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Population-based study of antiepileptic drug exposure *in utero*—Influence on head circumference in newborns

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ABSTRACT

Purpose: To study the effect of AED exposure on head circumference in the newborn.
Methods: Data on all Swedish singletons births between 1995 and 2005, over 900,000 births, were obtained from the Swedish Medical Birth Registry. The effects of AEDs on birth-weight-adjusted mean head circumference (bw-adj-HC) were estimated by comparison with data from all births in an analysis which was adjusted for year of birth, maternal age, parity, maternal smoking, and maternal body mass index.
Results: A significant reduction of mean bw-adj-HC was seen after both carbamazepine (CBZ) (standard deviation scores (SDS) = 0.15, $p < 0.001$) and valproic acid (VPA) (SDS = 0.10, $p = 0.04$) in monotherapy. No effect on mean bw-adj-HC was seen for phenytoin, clonazepam, lamotrigine and gabapentin. There was a significant increase in the occurrence of microcephaly (bw-adj-HC smaller than 2 SD below the mean) after any AED polytherapy (OR = 2.85, 95% CI: 1.74–4.78) but not after AED monotherapy or monotherapy with CBZ or VPA. CBZ or VPA was taken by 71% of the pregnant mothers on AED, and the usage increased over time.
Conclusions: CBZ and VPA in monotherapy during pregnancy reduce mean bw-adj-HC. AED polytherapy increases the rate of microcephaly but no significant effect is seen of AED monotherapy. The possible significance for the further development of the child is uncertain but should be explored.

1. Introduction

Teratogenic effects of antiepileptic drugs (AEDs) are well known.[1–4] Approximately 0.3% of all pregnant women have epilepsy and is in need of a balanced AED treatment.[5] To optimize AED treatment regimens, good characterization of risks is required not only for malformations but also for effects on fetal growth. To date, most attention regarding intrauterine effect of anticonvulsants has been given to the malformations. However, Hvas et al. showed that newborns of women with drug treated epilepsy had lower birth weight, length, and head circumference (HC) but normal gestational age compared to newborns of women without epilepsy, and that none of these negative effects was present in cases of untreated maternal epilepsy.[6] Also, a few other studies reported a decrease in body dimensions, especially a reduced HC, after AED exposure *in utero*, where polytherapy often showed stronger growth reduction effect than monotherapy did.[7–9] Of the "old generation" AEDs, phenobarbital, phenytoin, primidone, ethosuximide, carbamazepine (CBZ), clonazepam and valproic acid/valproat (VPA), some have been studied regarding effect on fetal growth in small samples. To the "new generation" of AEDs belong drugs introduced in the 1990 s and later, including vigabatrin, lamotrigine, gabapentin, felbamate, oxcarbazepine, topiramate, levetiracetam, pregabalin, zonizamide and clobazam. CBZ and VPA are still the most commonly used AEDs in most developed countries.

An AED-induced effect on fetal head growth has been found primarily for CBZ. Hiilesmaa et al. studied 133 Finnish children exposed to AEDs *in utero* and showed that CBZ alone, and in polytherapy with phenobarbital, was associated with fetal head growth retardation.[8] In a European material of 577 infants exposed to AEDs it was found that VPA treatment was associated with a doubling of the risk for major malformations, whereas CBZ had negative effects on body weight, length and HC at birth.[7] On the contrary, Battino et al. found a lower risk for small HC after exposure to CBZ compared to VPA and pentobarbital monotherapies among 315 newborns.[10] Interestingly, there was a significant trend for lower effect over time of CBZ on HC in a Swedish population-based study with births from 1973 to 1997.[9] Their data were based on a material of 963 women on AED treatment where HC and gestational age were reduced by CBZ, but neither intrauterine growth, birth weight or body length was. Other

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monotherapies were studied together as a group and no negative consequences on body dimensions were found.

With this investigation we have estimated the effect on head growth of exposure *in utero* to the new AEDs lamotrigine and gabapentin and the old AEDs phenytoin, clonazepam, CBZ and VPA. The large size of our material made it possible to study risks that were previously estimated based on few exposures. Further, we studied changes in the use and effects of AED over time.

2. Materials and methods

2.1. AED effect on birth-weight-adjusted head circumference (bw-adj-HC) in newborns after exposure in utero

We analyzed data from the Swedish Medical Birth Registry (SMBR) in which all newborns in Sweden are registered (National Board of Health). Information on maternal drug use was collected from a structured interview made by a midwife at the first antenatal visit (usually around 10–12 gestational weeks). Thereafter, prescriptions from the antenatal care system given after the first visit were recorded. In this study, a record any time during pregnancy counted as use of antiepileptic drug. All infants born 1995–2005 where the mother reported use of AEDs were selected ($n = 2718$). From this group the following numbers of newborns were excluded: six with reported CNS malformation and 64 who were twins or triplets, and 223 infants without known birth weight or HC. The remaining group consisted of 2426 newborns, that is, 0.27% of all singleton infants with known birth weight and HC, without known CNS malformations and with a record from the first antenatal care visit ($n = 900{,}739$ comprising the population group of comparison).

The population infants were grouped by birth weight in 500 g intervals. For each birth weight group the mean and SD of HC were calculated for all newborns for each stratum according to year of birth, maternal age (2 classes: <35 years, ≥35 years), parity (2 classes: 1, >1), maternal smoking (3 classes: 0 or no answer, <10, ≥10 cigarettes per day), maternal body mass index (3 classes: <19.8, $19.8 \leq \text{BMI} < 26$, ≥ 26 kg/m^2).

2.1.1. Quantitative analysis

For each infant exposed to AED *in utero*, its HC deviation from the mean HC of the infant's birth weight group in the population data, according to year of birth, maternal age, parity, smoking, and BMI, was calculated and expressed as the number of standard deviations (SDs) in that stratum, a standard deviation score (SDS). The mean of these SDS among the exposed infants was compared with zero in *t* tests using two-sided tests and the standard error of the mean (SEM) for the SDS. The effect of exposure to AED on bw-adj-HC was determined for infants exposed to any AED and also for infants exposed to some specific drugs individually, used in monotherapy or polytherapy. Differences in effects between the three periods 1995–1997, 1998–2001 and 2002–2005 were studied using analysis of variance.

2.1.2. Dichotomous analysis

We also estimated the impact of AED exposure on the occurrence of microcephaly (bw-adj-HC smaller than 2 SD below the expected mean) with a Mantel–Haenszel analysis, adjusting for the same confounders as above and using Miettineńs method to estimate approximative 95% CI.

2.2. Association between mothers' AED treatment during pregnancy and their own bw-adj-HC at birth

Among the mothers to the 2426 newborns exposed *in utero* to AED in 1995–2005, 1017 were born after 1973 and none after 1988. Of those, 862 had their own birth recorded in SMBR and for 850 of those there were data on birth weight and birth HC. The control population consisted of all now living women born 1973–1988 according to SMBR with data on birth weight and HC. The control population of women was grouped by birth weight in 500 g intervals. For each birth weight group the mean and SD of the womens' birth HC were calculated for each stratum according to year of birth. For each woman treated with AED, her birth HC deviation from the mean birth weight specific HC, expected from the population data according to year of birth was determined and expressed as standard deviation score (SDS). The mean of these SDS for those treated with AED was compared with zero in *t* tests using two-sided tests and the SEM for the SDS.

The Swedish ethical board at Karolinska Institutet approved the study.

3. Results

Table 1 presents population data on mean HC with SD according to birth weight class.

The frequencies of the various antiepileptic drugs among singleton pregnancies for the whole period are listed in Table 2. Monotherapies represented 90% of the cases ($n = 2195$). CBZ was clearly the most commonly used drug (50% of the monotherapies),

Table 1
Head circumference (HC) in 500 g birth weight classes among all infants born.

Birth weight	Number newborns	HC, mean ± SD (cm)
300–999	953	24.3 ± 2.7
1000–1499	2,039	27.6 ± 1.9
1500–1999	4,261	30.2 ± 1.5
2000–2499	16,211	32.1 ± 1.3
2500–2999	87,762	33.4 ± 1.2
3000–3499	281,025	34.4 ± 1.1
3500–3999	323,923	35.3 ± 1.1
4000–4499	147,461	36.1 ± 1.2
4500–6700	37,104	37.0 ± 1.2
Total	900,739	

Table 2
Number of infants exposed to AEDs during singleton pregnancies, 1995–2005. Only drugs available in Sweden.

Antiepileptic drug	Number of exposed infants	
	Monotherapy	Polytherapy
Phenobarbital	11	8
Primidone	6	4
Phenytoin	137	24
Fosphenytoin	0	0
Ethosuximide	7	15
Clonazepam	71	43
Clobazam	0	2
Carbamazepine	1094	128
Oxcarbazepine	10	6
Valproic acid	460	80
Vigabatrin	22	17
Lamotrigine	308	114
Felbamate	0	0
Topiramate	7	16
Gabapentin	56	13
Levetiracetam	5	8
Zonizamide	0	0
Pregabalin	0	0
Unknown sort	1	0
Total number	2195	231

Table 3
Effect of AEDs on mean birth-weight-adjusted HC, expressed as mean SDS from population control material. Only drugs with at least 50 exposed singleton pregnancies.

Antiepileptic drug	Mono/poly	SDS, mean ± SEM	*t*	*p*
Carbamazepine	Mono	−0.15 ± 0.03	4.8	2×10^{-6}
	Poly	−0.17 ± 0.09	1.7	0.09
Non-carbamazepine	Mono	−0.03 ± 0.03	1.3	0.21
	Poly	−0.18 ± 0.11	1.6	0.12
Valproic acid	Mono	−0.10 ± 0.05	2.12	0.04
	Poly	−0.18 ± 0.13	1.4	0.15
Phenytoin	Mono	−0.02 ± 0.09	0.25	0.39
Clonazepam	Mono	−0.01 ± 0.14	0.07	0.40
Lamotrigine	Mono	−0.004 ± 0.06	0.01	0.40
	Poly	−0.08 ± 0.10	0.8	0.30
Gabapentin	Mono	−0.02 ± 0.13	0.12	0.39

SDS, standard deviation score, i.e. the number of standard deviations that each AED-exposed infant's HC deviated from the mean HC in the population data in corresponding stratum.
SDS, mean ± SEM, the mean and standard error of the mean of SDS scores among the exposed infants.

followed by VPA (21%), and lamotrigine (14%). Among the 231 polytherapies, the majority (216) consisted of two AEDs.

3.1. Birth-weight-adjusted head circumference at birth (bw-adj-HC)

3.1.1. Quantitative analysis

A significantly smaller mean bw-adj-HC was found among newborns to mothers treated with AED compared to all births during 1995–2005 (0.10 SDS units from mean of the population, $t = 4.8$, $p < 0.001$). The effects on bw-adj-HC of the specific AEDs used in more than 50 cases were determined (Table 3). CBZ had the strongest negative effect on bw-adj-HC. The effect was found to be of the same order of magnitude for monotherapies (SDS = 0.15, $t = 4.8$, $p < 0.001$) and polytherapies (SDS = 0.17, $t = 1.9$, $p = 0.07$). VPA in monotherapy also had a negative effect on mean bw-adj-HC (SDS = 0.10, $t = 2.1$, $p = 0.04$). The other drugs analyzed; phenytoin, clonazepam, lamotrigine and gabapentin in monotherapy showed no effect on mean bw-adj-HC.

Analyses were performed in three groups of year of birth separately: 1995–1997, 1998–2001, and 2002–2005. The number of pregnancies reported with AED treatment increased over time from 150 per year during 1995–1997, 217 in 1998–2001 to 276 in 2002–2005. An increase was also found for CBZ use in monotherapy: 85, 104 and 106 per year during the three periods. VPA use also increased from 23 cases per year in 1995–1997 to 43 in 1998–2001 and 55 during 2002–2005. The negative effect of VPA on mean bw-adj-HC showed a variation over time, being much lower for 1998–2001 than in the other two periods ($F = 4.9$, $p = 0.01$). However, the effect on mean bw-adj-HC of AEDs as a group did not differ between the time periods (SDS = 0.11, 0.08 and 0.10, respectively) and neither did the effect of CBZ alone ($F = 1.2$, $p = 0.30$).

3.1.2. Dichotomous analysis

Microcephaly (a bw-adj-HC smaller than 2 SD below the expected mean) occurred in 2.6% of all infants and in 3.3% of the infants exposed to AED *in utero*. The adjusted odds ratio (OR) for having an infant with microcephaly after exposure to any AED in polytherapy was 2.85 (95% CI: 1.74–4.78). However, in monotherapy the risk for microcephaly was increased neither after any AED (OR = 1.17, 95% CI: 0.91–1.51), after CBZ alone (OR = 1.26, 95% CI: 0.89–1.77) nor after VPA alone (OR = 1.14, 95% CI: 0.65–1.98).

3.2. Mothers' AED treatment during pregnancy and their own bw-adj-HC at birth

Mothers on AED treatment during pregnancy in 1995–2005 born 1973–1988 had no different bw-adj-HC at birth compared to the all women born 1973–1988 (SDS = −0.01 ± 0.04).

4. Discussion

In this study we analyzed the effect on head circumference of exposure *in utero* to AEDs during 1995–2005 in a large nation-wide Swedish material. The analyses were adjusted for year of birth, maternal age, parity, smoking, and body mass index. The most commonly used monotherapies were CBZ, followed by VPA, lamotrigine, and phenytoin. A significant reduction of mean birth-weight-adjusted head circumference (bw-adj-HC) was seen after CBZ and VPA monotherapy. The effects of CBZ and VPA corresponded to 0.2–0.4 cm. An increased risk of microcephaly (HC smaller than 2 SD below expected mean) was statistically significant after polytherapy but not after monotherapy or monotherapy with CBZ or VPA. The possibility that the association between AED exposure and bw-adj-HC of the newborn was due to inheritance of small bw-adj-HC from the mother was tested. The mean bw-adj-HC of the mothers to the infants exposed to AED was compared to that of all women born in the same year interval, 1973–1988, adjusting for year of birth. The mothers treated with AED corresponded to almost half of the cohort of the AED-exposed infants studied. The mothers treated with AED had similar bw-adj-HC as the general female population suggesting that mothers' bw-adj-HC at birth was not a confounding factor.

CBZ was also previously shown to reduce body dimensions of the newborn, primarily HC.[8] However, a decline in the effect was previously suggested in an earlier Swedish study.[9] No decline in effect of CBZ on bw-adj-HC over time was observed in the present study spanning 7 additional years with more than double the population size. VPA was in a previous small study shown to reduce HC stronger than CBZ,[10] however other small studies ($n = 62$ and 30) showed no VPA effect on HC.[7,11] None of the other four AEDs studied, phenytoin, clonazepam, lamotrigine and gabapentin, showed a significant effect on mean bw-adj-HC. Previous findings on effects of *in utero* exposure to the AEDs studied here include the following. The effects on mean HC of CBZ and VPA are similar, if anything higher for CBZ than VPA,[7–10] whereas VPA but not CBZ has probable clinically relevant malforming effect.[12] Both CBZ and phenytoin monotherapies possibly increase the risk for cleft palate,[12] but phenytoin has not been associated with microcephaly.[13] Benzodiazepines usually have a low malforming potential and small studies of clonazepam in monotherapy ($n = 43$) had little information value.[14,15] Few studies on the fetal effect of gabapentin have been published. In a study of the safety of gabapentin exposure in human pregnancy no increased risk was found compared to the general population but also this study had a low power due to the small number of patients ($n = 39$).[16] A recent study showed various malformations of the brain in mice fetuses after gabapentin exposure *in utero*.[17] A dose-dependent malforming effect of lamotrigine has been published,[18] but this finding was not reproduced.[19] Hence there is insufficient evidence to determine if there is a malforming effect of clonazepam, gabapentin or lamotrigine.[12]

An increased risk for smaller HC by epilepsy *per se* has been discussed, which could confound the findings of the effect of CBZ and VPA on bw-adj-HC reported here. However, such confounding by epilepsy indication is less likely in our study because four of the six AEDs studied (phenytoin, clonazepam, lamotrigine and gabapentin) showed very low mean SDS of bw-adj-HC, that is estimated not to reach significance using the CBZ monotherapy

sample size of 1094 cases. Though, AEDs are not used only in epilepsy. However, CBZ and VPA are not to a lower extent used for non-epilepsy indications than the four AEDs with no effect on bw-adj-HC. During recent years, notably VPA, lamotrigine and CBZ are used as mood stabilizers in bipolar affective disorder, and also other non-epilepsy diagnoses are sometimes treated with AEDs. Moreover, Hvas et al. detected increased risk neither for lower weight, length nor smaller HC at birth in infants to non-treated epileptic mothers.[6] Information on the specific indication for the individual prescription of AED was not available for the studied cohort.

To analyze difference in effect over time we divided the material into three groups: 1995–1997, 1998–2001 and 2002–2005. The use during pregnancy of CBZ was found to increase by 25% and VPA by 140%, between the first and last period in spite of recent reports on negative effects on newborns of these AEDs. The effect of VPA on mean bw-adj-HC changed over time and was lowest in the middle period (1998–2001) while no variation with time was seen for CBZ or all AEDs as a group.

In utero exposure to AED polytherapy, and monotherapy with VPA and phenytoin probably contribute to reduced cognitive outcome (reviewed by Harden et al.[12]). Histopathologically, apoptotic neurodegeneration has been found in the brain after exposure of the young rodent to an AED (phenytoin, phenobarbital, diazepam, benzodiazepine, vigabatrin, and valproate),[20] which hypothetically could impair cognitive function.[21] In cell culture, CBZ has been shown to induce mitotic arrest,[22] and to inhibit differentiation of embryonic stem cells into later stages, whereas VPA was a potent inhibitor of all stages of mesodermal and endodermal development.[23] It is unknown if any of these mechanisms contributes to the, on average, small reduction in birth HC seen after *in utero* exposure to CBZ, VPA and AED polytherapy.

The clinical significance, at birth and in the developing child, of the small reduction in birth HC associated with certain AED exposures *in utero* is unknown. The high plasticity of the nervous system at young age may compensate for disturbances.[24]

5. Conclusion

We have used a large nation-wide population-based material and shown that there is an apparent difference between AED drugs with respect to their effect on bw-adj-HC at birth. The strongest effects were seen for CBZ and VPA. The effects were small, but were statistically significant and remained from 1995 to 2005. CBZ or VPA were given to 71% of the cases, a prescription rate that increased with 25% for CBZ and 140% for VPA over the last decade. Phenytoin, clonazepam, lamotrigine and gabapentin had no certain effect on bw-adj-HC. AED polytherapy increased the rate of microcephaly.

Conflict of interest

None of the authors has any conflict of interest to disclose.

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