CURRENT LITERATURE

COGNITIVE DEFICITS FROM IN UTERO AED EXPOSURE

Normal Intelligence in Children with Prenatal Exposure to Carbamazepine

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OBJECTIVE: To investigate the effect of antiepileptic drugs (AEDs), especially carbamazepine (CBZ) and valproate (VPA), on intelligence in prenatally exposed children of mothers with epilepsy.

METHODS: Intelligence of 182 children of mothers with epilepsy (study group) and 141 control children was tested in a blinded setting at preschool or school age by using Wechsler Preschool and Primary Scale of Intelligence–Revised or Wechsler Intelligence Scale for Children–Revised. Data on maternal AED treatment and seizures during pregnancy were gathered prospectively. The study group represented approximately 50% of the children born to mothers with epilepsy in Uusimaa province during 1989 through 1994. One hundred seven children were exposed to AED monotherapy: 86 to CBZ and 13 to VPA. Thirty children were exposed to polytherapy: 23 combinations included CBZ, and 17 included VPA. The median maternal doses and blood levels during the second half of pregnancy were 600 mg and 26 μM for CBZ and 950 mg and 300 μM for VPA.

RESULTS: The mean verbal and nonverbal IQ scores in the children exposed in utero to CBZ monotherapy were 96 (95% CI, 93–100) and 103 (95% CI, 100–106). They did not differ from control subjects, whose mean verbal and nonverbal IQ scores were 95 (95% CI, 92–97) and 102 (95% CI, CI, 100–105). Significantly reduced verbal IQ scores were found in children exposed to VPA (mean, 82; 95% CI, 78–87) and to polytherapy (mean, 85; 95% CI, 80–90) compared with the other study group children and control subjects.

CONCLUSIONS: CBZ monotherapy with maternal serum levels within the reference range does not impair intelligence in prenatally exposed offspring. Exposures to polytherapy and to VPA during pregnancy were associated with significantly reduced verbal intelligence. The independent effects of VPA remain unconfirmed because the results were confounded by low maternal education and polytherapy.

COMMENTARY

Children of mothers with epilepsy are at increased risk for developmental delay (1). Animal studies have demonstrated that in utero exposure to antiepileptic drugs (AEDs) can produce behavioral teratogenesis (e.g., cognitive deficits) at dosages less than those that produce anatomic teratogenesis. However, data in humans are insufficient and contradictory (1).

The investigation by Gaily et al. is very important because it is a well-designed prospective study, providing evidence that in utero monotherapy carbamazepine (CBZ) exposure with serum maternal levels in the reference ranges does not impair intelligence of the exposed children. Their cohort of children exposed to CBZ is larger than that in any previous study examining the effects of in utero CBZ on cognitive development. Standardized neuropsychological measures of IQ were used, and the majority of the children were 6 years old or older, which allows a good estimate of ultimate adult IQ. The study controlled for a variety of confounding factors.

One caveat is that the genetic influence on the child's IQ was estimated by the maternal education. Maternal education is a surrogate for maternal IQ, which has the highest correlation with the child's IQ in population studies. Further, the effects of epilepsy, underlying disease, AEDs, and psychosocial factors on the mother may have reduced her educational achievements and opportunities. Thus it is possible that her educational level underestimates the genetic contribution to the child's intelligence. The IQs of the father and maternal relatives might help address this issue.

In contrast to CBZ monotherapy, in utero exposure to valproate (VPA) or polytherapy was associated with lower verbal IQ in the Gaily et al. study. The authors conclude that the independent effects of VPA in their own study were unconfirmed because the effects were confounded by low maternal education and polytherapy. Although this is true, the difference for VPA was still marginally significant ($P = 0.02$) after covariance for maternal education and number of AEDs. Further, a marginally significant negative correlation was found between

verbal IQ and VPA dose ($P = 0.04$). A greater problem in interpretation of the VPA results is the small sample exposed to VPA monotherapy ($n = 13$). Nevertheless, the results raise concern and are consistent with a prior retrospective study, which demonstrated an increased need for special education in children exposed to VPA (2). As Gaily et al. noted, "Prospective studies including larger numbers of children exposed to valproate monotherapy are urgently needed."

A recent animal study revealed that several AEDs (i.e., benzodiazepines, phenobarbital, phenytoin, VPA, and vigabatrin) produce widespread neuronal apoptosis in the developing brain (3). The effect appears to result from reduced neurotrophins and protein kinases, which are important for neuronal survival. Given the lack of adverse effects of CBZ in the Gaily et al. study, is it possible that CBZ would not produce apoptosis in this animal model? Further, in animal models, several newer AEDs have exhibited less anatomic teratogenesis than the older AEDs. It would be of great interest to determine if they produce apoptosis in the developing brain.

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References

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