Characteristics of fetal anticonvulsant syndrome associated autistic disorder

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The aim of this study was to evaluate the clinical features and frequency of autistic disorder or Asperger syndrome (AS; according to Diagnostic and Statistical Manual of Mental Disorders, 4th edition [DSM-IV] criteria) in children exposed to anticonvulsant medication in utero. During a 20-year study period, 626 children were born in Aberdeen to mothers taking antiepileptic drugs (AEDs). The study examined long-term effects of prenatal exposure to AEDs in 260 children (122 males, 138 females). Of these, 26 (16 males) were reported by parents to have social or behavioural difficulties. Eleven children (6 males, 5 females) fulfilled the DSM-IV criteria for autistic disorder and one (female) fulfilled the DSM-IV criteria for AS. These children comprised 4.6% of the exposed children studied, and 1.9% of all exposed children born during the study period. Mean age of these children at diagnosis was 5 years 4 months (SD 2y 11mo) and 9 years 10 months (SD 3y 10mo) at the time of this study. Other children from the group of 26 had difficulties in areas of speech and language development and social communication but did not meet the criteria for an autism spectrum disorder (ASD). Sodium valproate was the drug most commonly associated with autistic disorder, five of 56 (8.9%) of the study children exposed to sodium valproate alone had either autistic disorder or AS. It was concluded that prenatal exposure to anticonvulsant medication is a risk factor for the development of an ASD. Fetal anticonvulsant syndrome associated autistic disorder is characterized by an even sex ratio, absence of regression or skill loss, and language delay in the absence of global delay.

See end of paper for list of abbreviations.

Fetal anticonvulsant syndromes (FACS) are a group of disorders in which malformations, developmental disorders, and other medical problems occur in association with a characteristic facial appearance, in children with prenatal exposure to antiepileptic drugs (AEDs; Moore et al. 2000). The risk of malformation, associated with commonly used AEDs such as carbamazepine, sodium valproate, and phenytoin, is around 6 to 9% (Kaneko et al. 1999), but evidence for the risk of neurodevelopmental effects is inconclusive (Dean et al. 2002). Sodium valproate exposure was associated with learning and developmental difficulties in a recent survey (Adab et al. 2001) and was implicated in most of the 15 published reports of FACS-associated autism (Christianson et al. 1994, Williams and Hersh 1997, Moore et al. 2000, Bescoby-Chambers et al. 2001, Williams et al. 2001). Around 6.1 per 1000 pregnancies occur in women with epilepsy, making this issue of considerable clinical importance (Fairgrieve et al. 2000). During a population-based study in the Grampian region of Scotland, UK of children whose mothers took AEDs in pregnancy (Dean et al. 2002), a number of parents reported that their children had symptoms consistent with an autism spectrum disorder (ASD).

ASDs are characterized by pervasive impairments in several areas of a child's development, such as reciprocal social interaction skills, communication skills, and the presence of stereotyped behaviour, interests, and activities. Manifestations of ASDs vary depending on developmental level and chronological age, but the impairment in reciprocal social interaction is gross and sustained. The diagnosis is based on criteria of the *Diagnostic and Statistical Manual of Mental Disorders,* 4th edition (DSM-IV; American Psychiatric Association 1994) or the *International Statistical Classification of Diseases and Related Health Problems* (10th revision; World Health Organization 1992). These provide definitions of autistic disorder, Asperger syndrome (AS), and Pervasive Developmental Disorder Not Otherwise Specified.

In this study we carried out a detailed review of the clinical findings in AED-exposed children whose parents had reported compatible symptoms, and then classified these according to the DSM-IV diagnostic criteria in order to determine the prevalence of ASD in this group. We also investigated whether the pattern of features made them distinct from idiopathic autism, and whether any correlation with specific AEDs could be identified.

Method

In a population-based study of the adverse fetal effects of prenatal exposure to AEDs in the Grampian region of Scotland, mothers who were prescribed AEDs at any time during a pregnancy were identified from Aberdeen Maternity Hospital records. Details of this study have been described elsewhere (Dean et al. 2002). In Grampian, all high-risk pregnancies (including those in women with epilepsy) are referred to the Aberdeen Maternity Hospital for delivery. Between 1st April 1981 and 31st March 2001, 626 AED-exposed pregnancies were identified from a total birth cohort of 125728 (5 per 1000 live births, 95% confidence interval [CI] 4.6 to 5.4 per 1000 live births). These children were born to 389 mothers, who were invited to participate in the study. Of these, 159 mothers with a total of 260 children agreed to participate and were recruited. At a structured interview undertaken by a trained research nurse, maternal medical history, family

history, and AED use in each pregnancy were recorded. AED dosage was verified from case records where possible. Malformations and medical histories for the children were documented and social, behavioural, and developmental difficulties were identified using a set of screening questions developed for a previous study (Moore et al. 2000). Parents reported behavioural or social difficulties in 26 AED-exposed children.

Medical records of these 26 children were reviewed by a child psychiatrist (ADR). In 14 of them, features were recorded in the notes or in correspondence suggesting a diagnosis of an ASD. Clinical assessment and diagnosis of these 14 children had been undertaken independently of the study by specialist clinical services (child psychiatry, child psychology, or child development). Their records were accessed and reviewed. Salient clinical and behavioural symptoms and findings recorded by the various professionals were analyzed by a child

psychiatrist and the features were classified according to DSM-IV criteria for Pervasive Developmental Disorders.

Parents gave informed consent to participate in this study, on their own behalf and on behalf of their children. Older children with sufficient understanding gave informed consent for themselves. The study was approved by the Joint Research Ethics Committee of NHS Grampian and the University of Aberdeen.

Results

Of the 14 children whose notes were reviewed in detail, an ASD had been diagnosed in 12. Eleven children (six males, five females) fulfilled the DSM-IV criteria for an autistic disorder while one child (female) met the criteria for AS (Table I). All children who fulfilled the criteria for either autistic disorder or AS had been assessed by professionals experienced in

Table I: Features of children fulfilling DSM-IV (American Psychological Association 1994) criteria for autistic disorders

Sex	F	M	F	F	M	F	M	F	M	M	M	Fa
IQ scores	N/A	79	100	57	91	83	56	N/A	98	62	67	82
DSM-IV criteria for autistic disorder:												
A. A total of six (or more) items from (1), (2), and (3), with at least two from (1), and one each from (2) and (3):												
1. Qualitative impairment in social interaction, as manifested by at least two of the following:												
1a A marked impairment in the use of multiple non-verbal behaviors such as eye-to-eye gaze, facial expression, body postures, and gestures to regulate social interaction	+	+	+	+	+	+	–	+	+	+	+	+
1b Failure to develop peer relationships appropriate to developmental level	+	+	+	+	+	+	+	+	+	+	+	+
1c A lack of spontaneous seeking to share enjoyment, interests, or achievements with other people (e.g. by a lack of showing, bringing, or pointing out objects of interest)	+	+	+	+	+	+	+	+	+	+	+	+
1d Lack of social or emotional reciprocity	+	+	+	+	+	+	+	+	+	+	+	+
2. Qualitative impairments in communication as manifested by at least one of the following:												
2a Delay in, or total lack of, the development of spoken language (not accompanied by an attempt to compensate through alternative modes of communication such as gesture or mime)	+	+	+	+	+	+	+	+	+	+	+	–
2b In individuals with adequate speech, marked impairment in the ability to initiate or sustain a conversation with others (not applicable as the child who did not have delayed speech had Asperger syndrome)												
2c Stereotyped and repetitive use of language or idiosyncratic language	+	–	–	+	+	–	+	+	–	+	–	–
2d Lack of varied, spontaneous make-believe play or social imitative play appropriate to developmental level	+	+	+	+	+	+	+	+	+	+	+	+
3. Restricted repetitive and stereotyped patterns of behavior, interests, and activities, as manifested by at least one of the following:												
3a Encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus	–	+	+	–	+	+	+	+	+	+	+	+
3b Apparently inflexible adherence to specific, nonfunctional routines or rituals	–	–	+	+	+	–	+	+	+	+	–	–
3c Stereotyped and repetitive motor mannerisms (e.g. hand or finger flapping or twisting, or complex whole-body movements)	+	–	–	+	+	+	+	+	+	+	+	–
3d Persistent preoccupation with parts of objects	–	+	+	–	–	–	–	–	–	–	+	–
B. Delays or abnormal functioning in at least one of the following areas, with onset prior to age 3 years: (1) social interaction, (2) language as used in social communication, or (3) symbolic or imaginative play	+	+	+	+	+	+	+	+	+	+	+	+
C. The disturbance is not better accounted for by Rett's disorder or childhood disintegrative disorder	+	+	+	+	+	+	+	+	+	+	+	+

aChild with Asperger syndrome. +, present; –, absent; N/A, not available.

diagnosing these conditions. Formal IQ testing had been carried out in 10 children whose mean IQ was 78 (SD 16). Two children had not had formal IQ testing but assessment using the Reynell Developmental Language Scales (Reynell and Huntley 1985) had shown substantial language delay. In one child other aspects of development were normal, while in the other generalized developmental delay was evident. All children fulfilled the diagnostic criteria according to DSM-IV, in that all children fulfilled more than six of the features, including more than two from section 1 and at least one each from sections 2 and 3 (see Table I). The features included difficulties in reciprocal social communication, delay in language development, and restricted and repetitive interests and activities. Eleven children showed language delay and fulfilled the criteria for autistic disorder, while the female child with AS had no language delay but received speech therapy for qualitative difficulties in speech and language development. There were two female sibling pairs: in one pair both had autistic disorder, while in the other, one child had autistic disorder and the other AS. Table II shows the other findings in these children with FACS-associated autistic disorder. The children were aged 5 years 11 months (SD 2y 11mo) at the time of diagnosis by their health care professionals, 6 years 7 months (SD 4y 1mo) at the time of the parental screening questionnaire, and 9 years 10 months (SD 3y 10mo) at the time of the case-note review.

Prevalence of an ASD in the 260 exposed study children, was 4.6% (95% CI 2.0 to 7.2). If no case occurred in any of the exposed children born during the study period, who were non-participants, the minimum prevalence estimate for the whole cohort would be 1.9% (12 of 626, 95% CI 0.8 to 3.0).

In the 12 children with an ASD, the male to female ratio was 1:1 (six males and five females had autistic disorder and one female had AS). All were exposed to either sodium valproate or carbamazepine. No child among the 82 participants was exposed to other AEDs.

In children exposed to sodium valproate alone, the prevalence of ASD was five of 56 (8.9%, 95% CI 1.3 to 16.5) while two of 80 (2.5%, 95% CI 0 to 6) exposed to carbamazepine alone were affected. Among children exposed to sodium valproate alone or in combination with other AEDs, nine of 77 (11.7%, 95% CI 4.4 to 19) had an ASD, while among those exposed to carbamazepine alone or in combination, five of 110 (4.5%, 95% CI 0.5 to 8.5) were affected. The frequency rates of affected children have been compared with the population prevalence of autistic disorder described by Chakrabarti and Fombonne in 2001, to calculate relative risks (Fig. 1).

The children also showed major and minor malformations, and three children had delayed motor milestones (see Table II). The mothers took AEDs for epilepsy, except one who received carbamazepine for bipolar affective disorder; one parent had a learning disability.* No mother or child had a diagnosis of tuberous sclerosis or other genetic disorder known to be associated with autism.

Discussion

Using the DSM-IV clinical criteria to define autistic disorder, AS, and pervasive developmental disorder not otherwise specified, a recent population-based survey in the UK found prevalences of 0.17%, 0.08%, and 0.36% respectively (Chakrabarti and Fombonne 2001). The combined prevalence of an ASD (autistic disorder and AS) was, therefore, 0.25% (95% CI 0.17 to 0.33). Using the same diagnostic criteria we found the prevalence of autistic disorder or AS in children with prenatal exposure to AEDs to be 8 to 18 times higher at between 1.9 (95% CI 0.8 to 3.0) and 4.6% (95% CI 2.0 to 7.2). Ascertainment of pregnancies exposed to AEDs in Grampian during the 20-year study period is probably virtually complete, as the incidence of 5 per 1000 live births is similar to the 6.1 per 1000 pregnancies observed in a previous study which

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*US usage: mental retardation.

Table II: Other clinical features of children with fetal anticonvulsant syndrome associated autistic disorder

Drug exposure	Sodium valproate alone	Carbamazepine alone	Sodium valproate alone and in combination	Carbamazepine alone and in combination	Total numbers
Numbers affected (total exposed)	5 (56)	2 (80)	9 (77)	5 (110)	12 (292)
Male:Female ratio	2:3	2:0	3:6	4:1	6:6
Head circumference >50th centile	4	2	6	5	9
Major malformations	1	1	3	3	5
Types of malformations	Accessory nipple, TEV, spina bifida occulta, pyloric stenosis, flexion contracture	Inguinal hernia, cleft uvula, nail hypoplasia	TEV, myopia, strabismus, joint laxity, hypospadias	Hernia, astigmatism cleft uvula, joint laxity, hypospadias strabismus	
Developmental delay					
Speech delay	3	2	5	4	11
Motor delay	0	0	1	0	1
Speech and motor delay	2	0	3	1	3
Neonatal withdrawal symptoms[a]	1	0	3	1	3
Family history of learning disability					
In parent	1	0	1	0	1
≥2nd degree relative	1	1	2	2	3

Developmental delay was defined as follows: speech delay, no words by 21 months; motor delay, not sitting unsupported by 10 months, not walking by 18 months. [a]Neonatal withdrawal symptoms: transient jitteriness, hypoglycemia, or abnormal tone in neonatal period. TEV, talipes equino varus.

included miscarriages, terminations, and stillbirths (Fairgrieve et al. 2000). Unfortunately, the prevalence of an ASD in the children who did not participate cannot be determined as some could not be traced. However, there is no a priori reason to suspect an excess of affected cases in that group. The figure of 1.9% is, therefore, a minimum estimate for the prevalence of an ASD in this group of children exposed to AEDs before birth, and the difference from the prevalence in the background population is statistically significant, in that 95% CIs do not overlap. In the study group, the children with autistic disorder and AS were mostly exposed to sodium valproate, although two were exposed to carbamazepine alone, and some to sodium valproate and carbamazepine in combination. In the group exposed to sodium valproate alone, 8.9% fulfilled the DSM-IV criteria for autistic disorder or AS, while in the carbamazepine group, only 2.5% were affected, although this difference is not statistically significant (95% CIs overlap) due to small numbers, particularly in the carbamazepine group. Children who develop ASDs after exposure to anticonvulsant medication show a distinct pattern of clinical features. Of the 12 children who had an ASD, 11 had significant speech delay but only two from this group had global delay including delay in motor milestones and significant learning difficulties. Mild motor delay was a feature in the child diagnosed with AS. The mean measured IQ of the group was below the population average, but was within the normal range at 78 (DSM-IV). Substantial cognitive impairment was, therefore, not a feature of this group. All the children were characterized by the absence of regression or loss of skills, which in the general population is seen in up to 20% of individuals with autism (Fombonne 1999).

Whereas in the general population ASDs are four times more common in males than in females (Fombonne 2001), males and females were equally frequently affected in the AED-exposed group. This relative excess of females derives from the group exposed to sodium valproate, suggesting that sodium valproate exposure may carry a particular risk for females. The reasons for this are not clear. It is possible that it could result from an effect of sodium valproate on the molecular mechanisms of gene imprinting, as it has recently been shown that valproate binds to and inhibits the activity of histone deacetylase proteins which are important in the DNA methylation-dependent control of gene expression (Gottlicher et al. 2001,

Phiel et al. 2001). DNA methylation is the mechanism of imprinting, and studies in Turner syndrome have suggested that an imprinted gene on the X chromosome may be involved in developmental pathways which affect social cognition and, therefore, the risk of ASDs (Skuse et al. 1997, Skuse 2000). This model does not fully explain the increased frequency of autism in the AED-exposed group generally, but it may provide a possible explanation for the even sex ratio in the sodium-valproate exposed children with ASDs. Further research is needed to explore these issues and determine what role, if any, altered imprinting plays in FACS-associated autistic disorder.

Communication disorders in children exposed to AEDs

A communication disorder, particularly affecting language, was common in our study population (Dean et al. 2002), with delay in the acquisition of speech and language skills being a particular feature in several of the children without autism. Overall, speech delay occurred in 12 of 41 (29.27%) children over 21 months of age who had been exposed to sodium valproate alone, 12 of 63 (19.04%) exposed to carbamazepine alone, and 12 of 41 (29.27%) exposed to polytherapy. A developmental disorder appears to have been common in children exposed to sodium valproate in utero in a retrospective questionnaire-based study undertaken elsewhere, in which 30% had additional educational needs (Adab et al. 2001). In another study, 23% of otherwise apparently healthy children exposed mainly to carbamazepine, phenytoin, and phenobarbitone in utero were shown to have impaired auditory phonemic skills on detailed psychometric testing (Gaily et al. 1990, Samren et al. 1997). This suggests that there may be a spectrum of language and communication disorders occurring in children exposed to AEDs such as sodium valproate, carbamazepine, and perhaps phenytoin and phenobarbitone.

Case reports

There have been 15 previous case reports of autistic disorder in children with FACS (Christianson et al. 1994, Williams and Hersh 1997, Kaneko et al. 1999, Moore et al. 2000, Bescoby-Chambers et al. 2001, Williams et al. 2001, Dean et al. 2002). The majority were exposed to sodium valproate alone, but one child was exposed to carbamazepine alone, three to sodium valproate and carbamezepine, and two to sodium valproate and phenytoin. This is in keeping with our study, which suggests that, while sodium valproate is the drug most commonly associated with autism, carbamazepine may also contribute. We did not find any association with phenytoin monotherapy, but only 25 children in our study population were exposed only to this drug, and so this could be due to the small sample size.

It is also noteworthy that whereas our population-based study has shown a much higher frequency in females than expected, in 12 of the 13 case reports where sex is recorded, the children are male. Males are overrepresented in clinics even more than the figures suggest they should be because their behaviour tends to be more troublesome (more aggressive, hyperactive, etc.). Therefore, males may be more likely to be identified in clinics and written up as case studies. Our methodology involving population-based ascertainment through maternity records should have avoided biases affecting the diagnosis in the children. A possible confounding factor is that there were two sibling pairs among the females in our study. Although there is no estimate of the risk of recurrence to
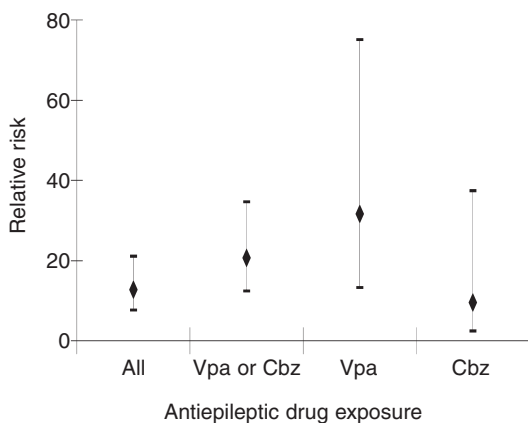

Figure 1: *Relative risk of autism spectrum disorder. Vpa, sodium valproate; Cbz carbamazepine.*

subsequent female children when the first female child has an ASD, recurrence rates for siblings have been variously calculated as ranging from 4.5 to 14.5% (Ritvo et al. 1989, Veenstra-Vanderweele et al. 2003). A genetic factor could, therefore, have contributed to the higher number of females in our study. It also remains possible that our population-based study has shown an excess of females by chance.

AEDs, especially sodium valproate, and to a lesser extent carbamazepine, are strongly implicated in increasing the risk of ASDs in children exposed in utero. Families and clinicians involved in the use of AEDs during pregnancy need to be aware of the association, and pregnancy counselling needs to be part of the management plan. Epilepsy and bipolar affective disorder remain difficult illnesses to treat and these findings add to the complex factors that need to be considered while formulating a treatment plan that is in the best interests of the patient and their family.

We have identified a likely cause of autism, and proposed a possible contributing mechanism. Exploration of the genetic and molecular mechanisms may also help to determine the neurodevelopmental origins of idiopathic autism.

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List of abbreviations

AEDs	Antiepileptic drugs
AS	Asperger syndrome
ASD	Autistic spectrum disorder
FACS	Fetal anticonvulsant syndromes