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Developing diagnostic criteria for the fetal anticonvulsant syndromes

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The prevalence of congenital malformations and cognitive disorders in children whose mothers took antiepileptic drugs in pregnancy is increased, compared with the background rate. Not all such cases are due to teratogenic effects of the mother's treatment. Certain problems, including neonatal withdrawal symptons, some malformations, characteristics facial features and a typical developmental and behavioural pattern may be indicators of a probable teratogenic event. We describe a set of diagnostic criteria which may assist in defining which children are likely to have a fetal anticonvulsant syndrome. This may help future research to identify risk factors which predispose to an adverse fetal outcome.

Key words: antiepileptic drugs; malformation; neurodevelopment; diagnosis.

Between 6 and 9 per cent of children exposed to antiepileptic (or anticonvulsant) drugs in utero are born with congenital malformations[1,2]. A further proportion have learning difficulties or behaviour problems[3]. Epilepsy is common, affecting about five out of 1000 mothers, therefore a large number of children are at risk. Any congenital malformations or cognitive disorders arising in these circumstances may be attributed to antiepileptic drug exposure, yet this attribution is likely to be incorrect some of the time. Certain malformation patterns are associated with particular drugs, such as neural tube defects with sodium valproate and carbamazepine, fingernail hypoplasia with carbamazepine and phenytoin, congenital heart disease with all three, and each syndrome has a characteristic face[4–6]. The diagnosis of a fetal anticonvulsant syndrome may be straightforward when a recognizable pattern of anomalies is seen, but it is not clear how many anomalies must be present to constitute one of the syndromes. In addition, it may be possible for exposure to antiepileptic drugs to cause a characteristic face, but a child's microcephaly, for example, may have some other cause. A distinction could be drawn between fetal anticonvulsant effects and a fetal anticonvulsant syndrome. To try to address these problems, we developed draft diagnostic criteria based on the model of the Marfan syndrome clinical diagnostic nosology[7]. This nosology was devised to help overcome the lack of a reliable diagnostic test in that disorder. Clinical signs in different body systems are assessed, and a scoring system is applied based on major and minor features. In a similar way, we considered the assessment of a child potentially affected by an antiepileptic drug through six clinical problem areas (Table 1). Firstly, evidence of neonatal withdrawal should be considered including jitteriness, feeding disorder, hypoglycemia, hypotonia, and seizures. Secondly, the characteristic facial appearance should be sought. This varies with age and with antiepileptic drug, and although lists of features can be devised, it is the overall gestalt which is important. Thirdly, the presence of typical malformations should be noted. These could be considered major if they are characteristic of the antiepileptic drug in question (e.g. neural tube defect for valproate or carbamazepine) or minor if they are less typical (e.g. renal malformation), or less objective (e.g. mild nail hypoplasia). Fourthly, the occurrence of certain medical problems in later child-

Table 1: Fetal anticonvulsant syndrome assessment.

Clinical problem area	Typical features
Neonatal withdrawal	Jittery, hypotonia, seizures, apnoeic episodes, hypoglycemia, feeding disorder
Characteristic facial appearance	Telecanthus, epicanthic folds, infraorbital groove, convergent squint, broad or flat nasal bridge, anteverted nares, broad or flat nasal tip in older children, shallow or smooth philtrum, thin upper lip, micrognathis, broad or tall forehead, metopic ridging, low set posteriorly rotated ears, overfolded helix, sometimes featureless helix
Congenital malformations	Cardiac malformation, genital anomaly, neural tube defect, orofacial cleft, hypoplasia of fingers or fingernails, toes or toenails, talipes equino-varus, other limb anomaly, congenital dislocation of hip, hernia, craniosynostosis, upper airway malformation
Childhood medical problems	Myopia, strabismus, otitis media with effusion requiring surgery, joint laxity
Neurodevelopment	Typically communication disorder with speech and language delay, sometimes also gross motor delay and/or fine motor delay
Behaviour	Autism, Asperger syndrome, Attention deficit hyperactivity disorder, or behaviour problems associated with attention deficit or communication disorder

Table 2: Diagnostic criteria.

1. History of in-utero antiepileptic drug exposure
2. Presence of characteristic facial appearance
3. Presence of at least one of the following
   (a) evidence of neonatal withdrawal
   (b) compatible malformation
   (c) compatible childhood medical problem
   (d) compatible developmental history
   (e) compatible behavioural problem
4. Normal relevant investigations for alternative aetiologies (e.g. karyotype, Fragile X mutation analysis, CATCH22 deletion studies)

hood is of importance. In a recent study of patients ascertained through the National Fetal Anticonvulsant Syndrome Association, a high frequency of problems such as joint laxity, myopia, and glue ear requiring grommets was recorded. This may help make the diagnosis in an older child. In the same study, a characteristic pattern of developmental delay was seen, particularly involving speech and language, and a pattern of behaviour ranging from poor social skills to autism at the extreme. Similar behavioural and learning disorders have been previously described[8]. The fifth and sixth areas are therefore neurodevelopment, and behaviour. At present, there are insufficient systematic data to permit weighting of these features in a diagnostic nosology. In the absence of a positive test for a fetal anticonvulsant syndrome it is also important that other causes of a child's malformations, medical, learning or behaviour disorders should be excluded. We suggest the diagnosis could therefore be considered when the four criteria shown in Table 2 are all met. Certain malformations may however be more specific than others, and it would be unwise, for example, to dismiss antiepileptic drug exposure as a cause of an otherwise isolated neural tube defect. As evidence accumulates about the newer drugs such as gabapentin, vigabatrin, topiramate and lamotrigine the features considered characteristic may change, and it is to be hoped with improving therapies, the incidence of the fetal anticonvulsant syndromes will diminish.

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