (58%)	2 (20%)
Narrow palpebral fissures	3 (9%)	4 (33%)	3 (30%)
Broad nasal root	23 (68%)	10 (83%)	5 (50%)
Short nose	12 (35%)	8 (67%)	2 (20%)
Anteverted nares	19 (56%)	8 (67%)	2 (20%)
Broad or flat nasal tip	20 (59%)	5 (42%)	6 (60%)
Long philtrum	17 (50%)	7 (58%)	3 (30%)
Smooth philtrum	23 (68%)	10 (83%)	7 (70%)
Thin upper lip	26 (76%)	11 (92%)	6 (60%)
Thick lower lip	9 (26%)	1 (8%)	3 (30%)
Downturned mouth	12 (35%)	2 (17%)	1 (10%)

Table 5 Recent prospective studies of children exposed to anticonvulsants in utero

Reference	Anticonvulsant exposure	Developmental delay	Dysmorphic features	Major malformations
11	Carbamazepine alone	5/25 (20%)	4/35 (11%)	3/35 (9%)
	Carbamazepine and another drug	8/35 (23%)	18/48 (38%)	5/48 (11%)
27	All anticonvulsants (40/60 phenytoin)	1/60 (2%)*		
18	All anticonvulsants			21/303 (7%)
24	All anticonvulsants		42/315 (13%)	27/318 (8.5%)†
8	Phenytoin alone	7/34 (20%)		2/34 (6%)
	Carbamazepine alone	3/36 (8%)		2/36 (5%)
25	Not specified	9/51 (18%)		
26	Carbamazepine alone	5/41 (12%)	6/47 (11%)	5/47 (11%)
12	Carbamazepine alone		26/33 (79%)	2/35 (5.7%)
	Phenytoin alone		26/33 (79%)	3/34 (8.8%)
34	All anticonvulsants			9%
	Primidone			14.3%
	Valproate			11.1%
	Phenytoin			9.1%
	Carbamazepine			5.7%
	Phenobarbitone			5.1%

\*One patient with Down syndrome excluded.

†Two patients diagnosed with Smith-Lemli-Opitz syndrome excluded.

conclusion was controversial.<sup>36–38</sup> In a Finnish study, the overall frequency of developmental delay (3.1%) was similar to that in the general population,<sup>39</sup> although specific cognitive dysfunctions were seen at high frequency (23% compared with 7%).<sup>40</sup> Maternal anticonvulsant doses and drug levels were relatively low in this population. The findings in a number of recent prospective studies are summarised in table 5. These show a risk of major malformation lying between 5 and 11%, and a risk of developmental delay for carbamazepine alone of between 8 and 20%, and for phenytoin of around 20%. Our patient group included four patients exposed to each of carbamazepine and phenytoin monotherapy, all of whom had developmental or behavioural problems and other features.

There has been no prospective study of developmental delay following maternal sodium valproate use, nor following use of the newer anticonvulsants. It is recognised that valproate may increase the risk of malformations and developmental delay when given with carbamazepine or phenytoin, as it is thought to inhibit epoxide hydrolase, an enzyme involved in the metabolism and detoxification of these drugs.<sup>28–41</sup> The findings of our study (in which 26/34 children exposed to valproate monotherapy had learning difficulties, and 29/34 had behavioural problems) and those of other studies and case reports suggest that valproate causes developmental delay independently.<sup>9–14–15–35</sup>

The profile of developmental delay in our patients shows an emphasis on speech delay and communication disorder. This supports the findings of Christianson *et al*,<sup>42</sup> who reported four cases with fetal valproate syndrome, of whom two had marked expressive speech delay, one had autism with greater delay in speech and personal/social development than other areas, and the fourth had diminished verbal abilities although overall intelligence was normal. Awareness of this developmental profile will enable prompt detection of language delay and early start of therapy, where appropriate. Further prospective studies, including suitable controls, are needed to estimate the true risk of developmental delay and

behaviour disorder associated with anticonvulsant exposure, and its relationship to drug dosage.

#### BEHAVIOURAL PHENOTYPE

Behavioural traits were mostly obtained from a standardised questionnaire developed for this study rather than clinical assessment, so there may be over-reporting of difficult behaviours. Despite this, the high frequency of autistic type behaviours (81%) and hyperactivity (39%) was striking, and in 10 (17%) a formal diagnosis of behavioural disorder had been made. Even allowing for ascertainment bias in our study group (parents of behaviourally disturbed children may be more likely to contact a parents' support group for help), these findings confirm the association of fetal valproate syndrome with autism previously reported in two cases.<sup>42–43</sup> The high prevalence of valproate exposure, either as monotherapy (60%) or with another anticonvulsant (21%), in our patient group may be the result of preferential prescribing of this drug in the UK, or because valproate is more likely to cause behavioural problems in the offspring. However, behavioural problems were also seen with carbamazepine and phenytoin exposure, suggesting that the association is not restricted to one anticonvulsant.

There is currently a reluctance among health professionals to accept behavioural disorder as attributable to fetal anticonvulsant exposure. Wider knowledge of this association would relieve a great deal of anxiety among parents of affected children, who are sometimes told that either their child must have more than one disorder, or that they have inadequate parenting skills.

#### RECURRENCE RISK

The recurrence risk in our families was high at 55%. In previous prospective studies, not more than 22% of children with prenatal anticonvulsant exposure have experienced any adverse outcome, so that the high risk of a second affected child in our study is suggestive of a genetic predisposition. The possibility that ascertainment through a parent support group may have biased our families towards severe cases with a high recurrence risk cannot be



excluded. In the counselling and management of women taking anticonvulsants who are planning a family, it is important to note that factors such as multiple therapy and higher dosage regimens may increase the risk of adverse fetal outcome.

### Conclusions

This cohort study of children with the fetal anticonvulsant syndromes has identified a number of features previously unrecognised or under-reported in these syndromes. These include glue ear, connective tissue problems (including joint laxity), ocular and refractive disorders, laryngeal anomalies, and autism or autistic spectrum behavioural problems. Developmental delay, particularly speech delay, was common and did not correlate with glue ear. The recurrence risk after a first affected child is high at 55%, which may reflect an underlying genetic predisposition.

We would like to thank Linda Todd for her help, Linda Hamilton and all the members of the National Fetal Anticonvulsant Syndrome Association who were involved in organising the clinic in Exeter, and the children and their families who participated. We are grateful to Karen Luyt and Gwyneth Garner for their help at the Exeter clinic. This work was supported by the National FACS Association, the Rescue Foundation, Aberdeen Royal Hospitals NHS Trust Endowments Fund and the Aberdeen Special Nursery Trust.

- 1 Eller DP, Patterson CA, Webb GW. Maternal and fetal implications of anticonvulsive therapy during pregnancy. *Obstet Gynecol Clin North Am* 1997;24:523-35.
- 2 Delgado-Escueta AV, Janz D. Consensus guidelines: preconception counseling, management, and care of the pregnant woman with epilepsy. *Neurology* 1992;42(suppl 5):149-60.
- 3 ACOG educational bulletin. Seizure disorders in pregnancy. *Int J Gynaecol Obstet* 1997;56:279-86.
- 4 Kelly TE. Teratogenicity of anticonvulsant drugs. *Am J Med Genet* 1984;19:413-34.
- 5 Meadow R. Anticonvulsants in pregnancy. *Arch Dis Child* 1991;66:62-5.
- 6 Clayton-Smith J, Donnai D. Fetal valproate syndrome. *J Med Genet* 1995;32:724-7.
- 7 Jick SS, Terris BZ. Anticonvulsants and congenital malformations. *Pharmacotherapy* 1997;17:561-4.
- 8 Scolnik D, Nulman I, Rovet J, et al. Neurodevelopment of children exposed in utero to phenytoin and carbamazepine monotherapy. *JAMA* 1994;271:767-70.
- 9 DiLiberti JH, Farndon PA, Dennis NR, Curry CJR. The fetal valproate syndrome. *Am J Med Genet* 1984;19:473-81.
- 10 Hanson JW, Smith DW. The fetal hydantoin syndrome. *J Pediatr* 1975;87:285-90.
- 11 Jones KLJ, Lacro RV, Johnson KA, Adams J. Pattern of malformations in the children of women treated with carbamazepine during pregnancy. *N Engl J Med* 1989;320:1661-6.
- 12 Nulman I, Scolnik D, Chitayat D, Farkas LD, Koren G. Findings in children exposed in utero to phenytoin and carbamazepine monotherapy: independent effects of epilepsy and medications. *Am J Med Genet* 1997;68:18-24.
- 13 Vestermark V, Vestermark S. Teratogenic effect of carbamazepine. *Arch Dis Child* 1991;66:641-2.
- 14 Ardinger HH, Atkin JF, Blackston D, et al. Verification of the fetal valproate syndrome phenotype. *Am J Med Genet* 1988;29:171-85.
- 15 Winter RM, Donnai D, Burn J, Tucker SM. Fetal valproate syndrome: is there a recognisable phenotype? *J Med Genet* 1987;24:692-5.
- 16 Thisted E, Ebbesen F. Malformations, withdrawal manifestations, and hypoglycaemia after exposure to valproate in utero. *Arch Dis Child* 1993;69:288-91.
- 17 Omtzigt JGC, Los FJ, Hagenaars AM, Stewart PA, Sachs ES, Lindhout D. Prenatal diagnosis of spina bifida aperta after first-trimester valproate exposure. *Prenat Diagn* 1992;12:893-7.
- 18 Omtzigt JGC, Los FJ, Grobbee DE, et al. The risk of spina bifida aperta after first-trimester exposure to valproate in a prenatal cohort. *Neurology* 1992;42(suppl 5):119-25.
- 19 Rosa FW. Spina bifida in infants of women treated with carbamazepine during pregnancy. *N Engl J Med* 1991;324:674-7.
- 20 Beighton P, Solomon L, Soskolne CL. Articular mobility in an African population. *Ann Rheum Dis* 1973;32:413-18.
- 21 Dean JCS, Moore SJ, Osborne A, Howe J, Turnpenny PD. Fetal anticonvulsant syndrome and mutation in the maternal MTHFR gene. *Clin Genet* 1999;56:216-20.
- 22 Emery AEH. *Methodology in medical genetics*. Edinburgh: Churchill Livingstone, 1986:51.
- 23 Lindhout D, Meinardi H, Meijer JWA, Nau H. Antiepileptic drugs and teratogenesis in two consecutive cohorts. *Neurology* 1992;42(suppl 5):94-110.
- 24 Battino D, Bimelli S, Caccamo ML, et al. Malformations in offspring of 305 epileptic women: a prospective study. *Acta Neurol Scand* 1992;85:204-7.
- 25 Leonard G, Prito A, Seni MH, et al. Cognitive performance in school-age offspring of epileptic mothers exposed to anticonvulsant therapy (AED) during pregnancy. *Am J Hum Genet* 1995;57(suppl):A136.
- 26 Ornoy A, Cohen E. Outcome of children born to epileptic mothers treated with carbamazepine during pregnancy. *Arch Dis Child* 1996;75:517-20.
- 27 D'Souza SW, Robertson IG, Donnai D, Mawer G. Fetal phenytoin exposure, hypoplastic nails and jitteriness. *Arch Dis Child* 1990;65:320-4.
- 28 Lindhout D, Hoppener RJEA, Meinardi H. Teratogenicity of antiepileptic drug combinations with special emphasis on epoxidation (of carbamazepine). *Epilepsia* 1984;25:77-83.
- 29 Waterston T, Platt MW, Helms P. *Paediatrics, understanding child health*. Oxford: Oxford University Press, 1997:227.
- 30 Hoyt CS, Billson FA. Maternal anticonvulsants and optic nerve hypoplasia. *Br J Ophthalmol* 1978;62:3-6.
- 31 Sutcliffe AG, Jones RB, Woodruff G. Eye malformations associated with treatment with carbamazepine during pregnancy. *Ophthalmol* 1998;19:59-62.
- 32 Astley SJ, Clarren SK. A case definition and photographic screening tool for the facial phenotype of fetal alcohol syndrome. *J Pediatr* 1996;129:33-41.
- 33 Autti-Ramo I, Gaily E, Granstrom ML. Dysmorphic features in offspring of alcoholic mothers. *Arch Dis Child* 1992;67:712-16.
- 34 Kaneko S, Battino D, Andermann E, et al. Congenital malformations due to epileptic drugs. *Epilepsy Res* 1999;33:145-58.
- 35 Koch S, Jager-Roman E, Losche G, Nau H, Rating D, Helge H. Antiepileptic drug treatment in pregnancy: drug side effects in the neonate and neurological outcome. *Acta Paediatr Scand* 1996;85:739-46.
- 36 Hanson JW, Myriantopoulos NC, Harvey MAS, Smith DW. Risks to the offspring of women treated with hydantoin anticonvulsants, with emphasis on the fetal hydantoin syndrome. *J Pediatr* 1976;89:662-8.
- 37 Shapiro S, Slone D, Hartz SC, et al. Anticonvulsants and parental epilepsy in the development of birth defects. *Lancet* 1976;i:272-5.
- 38 Nelson KB, Ellenberg JH. Maternal seizure disorder, outcome of pregnancy, and neurologic abnormalities in the children. *Neurology* 1982;32:1247-54.
- 39 Gaily E, Kantola-Sorsa E, Granstrom ML. Intelligence of children of epileptic mothers. *J Pediatr* 1988;113:677-84.
- 40 Gaily E, Kantola-Sorsa E, Granstrom ML. Specific cognitive dysfunction in children with epileptic mothers. *Dev Med Child Neurol* 1990;32:403-14.
- 41 Bennett GD, Lau F, Calvin JA, Finnell RH. Phenytoin-induced teratogenesis: a molecular basis for the observed developmental delay during neurulation. *Epilepsia* 1997;38:415-23.
- 42 Christianson AL, Chesler N, Kromberg JGR. Fetal valproate syndrome: clinical and neuro-developmental features in two sibling pairs. *Dev Med Child Neurol* 1994;36:361-9.
- 43 Williams PG, Hersh JH. A male with fetal valproate syndrome and autism. *Dev Med Child Neurol* 1997;39:632-4.