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Long-Term Developmental Outcome of Children of Women with Epilepsy, Unexposed or Exposed Prenatally to Antiepileptic Drugs

A Meta-Analysis of Cohort Studies

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Abstract

Background: Results of studies investigating the long-term effects of intrauterine exposure to antiepileptic drugs (AEDs) on cognitive functioning are limited and conflicting.

Objective: To estimate intellectual development of children prenatally exposed or unexposed to AEDs by assessing IQ scores in a systematic review and meta-analysis.

Methods: A literature search using Pubmed, EMBASE and Google Scholar from inception to 30 April 2009 was performed to identify all original cohort studies that investigated cognitive functioning after *in utero* exposure to AEDs. Studies had to include at least one group exposed to an AED and one unexposed group. Data from drug exposed and unexposed controls were combined using a random effects model.

Results: Eleven studies met the inclusion criteria. Eight studies (three for valproic acid and five for carbamazepine) evaluated IQ as a measure of cognitive development. IQ was assessed by the Wechsler, Bayley or McCarthy intelligence scales, depending on age. One study investigated phenytoin and one study investigated phenobarbital (phenobarbitone). Because one study was reported in two different publications, seven studies were included in the meta-analysis. In total, the seven selected studies included 67 children exposed *in utero* to valproic acid and 151 exposed to carbamazepine, and 494 unexposed controls born to healthy women or to women with untreated epilepsy.

The mean full-scale IQ (FSIQ), verbal IQ (VIQ) and performance IQ (PIQ) scores in children exposed to valproic acid *in utero* were 83.9 (95% CI 64.2, 103.6), 93.7 (95% CI 72.6, 114.7) and 88.3 (95% CI 69.9, 106.9), respectively. The mean FSIQ, VIQ and PIQ scores in the control group were 102 (95% CI 90, 116), 101 (95% CI 87, 114) and 99 (95% CI 90, 117), respectively. The

mean FSIQ, VIQ and PIQ were all significantly lower in the valproic acid group compared with the unexposed group.

The FSIQ and VIQ of children exposed to carbamazepine were not statistically different from those of the unexposed control group. In a sub-analysis of carbamazepine exposure in three studies using the Wechsler intelligence scale, PIQ was significantly lower in children exposed to carbamazepine than in unexposed children.

Conclusions: Although our analysis revealed no evidence that untreated maternal epilepsy was associated with a lower IQ in the child, there may have been confounding factors, such as milder epilepsy, in this group. Exposure to valproic acid in pregnancy is associated with significantly reduced intelligence in children whose mothers were treated for epilepsy. Exposure to carbamazepine in pregnancy does not appear to be associated with reduced FSIQ and VIQ in children, although PIQ was lower in the sub-analysis. Clinicians should inform families of the potential cognitive adverse effects of valproic acid. More studies are needed to corroborate these findings.

Background

Epilepsy has a prevalence of 5–10 persons/1000.[1] During pregnancy, women with epilepsy cannot generally safely discontinue their antiepileptic therapy, and the risks to the unborn child from maternal antiepileptic medication need to be balanced against the risk of uncontrolled epilepsy both to the mother and the baby. In the last decade, an increasing number of studies have addressed the long-term safety of these drugs on child development, with conflicting results.[2-4] Synthesizing these data into an overall risk assessment is critical for clinical counselling of women with epilepsy and their families.

The objective of this study was to perform a systematic review of the literature pertaining to long-term neurodevelopment after *in utero* exposure to antiepileptic drugs (AEDs) and to conduct a meta-analysis to allow overall risk estimation.

Methods

Literature Search Strategy

PUBMED, EMBASE and Google Scholar were searched from inception to 30 April 2009. The search was performed using the following entry terms and their combinations: 'antiepileptic(s)' OR 'anticonvulsant(s)' OR 'phenytoin', 'carbamazepine', 'valproic acid/valproate' OR 'barbiturates' AND 'pregnancy' AND 'cognitive development' OR 'development' OR 'neurodevelopment' OR 'IQ'. Although the newer AEDs were not excluded *a priori*, a review of the literature failed to identify studies examining their neurocognitive effects. All references, footnotes and other sources cited in the retrieved articles were examined.

All published cohort studies that met the following criteria were included:

- human studies;
- research papers published in the medical literature that examined the relationship between administration of phenytoin, carbamazepine, valproic acid/valproate and/or barbiturates during any trimester of pregnancy and any measure of cognitive function in the offspring;
- either case-control or cohort studies with one group of subjects who were exposed to any of the AEDs, and a control group who were not exposed to any AED;
- all relevant studies irrespective of language or time of publication. Searches were conducted by the researchers and supported by a librarian. Original articles not written in English but with

English abstracts were assessed by the reviewers to determine applicability. Other foreign language studies were translated by native speakers to determine applicability.

Case reports, editorials, reviews, animal studies and studies from which no specific data could be extracted, as well as those that did not provide sufficient data for analysis were excluded.

Data Collection and Analysis

Data were collected by two abstractors working independently. Results were compared and, in the case of disagreement regarding inclusion, a third abstractor was enlisted to make the final decision. Outcomes of interest were scores of cognitive outcome measured by the Wechsler, Bayley or McCarthy IQ scales, or any other measure. The collection of data followed the process of the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines.[5]

To examine the combinability of data across studies, we calculated c^2,[6] chi-squared (χ^2)[5] and I^2 [6] statistics. These tests aim at ensuring there is no heterogeneity across studies that would preclude their combination for the purpose of meta-analysis. Data were then combined using a random effects model,[5] with the considered effect being the difference in IQ scores between prenatally exposed and unexposed children, using inverse variance weighting. Where data were not available in head-to-head trials, results were combined across arms of the studies using a random effects model, and meta-analytic results were contrasted using a 2-tailed t-test with pooled variances. Analysis was conducted with the Cochrane software (Review Manager [RevMan] for Windows; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

Results

Figure 1 presents a flow chart of the reviewed studies.

Forty-four papers were identified in the initial research and the full papers reviewed. Eleven cohort studies met our inclusion criteria, but not all of them could be included in the meta-analysis for the reasons detailed herein.[2-4,7-14] No disagreement occurred between the two abstractors. Studies were grouped according to type of cognitive assessment. Eight studies[2-4,7-11] used IQ testing as a measure of cognitive development, and three studies[12-14] used other methods as follows: (i) the use of standardized Dutch testing for reading, spelling and arithmetic;[12] (ii) postal questionnaires about attendance at a special school or requiring help at a mainstream school;[13] and (iii) classifying speech delay as the need for speech therapy and motor delay if a child was not sitting by 10 months or walking by 18 months.[14] Since these methods are impossible to compare with standard IQ measurements, they were not included in the meta-analysis.

The eight studies that evaluated IQ were grouped by the type of IQ test used. Six studies[2-4,7-9] used the Wechsler IQ test, and two studies[11,12] used the Bayley or McCarthy scales depending on age (table I).

Among the six studies that used the Wechsler IQ scale, two studies[2,3] were found to have used the same data. The study by Vinten et al.[3] was selected for use over the study by Adab et al.[2] as it was more recent. Hence, seven studies were

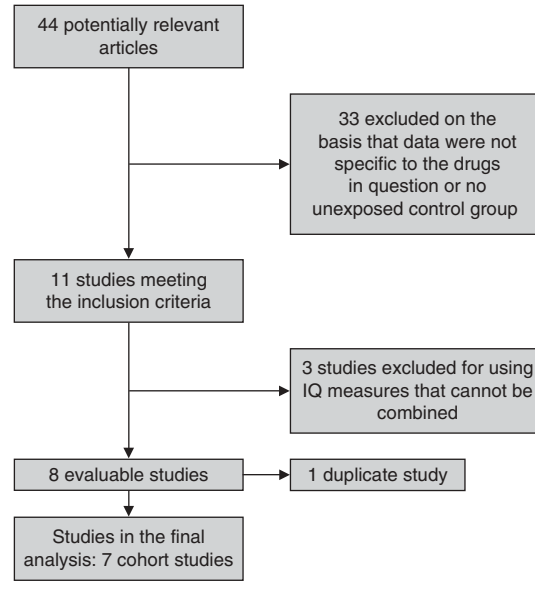

Fig. 1. Study selection from the literature search.

Table I. Characteristics of studies included in the meta-analysis

Study (y)	Exposure	Age at testing (range)	Drug exposure	Number of subjects	IQ [mean (standard error of the mean)]		
					VIQ	PIQ	FSIQ
Vinten et al.[3] (2005)	Exposed	6–16 y	Valproic acid	41	84 (1.5)	94 (2.5)	87 (2.5)
			Carbamazepine	52	94 (2)	89 (2)	91 (2.5)
			Phenytoin	21	99 (4)	97 (2.5)	98 (4)
	Control		None	80	92 (2)	91 (2)	90 (2)
Eriksson et al.[8] (2005)	Exposed	6.6–13.4 y	Valproate	13	85.1 (2.5)	84.7 (8)	84.5 (7.5)
	Control		Carbamazepine	13	96.5 (1)	102.5 (4.5)	98.9 (3.5)
			None	13	98.2 (1.5)	102.1 (9)	99.6 (2.5)
Scolnik et al.[10] (1994)	Exposed	18–36 mo	Carbamazepine	36	NA	NA	111.5 (3.3)
			Phenytoin	34	NA	NA	103.1 (4.3)
	Control		None – serves as a control to carbamazepine	36	NA	NA	114.9 (2.2)
			None – serves as a control to phenytoin	34	NA	NA	113.4 (2.2)
Koch et al.[4] (1999)	Exposed	10–19 y	Phenytoin	12	NA	NA	
			Primidone	9	NA	NA	
	Control		None, mother epileptic	13	100.8 (4.2)	98.6 (6.2)	101.8 (4.6)
			None, mother not epileptic	49	103.1 (1.3)	106.7 (1.6)	105.4 (1.6)
Reinisch et al.[9] (1995)[a]	Exposed	Young adults	Phenobarbital (study 1)	33	100.69 (4)	99.85 (4.2)	100.36 (4.1)
			Phenobarbital (study 2)	81	NA	NA	NA
	Control		None (study 1)	52	107.86 (4)	104.77 (4.2)	106.97 (4.1)
			None (study 2)	101	NA	NA	
Ornoy and Cohen[11] (1996)	Exposed	6 mo–6 y	Carbamazepine	47	NA	NA	100.3 (2)
	Control		None	47	NA	NA	112.4 (0.6)
Gaily et al.[7] (2004)	Exposed	5–9 y	Carbamazepine	86	96.2 (1.9)	103.1 (1.5)	99.7 (1.8)
			Valproate	13	83.5 (3.8)	96.3 (4.8)	89.7 (3.6)
	Control		None, mother epileptic	45	94.3 (2.6)	98.6 (2.9)	95.6 (2.8)
			None, mother not epileptic	141	94.9 (1.2)	102.4 (1.2)	97.6 (1.4)

a The publication by Reinisch et al.[9] describes 2 cohorts that are reported here separately due to their differences in the available details of results.

FSIQ = full-scale IQ; **NA** = not applicable; **PIQ** = performance IQ; **VIQ** = verbal IQ.

included in the meta-analysis (table I). Koch et al.[4] did not provide IQ values for specific monotherapies, instead providing IQ values for all monotherapies combined. Therefore, the monotherapies analysed in this study could not be added to the meta-analysis. However, since separate IQ values were provided for controls, the IQ values for the controls were incorporated into the control portion of the meta-analysis as they used a similar methodology and would have otherwise been accepted to this meta-analysis. Two of the studies[4,7] provided two sets of controls (mothers with epilepsy and mothers without epilepsy), both of which were incorporated into the meta-analysis.

Hence, the total numbers of monotherapy studies with Wechsler data that were suitable for analysis were three for valproic acid and three for carbamazepine. Because only one study was identified for phenytoin and one for phenobarbital (phenobarbitone), no formal meta analysis could be performed for these drugs. The outcome measures were verbal IQ (VIQ), performance IQ (PIQ) and full-scale IQ (FSIQ), a composite of VIQ and PIQ.

Among the studies that used the Bayley or McCarthy IQ scales depending on age (Bayley ≤30 months, McCarthy >30 months) there were two studies for carbamazepine and one study for phenytoin. The outcome measure was FSIQ (table I). There were insufficient data on phenytoin to allow useful meta-analysis.

The selected studies included 67 children exposed *in utero* to valproic acid, 151 exposed to carbamazepine, 21 exposed to phenytoin, 58 unexposed children born to mothers with epilepsy (control–epilepsy) and 436 unexposed children born to mothers without epilepsy (control–no epilepsy) [table I]. In total, the control group of unexposed children of mothers both with and without epilepsy was 436 (table I).[3,7,8] Although controls were recruited in different ways by different studies, they all included children born to healthy women who did not have epilepsy and who were not receiving AEDs. All groups were assessed using the Wechsler IQ scale. For both valproic acid and carbamazepine, there was no heterogeneity in the pooled studies that would preclude their combination for the purpose of meta-analysis.

Valproic Acid

The mean VIQ, PIQ and FSIQ scores in children exposed to valproic acid *in utero* were 83.9 (95% CI 64.2, 103.6), 93.7 (95% CI 72.6, 114.7) and 88.3 (95% CI 69.6, 106.9), respectively. The mean VIQ, PIQ and FSIQ scores in the control with epilepsy group were 97.5 (95% CI 73.3, 121.7), 98.6 (95% CI 70.4, 126.8) and 98.7 (95% CI 73.1, 124.3), respectively. The mean VIQ, PIQ and FSIQ scores in the control–no epilepsy group were 99.7 (95% CI 87.8, 111.6), 100.5 (95% CI 86.1, 114.8) and 99.6 (95% CI 88.1, 111.2), respectively (figures 2 and 3). There was no difference between the IQ of the children of mothers in the control group with epilepsy and the IQ of children of mothers who did not have epilepsy. The mean VIQ, PIQ and FSIQ scores in the control–all group (comprising mothers with and without epilepsy) were 99.1 (95% CI 88.2, 109.9), 102.1 (95% CI 90.7, 113.4) and 100.5 (95% CI 90.6, 110.4), respectively.

The mean VIQ, PIQ and FSIQ were significantly lower in the valproic acid group compared with the control–all group ($p = 0.001$, $p = 0.007$ and $p = 0.001$, respectively).

Carbamazepine

We conducted two meta-analyses for prenatal exposure to carbamazepine as some studies used the Wechsler IQ scale to measure IQ whereas others used the Bayley or McCarthy IQ scales, depending on age.[3,7,8,10,11] In the first meta-analysis, using the Wechsler scale the mean VIQ and FSIQ of children exposed to carbamazepine were not statistically different from the control–all group ($p = 0.097$ and $p = 0.095$). However, the mean PIQ of children exposed to carbamazepine was statistically significantly lower than the control–all group ($p < 0.002$). The mean VIQ, PIQ and FSIQ of children exposed to carbamazepine was not statistically different from the control–epilepsy group ($p = 0.39$, $p = 0.19$ and $p = 0.41$) [figures 2–4].

In our second meta-analysis using the Bayley/McCarthy scale, 166 subjects were selected for the final analysis. The exposure categories consisted of

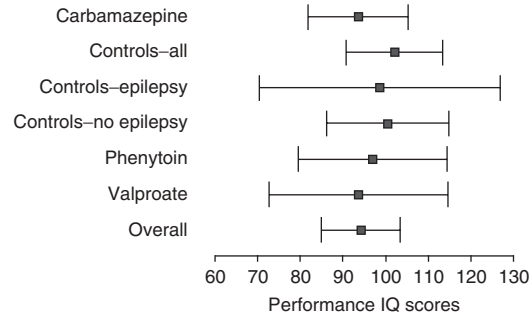

Fig. 2. Pooled mean performance IQ scores in children with prenatal exposure to various antiepileptic drugs. The bars represent 1 standard deviation.

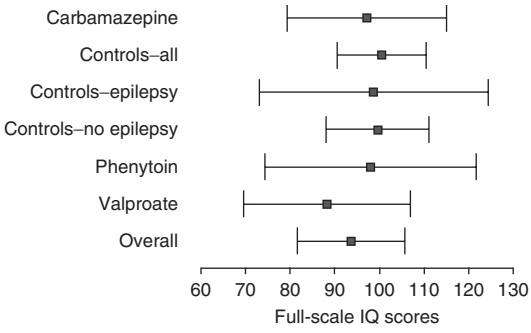

Fig. 3. Pooled mean full-scale IQ scores in children with prenatal exposure to various antiepileptic drugs. The bars represent 1 standard deviation.

83 children exposed to carbamazepine and 83 unexposed children of mothers with no epilepsy as a control group. Both groups were assessed according to the Bayley/McCarthy IQ scale. The mean FSIQ of children exposed to carbamazepine was not statistically different from the unexposed control group (98 vs 102 points, respectively; $p = 0.3$).

Discussion

The results of this meta-analysis provide evidence that prenatal exposure to valproic acid results in lower VIQ, PIQ and FSIQ scores when compared with a group of unexposed children of both mothers with or without epilepsy. These data are of substantial clinical relevance. Until recently, the main known disadvantage of the use of valproic acid in pregnancy was a 2% rate of neural tube defects, a malformation that can be detected sonographically and by α-fetoprotein levels.[15] While folate supplementation can prevent up to 70% of neural tube defects, there is no evidence that it can prevent valproic acid-induced neural tube defects. In contrast, neurotoxic insults, resulting in functional effects, cannot presently be detected *in utero*.

Carbamazepine has been regarded by many as the AED of choice in pregnancy. Our first meta-analysis of the studies using the Wechsler test did not reveal any adverse effect of carbamazepine on VIQ or FSIQ. We did detect an apparent decrease in PIQ with carbamazepine. The second meta-analysis for carbamazepine of the studies that used the Bayley/McCarthy scales also did not reveal any adverse effect on FSIQ. Although these results may be reassuring, longer studies are needed to address the apparent association of carbamazepine with lower PIQ. The available sample size had 80% power to show 8 points of IQ difference with an alpha of 5%. While no attempt has been made to adjust data for the quality of included studies, they all meet the reporting criteria for authors, editors and reviewers of meta-analyses of observational studies.[5]

Our study revealed no evidence that children born to untreated women with epilepsy have lower cognitive function. For decades, women with epilepsy were advised that their condition itself, even when untreated, can adversely affect child cognitive function.[16] It is interesting to note that a previous meta-analysis also showed no associated increased risk of morphological malformation in children of untreated mothers with epilepsy.[17] However, although our analysis revealed no evidence that untreated maternal epilepsy was associated with a lower IQ in the child, there may have been confounding factors, such as milder epilepsy, in this group. Furthermore, Adab and colleagues[2] have shown that seizures in pregnancy are associated with decreased VIQ in offspring.[2] Moreover, child cognitive development is affected by maternal IQ, socioeconomic status and other potential confounders that must be further addressed in future studies.[10]

While more research is needed to corroborate these results, it is important to inform women

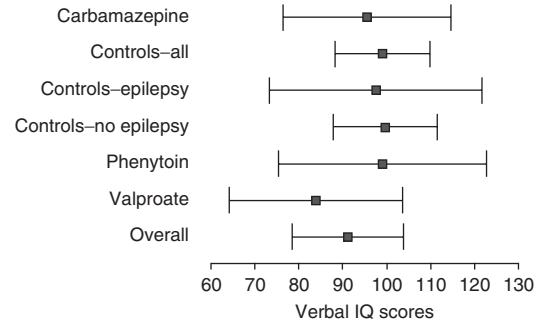

Fig. 4. Pooled mean verbal IQ scores in children with prenatal exposure to various antiepileptic drugs. The bars represent 1 standard deviation.

treated with valproic acid of the apparent developmental toxicity of this drug.

Conclusion

Our analysis revealed that exposure to valproic acid in pregnancy is associated with significantly reduced intelligence in children whose mothers were treated for epilepsy. Exposure to carbamazepine in pregnancy does not appear to be associated with reduced FSIQ and VIQ in children. Clinicians should inform families of the potential cognitive adverse effects of valproic acid. More studies are needed to corroborate these findings.

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