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Anticonvulsant medication

The teratogenicity of anticonvulsant drugs: a progress report

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Antiepileptic medication in pregnancy

Exposure to anticonvulsant drugs during pregnancy is one of the most common potentially teratogenic exposures, occurring in 1 in 250 (0.4%) of pregnancies in a recent study in Boston.[1] The teratogenicity of these drugs was first postulated in the 1960s, with a consensus developing in the 1970s that a distinctive anticonvulsant embryopathy was produced. Two theories developed as to the cause: (1) the mother's underlying epilepsy[2] and (2) the anticonvulsant drug.[3]

All anticonvulsants marketed up to 1976 have been shown to be teratogenic, with varied manifestations and degrees of severity. Hopefully some of the "new" anticonvulsants marketed in the 1990s, for example, gabapentin (1993), lamotrigine (1994), and topiramate (1996), will be shown not to be teratogenic.

PATTERNS OF EFFECTS

I define a teratogenic effect as any harmful fetal effect from an exposure during pregnancy. Some effects are apparent at birth and others at older ages. The most common abnormalities identified in newborn infants are major malformations, midface and digit hypoplasia, microcephaly, and growth retardation. Experience has shown the importance of systematic evaluations[4] for these outcomes, including definitions of the physical features being looked for, measurements, inclusion and exclusion criteria[5] for major malformations, and regular assessments of the reproducibility of the findings.[6 7]

Major malformations

Theoretically each anticonvulsant drug could produce specific or distinctive abnormalities; a few have been identified. Five percent of valproic acid exposed infants in one large study[8] and 1% of carbamazepine exposed infants[9] had spina bifida; nothing distinctive about the spina bifida lesion has been reported and the frequency of other neural tube defects, such as anencephaly, is not increased. Long bone and preaxial deficiencies in valproic acid exposed infants have been reported.[10] Stiff, tapered fingers with absent or very small nails in phenytoin exposed infants, in association with radiographic changes, for example, coned epiphyses and shortened and hypoplastic distal phalanges, have been found in phenytoin exposed infants.[11] Vascular disruption limb anomalies, such as terminal transverse limb defects with nubbins,[12] have been seen in occasional phenytoin exposed infants.

Since these associated major malformations are relatively uncommon, even in infants exposed to these specific drugs, the major malformations identified most often in anticonvulsant exposed children are those which also occur in unexposed children: heart defects, hypospadias, club foot, and cleft lip or palate.[13–15]

It is usually difficult to know if an infant's major malformation is "the result of" the fact that his/her mother had taken an anticonvulsant drug during pregnancy. Theoretically, this could be presumed if the infant has some of the other features of the anticonvulsant embryopathy, such as the infant with holoprosencephaly who had the minor craniofacial and digit anomalies of the phenytoin embryopathy.[16] In one analysis,[17] the infants with a drug specific feature, such as the "anticonvulsant face" or midface hypoplasia, were more likely to have the other features of the embryopathy than control infants.

Microcephaly and growth retardation

Initial reports of children with the hydantoin,[3] carbamazepine,[18] and phenobarbital embryopathy[19] proposed that microcephaly and growth retardation were fetal effects of these exposures. But this outcome could have reflected the effect of polytherapy in some of the children evaluated. More recent studies of infants exposed to phenytoin, carbamazepine, and phenobarbital as monotherapy did not identify an increased frequency of microcephaly.[20 21] An appropriate comparison group by race and altitude[22] is crucial to these analyses.

Midface hypoplasia

The most common features are depressed bridge of the nose, short nose with anteverted nostrils, and long upper lip. Less common features are a broad bridge of the nose, thin vermilion, a small mouth, and a wide philtrum.[23]

Cephalometric radiographs of children who had been exposed to either phenytoin alone or phenytoin plus phenobarbital have shown significant changes in the facial bones and the cranial base: decreased length and height of the maxilla, decreased length of the posterior cranial base and mandible, altered maxillomandibular relationship, and shortened nasal bone.[24] These changes persist beyond childhood.

Because two other teratogens, thalidomide and tetracycline, affect the teeth of children exposed in utero, the size and shape of the teeth in panoramic radiographs and dental casts from children exposed to either phenytoin alone or phenytoin and phenobarbital as polytherapy were analysed.[25] An increased frequency of missing teeth and an increase in the mesiodistal diameter, particularly in the maxillary molars, was found. It will be important to determine whether other anticonvulsants produce similar changes in cranial structures and teeth.

Digit hypoplasia

An increased frequency of arch patterns and shortening of the distal phalanges has been reported in several studies.[26–28] Changes in the frequency of other dermal ridge patterns also occur, but are less common.[29] The higher frequency of arch patterns could reflect the fact that the prenatal exposures made the developing pad on the ends of the fingers lower than the pads associated with developing whorl and loop patterns.[30]

Hand radiographs of anticonvulsant exposed children show hypoplastic or malformed distal phalanges, coned epiphyses, pseudoepiphyses, and shortened metacarpals.[11] In a study of 46 children between the ages of 5 and 29 years, 14% of the phenytoin and/or phenobarbital

exposed subjects had at least two of these changes.[11] Since the measured nail sizes of these children in this study were not reduced, it was concluded that the presence of digit hypoplasia was determined most consistently from examining dermal ridge patterns and radiographs, not clinical inspection. The radiographs of the toes of the same subjects did not show a significant increase in the frequency of epiphyseal changes.[31]

Cognitive function

Assessments of intelligence have been the most common studies reported in older anticonvulsant exposed children and teenagers,[3 18 19 32–35] some of whom have shown evidence of cognitive dysfunction.

Phenobarbital

The evaluation of 33 adult men showed a deficit of 7 IQ points[32] with confounding by socioeconomic factors and a dose response relationship; another study[33] of 23 matched pairs aged 6.5 to 16 years showed a difference of 11 full scale IQ points, with the phenobarbital exposed also having specific problems with either language expression or reception.

Phenytoin

The study[34] of 34 mother-child pairs showed a 10.6 (±27.9) IQ point difference in 2 to 3 year olds compared to 34 matched pairs. Adams *et al*[33] evaluated 21 phenytoin exposed children aged 6.5 years and older in comparison to matched controls and found no difference in comparison to 21 matched controls.

Phenytoin and phenobarbital

A study[35] of 15 drug exposed children showed, in comparison to controls, a deficit of 10 IQ points in both the Wechsler Full Scale IQ and the Performance IQ at 4.5 years and older.

Carbamazepine

Thirty-six mother-child pairs showed no difference at ages 2 to 3 years between those exposed to carbamazepine and the 33 mother-child pairs in the comparison group.[34]

Based on the information published so far, the greatest concern about cognitive dysfunction is for children exposed in utero to valproic acid. Since the reports have come from case series[36 37] and not systematic, controlled studies, it is difficult to know how frequent developmental delay and mental retardation are in valproate exposed children. An additional concern is the occurrence of autism in case reports of children exposed to valproic acid during pregnancy[38 39]; a systematic study of this very serious potential fetal effect is needed.

While these small systematic studies and case series show that cognitive dysfunction can be an effect of prenatal exposure to anticonvulsants, the limitations of the studies cited above illustrate the major issues and potential confounding factors to be considered: the test instruments and subtests used; the sample size should have adequate statistical power; the comparison group should be well matched; the evaluators should be masked as to exposure status; the age of the children being evaluated, children aged 6 years and older have a larger repertoire of knowledge to be tested and the findings should be more consistent than those in 2 and 3 year-olds; the intelligence of the parents of the exposed and comparison child should be assessed and considered in the analysis; the mother's history of epilepsy posing a "genetic" risk to each of her infants; the seizures which the mother had during the child's pregnancy; the presence of the features of the anticonvulsant embryopathy in the drug exposed child and the comparison child.

Hopefully future studies will include as many of these confounders as possible with the detailed analysis of the children and their parents.

The fetal effect of each potential confounding factor could theoretically be evaluated in separate studies. This has been done for the potential "genetic" risk to the fetus from the mother's history of epilepsy in a pregnancy when she was not taking an anticonvulsant drug and did not have seizures severe enough to make her unconscious.[40] In this study, 57 seizure history (no drug) exposed children had no dysmorphic features and their intelligence was the same as that of the 57 matched controls. The power of the study was adequate to rule out a difference of 7 IQ points.

Late onset effects

An exposure during pregnancy can also produce fetal effects that are only apparent when that person is a teenager or young adult. Two examples from studies of other teratogens are the altered social behaviour in adult men who had been exposed in utero to diethylstilbestrol[41] and the higher frequency of diabetes mellitus in adults with congenital rubella.[42]

Recently, Dessens *et al*[43] reported an increased frequency of cryptorchidism in males exposed to phenytoin and/or phenobarbital during pregnancy and, later, menstrual irregularities in adult women. Dean *et al* report on page 251 of this issue of JMG the findings in a retrospective review of the medical records of 293 anticonvulsant exposed children. They identified an increased frequency of developmental delay, behaviour disorders, and a diverse group of medical problems that included refractive errors in vision, joint laxity, and otitis media (only in valproate exposed children).

Genetic susceptibility

Twenty years ago, David Smith[44] presented his clinical observation that parents with one child with phenytoin embryopathy had a higher risk of having a second affected child than the parents whose anticonvulsant exposed fetus showed no signs of the embryopathy in childhood. Both Van Dyke *et al*[45] and Moore *et al*[37] confirmed the increased recurrence risk after the birth of an infant with the anticonvulsant embryopathy.

Several hypotheses have been developed to explain why some infants of mothers taking anticonvulsant drugs have this apparent genetic susceptibility: (1) decreased function of epoxide hydrolase (EPHX1), an enzyme which metabolises phenytoin, postulated to be the result of an autosomal recessive gene in one study[46] and an autosomal dominant mutation in another[47]; (2) altered distribution of polymorphisms in microsomal EPHXI, no abnormalities were identified in one study of 16 subjects with the anticonvulsant embryopathy (L Walsh, J K Hartsfield Jr, personal communication); (3) production of free radicals by phenytoin[48]; (4) inhibition of potassium channel function[49], which produces injury by hypoxia and reperfusion; (5) decreased maternal serum folate, possibly associated with a deficiency of methylene tetrahydrofolate reductase.[50]

Counselling the pregnant woman taking an anticonvulsant

Because exposure to anticonvulsants is so common among pregnant women, it is important that all health care professionals be able to inform her of the potential for fetal effects and her options in her treatment, which include: take a daily folic acid supplement before conception; take the anticonvulsant drug as monotherapy, if possible; keep the dose of the anticonvulsant drug during pregnancy as low as possible, as the lower the dose presumably the lower the risk of a harmful fetal effect. Describe the increased risk for the spectrum of common malformations; do not emphasise an increased risk for cleft lip and palate, as this has been notable only for phenobarbital with an odds ratio of about 3.[15] Even when the mother takes phenobarbital, that risk should be put in the context of the rate in that mother's ethnic group: if she is white, the baseline risk is about 1:1000 or 0.1% and a three-fold increase makes the risk 1:333 or 0.3%. This de-emphasis would help make her concerns more realistic.

Future directions

This review highlights the need for more information on many aspects of the teratogenicity of anticonvulsants. First, hopefully the "new" anticonvulsants will be shown not to be teratogenic. Second, determine whether taking folic acid conception reduces the risks for a harmful

fetal effect. Third, do anticonvulsant exposed children have an increased risk for cognitive dysfunction? Fourth, the "anticonvulsant face" is a common effect; is its presence associated with an increased risk for cognitive dysfunction? Fifth, studies are needed to identify the candidate genes that are associated with the familial clustering of children with the anticonvulsant embryopathy. One would predict that each drug will have its own molecular mechanism for conveying this risk. Hopefully, it will be possible to identify the woman with a high risk for a teratogenic effect from taking one anticonvulsant drug and to select a lower risk treatment for her.

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