

Outcome of children born to epileptic mothers treated with carbamazepine during pregnancy

A Ornoy, E Cohen

Abstract

Aim—The purpose of the study was to assess whether there was an increased rate of congenital anomalies or significant developmental delay in infants of women with epilepsy who had been treated with carbamazepine during pregnancy.

Methods—47 children were studied, aged 6 months–6 years, who were born to 37 epileptic mothers on carbamazepine monotherapy (group A). All children had a complete physical and neurodevelopmental assessment by a developmental paediatrician, and 41 a complete psychological evaluation. They were compared with 47 children of similar socioeconomic status (group B).

Results—Six of the 47 children in group A had typical facial features of 'carbamazepine syndrome'. The average cognitive score of children in group A was significantly lower than in group B. This was mainly because all six children with carbamazepine syndrome had a development quotient or intelligence quotient below 90. There were no differences between the two groups in physical growth or in the rate of major anomalies. Two children in group A had cleft palate but in each case this was found in a parent as well.

Conclusions—In utero exposure to carbamazepine may result in 'carbamazepine syndrome' characterised by facial dysmorphic features and mild mental retardation. Prevalence of carbamazepine syndrome does not seem to be related to the dose of carbamazepine or the presence of maternal convulsions. It may depend upon hereditary factors that have yet to be defined. One possible factor is decreased activity of the enzyme epoxide hydrolase with resulting increased concentrations of carbamazepine epoxide which may be teratogenic.

(*Arch Dis Child* 1996;75:517-520)

Keywords: 'carbamazepine syndrome' pregnancy, cognitive and motor function.

Carbamazepine is used for various central nervous system disorders including trigeminal neuralgia and cyclic manic-depressive disorder (bipolar disorder) and commonly in women with epilepsy.¹ It is usually well tolerated and is therefore used in pregnancy. The question whether this drug may affect the developing

embryo and fetus is therefore of primary importance.¹⁻¹³

While several investigators found no increase in the rate of congenital anomalies among offspring of epileptic mothers treated with carbamazepine during pregnancy,^{2 4 7} others have described an increased rate of congenital anomalies, further increased when epileptic women were treated with a combination of carbamazepine and other drugs such as valproic acid and phenobarbitone.⁸⁻¹³ Although most investigators were not able to delineate a specific 'carbamazepine syndrome' Jones *et al* found an increase in facial dysmorphic features, that is short nose, long philtrum, upslanting palpebral fissures, hypertelorism, epicanthal folds, and nail hypoplasia.^{11 12} These authors also described developmental delay in 20% of children (5/25).¹²

The purpose of our study was to assess the incidence of congenital anomalies and the developmental outcome of 47 children born to epileptic women treated during pregnancy with carbamazepine alone in comparison to matched control children.

Patients and study design

The Israeli Teratogen Information Service receives queries regarding the possible adverse effects of maternal exposure to potential teratogens. During 1988-94 we received 119 calls about epileptic women who were treated with carbamazepine alone, or in combination with other anticonvulsants. Of these, 13 women were not pregnant at the time of referral. Of the remaining 106, 48 were on carbamazepine monotherapy throughout pregnancy. Of these, eight had spontaneous or induced abortions and three were lost to follow up. The remaining 37 women had 49 children who we examined at ages of 6 months-6 years. Each woman was interviewed by us in relation to drug use and dosage and presence of convulsions during pregnancy. In addition we asked about the type and time of onset of epilepsy and the existence of other diseases.

The children were examined physically and neurologically by a developmental paediatrician, and if 1 year of age or more, were evaluated by a developmental psychologist using the Bayley developmental scales for children up to 2.5 years of age,¹⁴ or McCarthy's developmental scales for children above 3 years.¹⁵ The latter test evaluates the cognitive and motor abilities of 3-8 year old children and is used by developmental psychologists in many child development centres.

Laboratory of Teratology, Department of Anatomy and Cell Biology and the Jerusalem Institute of Child Development, Hebrew University Hadassah Medical School and Ministry of Health, Jerusalem, Israel
A Ornoy
E Cohen

Correspondence to:
Dr A Ornoy, Department of Anatomy and Cell Biology, Hebrew University Hadassah Medical School Jerusalem, PO Box 12272, Jerusalem 91120, Israel.

Accepted 19 July 1996

Table 1 Parental socioeconomic status, gestational age, birth weight, age, weight, and head circumference at examination in 47 research and 47 control children; values are mean (SD) [number of children]

	Children of epileptic mothers	Controls
Parental socioeconomic status	2.31 (0.8) [33]	2.14 (0.8) [43]
Gestational age (weeks)	39.3 (1.8) [47]	39.8 (1.6) [47]
Birth weight (g)	3187 (530) [47]	3162 (680) [47]
Age at examination (months)	31 (15) [45]	24 (16) [47]
Weight (centile)	43 (25) [37]	32 (22) [38]
Head circumference (centile)	24 (23) [43]	29 (21) [44]
Facial dysmorphism (carbamazepine syndrome)	6*	0

* Significantly higher than controls, χ^2 , $p < 0.05$.

Table 2 Mental and motor scores of control and research children in Bayley and McCarthy tests; values are mean (SD) [number of children]

	Children of epileptic mothers	Controls
Bayley MDI	101.1 (14.8) [22]*	112.0 (10.0) [35]
Bayley PDI	97.5 (18.0) [20]	101.0 (11.6) [34]
McCarthy GCI	99.4 (21.1) [19]*	113.0 (15.0) [12]
McCarthy	52.4 (10.5) [13]	49.5 (7.0) [11]

* Significantly lower than appropriate controls, $p < 0.05$.

Two of the 49 children were excluded from analysis because of prematurity (born before 32 weeks of gestation). We matched 47 control children (group B) to the remaining 47 children (group A). These control children were matched by birth weight, gestational age, and parental socioeconomic status. Socioeconomic status was ascertained according to parental profession and education, with one average score given to each family on a scale of 1–5, 1 being the highest.¹⁶ The developmental psychologist did not know to which group a child belonged but the developmental paediatricians were not blinded.

The ethnic origin of the parents and grandparents of the research group children was assessed, as 'Oriental' or 'Ashkenazi' (Eastern European). Among the 37 mothers there were 12 Ashkenazi women who gave birth to 17 children, 19 women of Oriental origin who gave birth to 24 children, and six women of unknown ethnic origin.

Results

The average birth weight, parental socioeconomic status, gestational age, age at examination, and several physical parameters are given in table 1. As observed, there were no differences between the groups in parental socioeconomic status, gestational age, birth weight, and average age at examination. The average height and head circumference at examination (shown in centiles) was similar in both groups.

All the mothers used carbamazepine as their sole anticonvulsant. The mean (SD) daily dose was 658 (329) mg, with a range of 200–1800 mg/day. Three mothers also used benzodiazepines for 1–3 weeks and five occasionally used drugs that have little or no effect on the central nervous system (antibiotics (2), analgesics (2), and glucocorticosteroids (1)).

Fourteen of the mothers (47 pregnancies) had convulsions during their pregnancy. Among the 47 children in group A there were five children with major anomalies: hydrocephalus (1), ventricular septal defect (1), dila-

Table 3 Average mental and motor scores on Bayley and McCarthy scales of 41 children exposed in utero to carbamazepine in comparison to 47 controls; values are mean (SD)

	Children of epileptic mothers (n=41)	Controls (n=47)
MDI, GCI	100.3 (15.0)*	112.4 (4.0)
Motor†	100.3 (21.0)†	100 (11.7)

* Significantly lower than controls, $p < 0.05$.

† The motor score on McCarthy scales was multiplied by two to equalise it to the average normal motor scores (MDI) on the Bayley.

tation of the pelvis of the kidney (1), and cleft palate (2). The two children with cleft palate belonged to two families: only one had other features of carbamazepine embryopathy; his father also had cleft palate. The other child also had visual impairment and nystagmus and resembled his mother who had similar clinical findings. Of 47 children in group B there were three with major anomalies (one each with: pulmonic stenosis, hypospadias, and a solitary cyst of the kidney). Two additional children (one from each group) had unilateral dislocation of the hip.

The striking finding was that in group A six children (table 1) had typical facial dysmorphic features as described in carbamazepine syndrome: upslanting palpebral fissure (6), epicanthic folds (6), micrognathia (4), broad nasal bridge (4), high arched palate (2), or cleft palate (1). Two of these children also had strabismus, and one child had hypoplasia of the toe nails. Two of the children were born to Ashkenazi mothers and four to Oriental mothers, with no significant difference in ethnic origin. None of these six children were siblings. None of the control children had dysmorphic features or significant neurological impairment.

The cognitive and motor scores of the children are described in table 2. As observed, there was a lower average mental (mental developmental index (MDI) on Bayley) and cognitive (general cognitive index (GCI) on McCarthy) score in children born to mothers treated with carbamazepine, when compared with controls. There were no differences in the motor scores (PDI, psychomotor developmental index) between the groups, on both tests. The results of the combined mental and motor scores (of both tests), are given in table 3, demonstrating the same findings as in table 2.

Of the 41 children in group A examined by the psychologist, four had MDI or GCI scores between 81 and 90 and five had scores of 80 or below. Of these nine children, six had the typical facial dysmorphic features of carbamazepine syndrome. Thus all children with facial dysmorphic features (carbamazepine syndrome) had a development quotient (DQ) or intelligence quotient (IQ) below 90. The child from group A with hydrocephalus had no facial dysmorphic features. He was mentally retarded but did not have a formal psychological evaluation. In group B there was no child with a MDI or GCI below 81, but two children had scores below 90.

We found no correlation between the daily dose of carbamazepine and outcome. Of the

four women on higher doses (1800 mg/day in one case and 1200 mg/day in three other cases), one child (in a woman treated with 1200 mg/day) had carbamazepine syndrome and a mental score (MDI) of 78. No correlation was found with the incidence of maternal convulsions during pregnancy. Of the 14 pregnancies complicated by convulsions only one child had carbamazepine syndrome. The mean (SD) socioeconomic status of the parents of the six children with carbamazepine syndrome was 2.8 (0.4), not statistically different from that of the other parents in group A (2.31(0.8)) or group B (2.14(0.8), table 1).

Discussion

The children born to epileptic mothers who were on carbamazepine monotherapy had lower average cognitive scores than controls, with six of the 47 children also exhibiting typical facial features of carbamazepine syndrome. The group is too small to conclude that the four major anomalies observed—hydrocephalus, cleft palate, ventricular septal defect, and hydronephrosis were related to carbamazepine, especially as three control children had congenital anomalies.

Waters *et al* found three times more abnormal outcomes among offspring of epileptic women treated with anticonvulsants, when compared with controls.¹⁷ These included neonatal death and congenital anomalies. The higher rate of poor outcome was found in pregnant mothers treated with phenobarbitone.

Scolnick *et al* studied the outcome of women on carbamazepine or phenytoin monotherapy, and compared the results to matched controls.¹⁸ They found that the global IQ of the children born to mothers on phenytoin monotherapy was 10 points lower than that of matched controls. However, the children born to carbamazepine exposed mothers did not differ from controls on various neurodevelopmental tests.¹⁸ The average daily dose of carbamazepine used by the pregnant mothers was lower than the recommended adult maintenance dose, which may explain the lack of effects of carbamazepine in this study.¹⁹ Women receiving phenytoin were on the conventionally recommended dose.¹⁹

An obvious question when analysing our results is whether maternal epilepsy alone may be related to a reduction in a child's cognitive function. Holmes *et al* studied the mental development of 57 children born to epileptic women who had not received any medication during pregnancy.²⁰ They found that the cognitive scores of these children, as measured by the Wechsler intelligence test, were similar to that of a group of matched control children.

Therefore, we suggest that the lower cognitive scores observed in our study were attributable to carbamazepine rather than to maternal disease. Moreover, low scores were mainly observed in the children that also had the typical facial dysmorphic features of carbamazepine syndrome.

Although one third of the women had seizures during their pregnancies, there was no

association between the lower cognitive scores of the children or the appearance of clinical features of carbamazepine syndrome and the incidence of maternal seizures. Nor was there any association with the daily dose of carbamazepine. Scolnick *et al*¹⁸ and Waters *et al*¹⁷ also found no correlation between the occurrence of seizures during pregnancy and outcome.

In our study, the six children with carbamazepine syndrome have an IQ or DQ below 90. Cognitive function is directly influenced by parental IQ and socioeconomic status.²¹ We did not measure the IQ of any of the parents of the children participating in our study. However, the socioeconomic status of the parents of the children with carbamazepine syndrome was not different from that of the rest of the group, or from that of the controls.

The results of follow up studies in children born to epileptic mothers treated with carbamazepine during pregnancy are inconsistent, inasmuch as there are different reports on the presence or absence of a carbamazepine syndrome, and the percentage of affected children. Phenytoin embryopathy is now considered to be a result of genetic predisposition because the anomalies seem to appear mainly in children where the activity of the enzyme epoxide hydrolase in amniocytes is below 30–35% of normal,^{22–24} pointing to a parentally transmitted anticonvulsant embryopathy.²⁵ Although the epoxide pathway seems to be the predominant metabolic pathway for carbamazepine, converting it to 10,11 epoxide, this metabolite seems to be as active as the parent compound.^{1–8} In contrast to the arene oxide intermediate of phenytoin, which is considered to be toxic, there is no proof that 10,11 carbamazepine epoxide is toxic.^{1–13} Carbamazepine epoxide is actually found in the plasma of treated patients. It was found to be neither cytotoxic nor mutagenic, and the lethal dose is the same as that of carbamazepine.^{1–13} However, it is unproved whether carbamazepine epoxide is devoid of teratogenic effects. It is plausible that this or other enzymatic pathways may play a major part in carbamazepine induced embryopathy. Moreover, a low activity of epoxide hydrolase was found by Raymond *et al* in the amniocytes and placentas of two children with what appears to be carbamazepine induced congenital anomalies.²⁴ It is therefore possible that there are genetic differences in the prevalence of people with low activity of epoxide hydrolase (or other enzymes) between populations, which may explain the different rates of carbamazepine induced congenital anomalies.

We found no difference in the ethnic origin of the children with and without carbamazepine syndrome in our study.

Dr B Beuhler of the University of Nebraska Medical Center, Omaha, Nebraska has analysed for us 13 samples of amniocytes from epileptic women treated with phenytoin. In three cases enzyme activity was below 35%. The test was performed to evaluate the risk of the fetuses exposed in utero to phenytoin to develop phenytoin embryopathy. This is a rela-

tively high rate and if low activity of epoxide hydrolase is related to carbamazepine embryopathy, it may explain the relatively high rate of carbamazepine syndrome in our study. We would therefore also expect to have a high prevalence of phenytoin embryopathy in our country, and these studies are now beginning to assess this.

We wish to thank Dr L Schwartz, Dr J Arnon, and Mr J Segal for their valuable help in this study, and to Mrs Z Ronen for the typing.

- 1 Macdonald R. Carbamazepine mechanism of action. In: Levy H R, Dreifuss F E, Mattson RH, Meldram BS, Penry JK, eds. *Antiepileptic drugs*. 3rd Ed. New York: Raven Press, 1989:447-445.
- 2 Bertollini R, Mastroiacovo P, Segni G. Maternal epilepsy and birth defects: a case-control study in the Italian Multi-centric Registry of Birth Defects (IPIMC). *Eur J Epidemiol* 1985;1:67-72.
- 3 Battino D, Binelli S, Caccamo ML, et al. Malformations in offspring of 305 epileptic women: a prospective study. *Acta Neurol Scand* 1992; 85:204-7.
- 4 Czeizel AE, Bod M, Halasz P. Evaluation of anticonvulsant drugs during pregnancy in a population-based Hungarian study. *Eur J Epidemiol* 1992; 8:122-7.
- 5 Dansky LV, Finnell RH. Parental epilepsy, anticonvulsant drugs, and reproductive outcome: epidemiologic and experimental findings spanning 3 decades. Human studies. *Reprod Toxicol* 1991;5:301-35.
- 6 Lindhout D, Meinardi H, Meijer JWA, Nau H. Antiepileptic drugs and teratogenesis in two consecutive cohorts: changes in prescription policy paralleled by changes in pattern of malformations. *Neurology* 1992;42 (suppl 5):94-110.
- 7 Van der Pol, MC, Hadders-Algra M, Huisjes M J, Touwen BCL. Antiepileptic medication in pregnancy. Late effects on the children's central nervous system development. *Am J Obstet Gynecol* 1991;164:121-8.
- 8 Lindhout D, Hoppener RJ, Meinardi H. Teratogenicity of antiepileptic drug combinations, with special emphasis on epoxidation (of carbamazepine). *Epilepsia* 1984;25:77-83.
- 9 Shakir RA, Abdulwahab B. Congenital malformations before and after the onset of maternal epilepsy. *Acta Neurol Scand* 1991;84:153-6.
- 10 Kaneko S, Otani K, Kondo T, et al. Malformation in infants of mothers with epilepsy receiving antiepileptic drugs. *Neurology* 1992;42 (suppl):68-74.
- 11 Jones KL, Johnson K.A, Adams J, Lacro RV. Teratogenic effects of carbamazepine [letter]. *N Engl J Med* 1989;321:1480-1.
- 12 Jones KL, Lacro RV, Johnson KA, Adams J. Pattern of malformations in the children of women treated with carbamazepine during pregnancy. *N Engl J Med* 1989;320:1661-6.
- 13 Omtzigt JGC, Los FJ, Meijer JWA, Lindhout D. The 10,11-epoxide-10,11-diol pathway of carbamazepine in early pregnancy in maternal serum, urine and amniotic fluid. Effects of dose, comedication in relation to outcome of pregnancy. *Ther Drug Monit* 1993;15:1-10.
- 14 Bayley scales of infant development. New York: Psychological Co, 1978.
- 15 McCarthy's scales of child development. New York: Psychological Co, 1978.
- 16 Kraus V. The perception of professions in Israel. *Megamot* 1981;26:283-94.
- 17 Waters CH, Bellai I, Gott, PS, Shen P, De Giorgio CM. Outcomes of pregnancy associated with antiepileptic drugs. *Arch Neurol* 1994;51:250-3.
- 18 Scolnik D, Nulman I, Rovet J, et al. Neurodevelopment of children exposed in-utero to phenytoin and carbamazepine monotherapy. *JAMA* 1994;271:767-70.
- 19 Jeret JS. Neurodevelopment after in-utero exposure to phenytoin and carbamazepine [letter]. *JAMA* 1994;272:850.
- 20 Holmes LB, Rosenberger PB, Harvey EA. An evaluation of whether maternal epilepsy (no drugs) is associated with an increased rate of cognitive dysfunction. *Teratology* 1995;51:165 (abst 37).
- 21 Ornoy A, Michailovskaya V, Lukashov I, Bar-Hamburger R, Harel S. The developmental outcome of children born to heroin dependent mothers raised at home or adopted. *Child Abuse Negl* 1996;20:385-96.
- 22 Buehler BA, Delmont D, Van Waes M, Finell RH. Prenatal prediction of risk of the fetal hydantoin syndrome. *N Engl J Med* 1990;322:1567-72.
- 23 Buehler BA, Bick K, Delmont D. Prenatal prediction of risk of fetal hydantoin syndrome. *N Engl J Med* 1993;329:1660-1.
- 24 Raymond GV, Buehler BA, Finell RH, Holmes LW. Anticonvulsant teratogenesis: 3. Possible metabolic basis. *Teratology* 1995;51:55-6.
- 25 Holmes LB, Harvey EA, Brown KS, Hayes AM, Khoshbin S. Anticonvulsant teratogenesis: I. A study design for newborn infants. *Teratology* 1994;49:202-7.