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Findings in Children Exposed In Utero to Phenytoin and Carbamazepine Monotherapy: Independent Effects of Epilepsy and Medications

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Our objective was to evaluate the patterns of malformations in children exposed in utero to phenytoin (DPH) and carbamazepine (CBZ) monotherapy, and to compare them prospectively with matched mother-child pairs exposed to nonteratogens, and to separate the effects of antiepileptic drugs (AEDs) from those of epilepsy by collecting groups of untreated epileptics and those treated with DPH and CBZ for conditions other than epilepsy. This was a prospective, controlled, and blinded observational study. Thirty-six mother-child pairs exposed to CBZ monotherapy, 34 pairs exposed to DPH monotherapy, and 9 nonmedicated epileptic women and their children were compared with matched mother-child pairs exposed to nonteratogens. The control mothers were matched for maternal age, time of consultation, obstetric history, and socioeconomic status (SES). One main outcome measures a "blinded" morphological assessment of the offspring.

We found that minor anomalies were significantly more common among children of epileptics on either drug ($P = 0.01$) and among DPH-treated nonepileptic offspring ($P = 0.03$). Among epileptics, the relative risk for minor anomalies following DPH (2.1) was similar to that after exposure to either DPH ($P = 0.006$) or CBZ ($P = 0.01$). Increased rates of hypertelorism were detected among DPH-exposed offspring. High forehead, frontal bossing, malar hypoplasia, epicanthus and micrognathia were associated with untreated epilepsy, as well as with DPH and CBZ treatment. Am. J. Med Genet. 68:18–24, 1997 © 1997 Wiley-Liss, Inc.

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INTRODUCTION

Maternal epilepsy has been associated with higher rates of malformations in the offspring than in the general population [Schardein, 1985]. While women at risk of seizures during pregnancy should be treated with effective antiepileptic therapy, several drugs commonly used in epilepsy are teratogenic in humans. The fetal hydantoin syndrome (FHS) is characterized by growth and mental deficiencies, digit and nail hypoplasia and craniofacial anomalies. The exact rate of this syndrome among infants exposed to this drug has been estimated to be between 6% and 30% [Hanson and Smith, 1975; Kaneko, 1991]. Children with phenotypic characteristics of FHS have also been described among untreated epileptics, suggesting that fetal malformations are not necessarily caused by this antiepileptic medication. The etiology and severity of the underlying disease, genetic and environmental factors must also be considered [Shapiro et al., 1976; Janz, 1982].

During the last two decades, carbamazepine (CBZ) has been proven effective for various types of seizures [Olpe and Jones, 1983; Margcurgos, 1983]. Preliminary reports of its use in pregnancy were controversial with nonadverse and adverse fetal effects described. However, as in studies with phenytoin (DPH), these reports were not controlled for a variety of confounders that may affect pregnancy outcome.

While many groups have reported on malformations associated with these two drugs, no controlled studies have compared rates of minor anomalies of DPH and CBZ, the two major antiepileptics used during pregnancy. As important, no study has addressed in a controlled manner the rates of anomalies caused by the epilepsy itself.

Our goals in this prospective study were to evaluate the rates of developmental anomalies associated with

maternal phenytoin and carbamazepine monotherapy in the treatment of maternal epilepsy, and to separate the effects of antiepileptic drugs from those of epilepsy itself. The results of the neurobehavioral testing of most of this cohort were published recently [Scolnik et al., 1993].

PATIENTS AND METHODS

This protocol was approved by the Research Ethics Committee at the Hospital for Sick Children in Toronto. The study group consisted of groups of pregnant women treated with either DPH or CBZ monotherapy and an additional group of women with epilepsy who did not take medications during the index pregnancy and seen between 1987 and 1992 by the participating centers. Twenty-nine women were treated with DPH and 30 women with CBZ for idiopathic epilepsy.

The women were recruited either by the Motherisk Program at the Hospital for Sick Children, by neurologists at The North York General Hospital, Toronto, and the Toronto Hospital (Western Division), or by the Genetic Services at Oshawa General Hospital (Ontario). Each mother exposed to DPH or CBZ was paired with the next woman attending the Motherisk Clinic who matched the index mother on age (± 2 years), gravidity (± 1), parity (± 1), and socioeconomic class (± 2 points on the Hollingshead and Redlich scale) whose reason for attendance was counseling after gestational exposure to nonteratogens (e.g., penicillin, acetaminophen, dental x-ray), thus ensuring similar ages of the offspring. Mothers that ingested alcohol routinely or were binging were excluded from the study.

The following details were recorded for each woman (study and control) at the first visit during the first trimester of pregnancy: age, medical and obstetric history, clinical diagnosis, last menstrual period, time and dose of the antiepileptic drugs before and during pregnancy, and cigarette smoking and alcohol drinking before and during pregnancy. Details on pregnancy course, mode of delivery, and pregnancy outcome were retrieved from the medical records. Information on birth weight, neonatal course, and complications were obtained from the mothers within 6 months of delivery, and further details of psychomotor development were obtained by interviewing the mothers during the neurobehavioural testing and by a report from the children's pediatricians.

For morphological testing, all but 3 participating mothers and children (study and controls) were studied in our laboratory at the Hospital for Sick Children by a team of pediatricians, neurologists and geneticists. In 3 cases we located mothers who had originally resided in Toronto but who later moved to other Canadian cities, and they and their children were tested in a similar protocol. Informed consent was obtained from study and control group parents before the examinations.

The study groups were additionally divided into subgroups of those treated with DPH and CBZ for other conditions than epilepsy (e.g., neuralgias, psychiatric disorders, postsurgery prophylaxis), and were compared to their matched controls separately.

Malformations are structural abnormalities of embryonic origin present at birth [Heinonen et al., 1977; Eurocat Working Group, 1991]. Major malformations were defined by us as structural or functional defects for which medical or surgical intervention is necessary or a defect that can impair the child's future lifestyle. Minor anomalies were defined as unusual morphologic traits that are of no serious medical or cosmetic consequence to the patient [Smith, 1982] but that might signify a major malformation complex, a syndrome comprised of only minor anomalies or have a predictive value in identifying future neurobehavioral problems [Smith, 1982; Burdic et al., 1985].

The following anthropometric measurements were obtained by a single examiner (I.N.) unaware of the mother's gestational therapy: head circumference (OFC), height, weight, palm and finger lengths and canthal measurements. A flexible steel tape was applied above the supraorbital ridges anteriorly and the occipital prominence posteriorly to obtain the maximal OFC. Microcephaly was defined as head circumference below or equal to two standard deviations from the mean of children of the same age and sex. The length of the palm was measured by a tape from the distal volar wrist crease to the metacarpophalangeal joint of the middle finger. The length of the middle finger was obtained from the metacarpal joint to the tip of the distal phalanx.

Assessments of photographs of the children's faces, hands and toes were performed by a single clinical geneticist (D.C.) who was blinded. Facial characteristics were assessed from standardized frontal and lateral 9×7 cm photographs of the face. The children were asked to hold a comfortable pose with their mouth closed and the pictures were obtained from a distance of 125 cm. Examination of photographs allows minimization of the interobserver variability, reproducible and permits the use of other methods of assessments such as computerized morphometric assessment. Palms and fingers were photographed using a magnifying lens from a distance of 25 cm. Palm or finger hypoplasia were defined as length equal or less than the third centile for age and sex.

Two projective linear measurements were obtained with a 1-mm interval ruler with a bolted pointer directly from the orbits of the patients: the intercanthal and the binocular widths. The relationship between these two measurements was analyzed using the intercanthal index which is equal to the ratio between the intercanthal and binocular widths expressed in percent. The intercanthal width was considered abnormal (small or large) if it was outside 2 standard deviations of the normal range for age, sex and race. The degree of abnormality was defined as the distance between the measurement and the closest normal measurement, expressed as a percentage of the closest normal value: mild, $\leq 2.9\%$, moderate, 3% to 9.9% and severe, $\geq 10.0\%$ [Farkas et al., 1989].

Craniofacial and digital anomalies previously reported to occur in children of epileptic mothers exposed to antiepileptic drugs were assessed using the following checklist: high forehead, frontal bossing malar

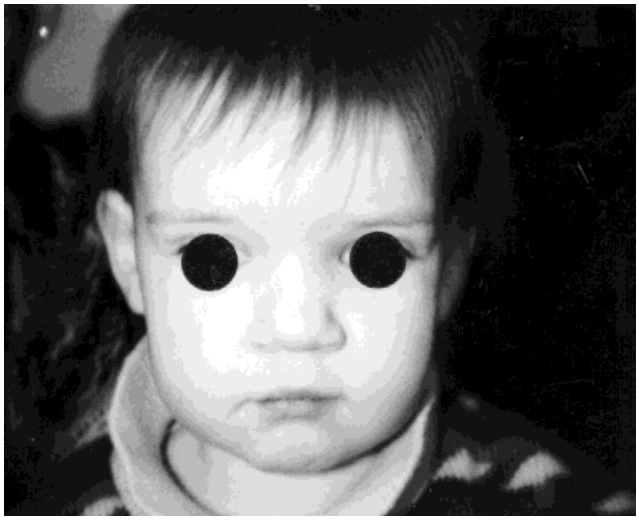

Fig. 1. High forehead, frontal bossing and wide nasal bridge in a patient exposed in utero to DPH.

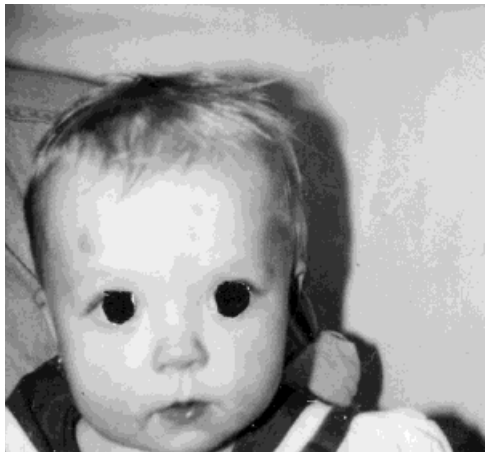

Fig. 3. High forehead, frontal bossing, wide depressed nasal bridge, epicanthal fold, narrow upper lip and micrognathia in a patient exposed in utero to DPH.

hypoplasia, epicanthal fold, strabismus, depressed nasal bridge, long philtrum, narrow upper lip, micrognathia, finger/toe nail hypoplasia, finger and/or toe hypoplasia. These characteristics were defined qualitatively by one clinical geneticist, blinded to the maternal exposure history. High forehead was considered when the forehead was disproportionally high relative to face. Frontal bossing was defined as a prominent forehead; malar hypoplasia was defined as flattening of the maxillary area. Epicanthal fold is a presence of vertical skinfold at the base of the nasal root near the inner canthus. Strabismus was recorded by observing eye deviation by the covering test, and was also based on previous diagnoses when appropriate. Depressed nasal bridge was considered as deep nasal root. Narrow upper lip and philtrum length were assessed qualitatively in relation to other parts of the face. Figures 1–4 demonstrate examples of typical findings. The parents were not assessed for dysmorphic features.

STATISTICAL ANALYSIS

Women and their offspring exposed to AEDs were compared to their controls in a large number of values by means of the Student t-test for paired data. Children of untreated epileptic women were compared to their controls in a similar way.

Comparisons between rates of specific endpoints were performed by the chi-square test and by Fisher exact test wherever appropriate. Odds ratios (OR) and relative risk estimates are presented with their 95% confidence intervals (CI).

RESULTS

A total of 36 mother-child pairs exposed to CBZ and 34 exposed to DPH were studied and compared with an equal number of matched controls. In addition, there

Fig. 2. Fingernail hypoplasia in a patient exposed in utero to DPH.

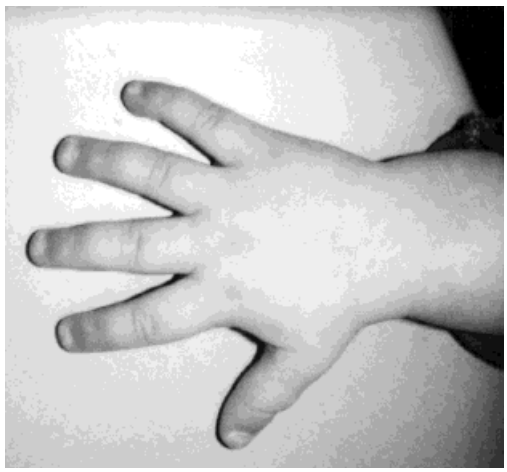

Fig. 4. Finger-toe abnormalities in a patient exposed in utero to CBZ.

were 3 cases of spontaneous abortions (2 in the CBZ group and 1 in the DPH group) and 2 therapeutic abortions (one for each drug). The recruited women treated with DPH had epilepsy except for 5 who received the drug prophylactically after craniotomy. Seven women in the CBZ group were not epileptic and were treated for other conditions (bipolar affective disorder in 3, glossopharyngeal neuralgia in one, trigeminal neuralgia in one and postcraniotomy prophylaxis in 2). None of the women in either group received concomitantly any other antiepileptic drug during the index pregnancy. An additional group of 9 epileptic women who did not receive drug therapy during the index pregnancy was recruited and matched to controls.

All treated women received either DPH or CBZ during the first trimester, 29 women took DPH throughout pregnancy, and 30 women continued taking CBZ throughout gestation. Twenty-three out of 29 women were taking DPH and 24 out of 30 took as a treatment CBZ for generalized tonic-clonic seizures. A few were treated for partial complex seizures (one with DPH and one with CBZ) or a combination of two types of seizures (9 with phenytoin and 5 with CBZ), 8 women treated with DPH and 6 with CBZ experienced one or two episodes of seizures during pregnancy ($P = 0.3$). The morphological findings in the groups with epileptic seizures was similar to that of nonseizing mothers. There was no correlation between the daily dose of either DPH or CBZ and number of malformations or anomalies.

Mothers from the study group were similar to their matched controls in many characteristics, including age at conception, gravidity, parity, rates of miscarriage, of cigarette smoking and alcohol consumption. No woman drank heavily or smoked more than 10 cigarettes per day. Offspring exposed to DPH or CBZ were similar to their controls in many neonatal and infancy characteristics, including gestational age, birth weight, proportions of modes of delivery, neonatal course, and time of attainment of psychomotor development according to the Denver scale (data not shown).

The mean OFC was not different between groups and subgroups. Microcephaly (≤−2 S.D.) was diagnosed in 2 of 33 (6%) available children exposed to DPH and in 3 of the 34 (8.8%) children exposed to CBZ (not significant) independent of the doses of AEDs. One of the microcephalic children in the DPH group had a microcephalic mother. There were no microcephalic children among the medicated nonepileptic or the nonmedicated epileptic subgroups.

After adjustment for maternal head circumference the difference between DPH and CBZ group was still not significant. One microcephalic child in the DPH group and one in the CBZ groups had low IQ (80 and 76, respectively). Weights and heights were available in 27 of DPH- and 33 of CBZ-exposed children. Five children of DPH group had height ≤−2 S.D. and one had ≤−2 S.D. weight, versus 4 children from CBZ group that had ≤−2 S.D. height and 2 children ≤−2 S.D.weight, (N.S.). However, the mean centile weight values in the DPH children was significantly different ($P = 0.04$) (47.1) than the CBZ (62.1) children. The median weight and height for DPH controls were 42.5 (4–97) and 47.5 (3–97) and for CBZ controls 40 (3–97) and for CBZ controls 40 (3–97) and 42.5 (3–97), respectively.

Malformations were observed in 3 (8.8%) of 34 DPH-exposed children and 2 (5.7%) of 35 CBZ exposures. Among the 34 DPH controls there were 2 (6%) malformations and among the 36 CBZ controls there were 2 (5.6%; Table I). The differences between the two groups and their controls were not significant.

One child in the DPH group was born without a distal phalan of the right index, another with hypospadias, and one with clubfoot. An additional child who suffered from massive adrenal hemorrhage was not classified as malformed. Both malformed children in the CBZ group had multiple anomalies (one of them was born with spina bifida and meningomyelocele, hydrocephalus, pneumothorax, hip dislocation and clubfoot; the second with inguinal hernia, hypospadias, cleft palate) and IQ 76 and 82, respectively. In the DPH control group, clubfoot (n = 1) and congenital heart disease (n = 1) were found. In the CBZ control group, there was one child with hip dislocation and a second with undescended testes.

The total number of minor anomalies and the distribution per child are shown in Tables II and III. The typical findings are summarized in Table IV. Children exposed to AEDs in utero had significantly more minor anomalies ($P < 0.01$) than their matched controls. There were no differences between the DPH and CBZ groups. The number of children with facial anomalies was significantly higher in children of nonepileptic mothers treated with DPH ($P = 0.03$) than in their controls.

TABLE I. Malformations*

	DPH			CBZ		
Group	n	No. of malf.	*P*	n	No. of malf.	*P*
Study	34	3 (8.8%)	NS	35	2 (5.7%)	NS
Control	34	2 (6%)		36	2 (5.6%)	
	Case 1: Clubfoot Case 2: Hypospadias Case 3: Missing distal phalang of right index			Case 1: Microcephaly, hypospadias, inguinal hernia, cleft palate Case 2: Spina bifida, meningomyelocele, hip dislocation, hydrocephaly, pneumothorax, club foot		

* NS, not significant.

TABLE II. Children With Minor Anomalies*

Groups	DPH Total no.	DPH No. of anomalies	DPH RR[a]	CBZ Total no.	CBZ No. of anomalies	CBZ RR
Study	33	26		33	26	
Control	33	16	2.122	34	17	2.073

* $P < 0.01$.
[a] RR, relative risk.

The values of the intercanthal index are given in Table V. The total number of children with hypertelorism as well as the number of severe and moderate cases were significantly higher in the DPH-treated group than among their controls ($P = 0.04$). The mean intercanthal index (40.2) was similar in the DPH group and their matched controls (39); the values were 38.4 and 37.4 in the CBZ-exposed children and their controls (N.S.).

Finger and palm lengths were not different in any of the AED groups. Seventeen children of the DPH group had fingernail and/or toenail dysplasia versus 9 of their matched controls ($P = 0.02$). However, there was no significant difference between the two drug groups ($P = 0.4$). Finger and toe anomalies, including tapering, were found in 6 children in the DPH group (3 children with tapering, one with absence of the distal phalan of the right index, one with clinodactyly of both 5th fingers and one with short toes), and in 2 children of their controls (one with tapering and one with short thumbs); $P = 0.1$). Four children in the CBZ group (3 with tapering and 1 with clinodactyly of the 5th fingers) versus 0 in their control group had finger abnormalities ($P = 0.05$).

DISCUSSION

The incidence of malformations in children of epileptic mothers has been reported to be higher than in the general population. Careful analysis of available prospective studies [Kelly et al., 1994] suggests that many of the minor craniofacial anomalies in these children, previously considered to be the consequence of intrauterine exposure to AEDs, may in fact be linked to epilepsy itself and may be genetically determined. It is possible that the anticonvulsant medications increase the frequency of anomalies that are already genetically predicted. Minor anomalies may be caused by different mechanisms [Spranger et al., 1982; Cohen, 1982]. They arise during phenogenesis, persist throughout life and may serve as indicators of altered morphogenesis, thus suggesting the presence of a more serious underlying defect. Teratogenic insult during gastrulation could reduce the cell population of the early neural plate, so that there are insufficient cells to form a normal size forebrain.

The large amount of physiologic cell deaths in the neural plate during gastrulation makes them very vulnerable to teratogens [Sulik et al., 1988]. Head defects are the severe end of abnormalities that extend to relatively mild facial and central nervous system (CNS) anomalies. Ocular hypotelorism, iris colobomas, flat nasal bridge and midface hypoplasia can all be induced by damage during gastrulation [Sulik and Johnson, 1985]. Furthermore, patterns of associated anomalies are important in the diagnosis of specific known malformation syndromes [Smith, 1982]. Examination of the pattern of minor anomalies is therefore important before one makes any conclusions about the fetal effects of AEDs.

Rates of minor anomalies and their risk have varied in different studies, but at the present time no controlled studies using anthropometric methods have compared rates of abnormality associated with DPH and CBZ monotherapy, considering the complex interaction between epilepsy, genetic and environmental factors. Our study addresses these points by performing a controlled, blinded assessment and examining unique groups of untreated epileptics on the one hand and a group treated with AEDs for conditions other than epilepsy.

Our data confirm the previously shown increased risk of minor anomalies among offspring of medicated epileptics. As we found similar rates among DPH-treated nonepileptics, it is conceivable that this antiepileptic medication has a causative role in the appearance of some minor anomalies.

Microcephaly has been suggested to be a common sign of AEDs teratogenicity. The risk of microcephaly in children with intrauterine AEDs exposure has varied among studies from no risk [Kelly et al., 1984] to 25–30% [Hauson et al., 1976; Vent et al., 1982]. Gaily et al. [1990] proposed that genetic causes may contribute to the cause of reduced head circumference in AED-exposed children. Our DPH and CBZ groups had 6% and 8.8% rates of microcephaly, respectively, probably higher than the 1.9% prevalence observed in a normal school population [Sells, 1977]. When compared to their controls, these figures did not reach a statistical level of significance, possibly due to insufficient sample size.

Children exposed in utero to AEDs had significantly more minor anomalies than their controls; a similar trend of some anomalies was shown among offspring of

TABLE III. Number of Minor Anomalies Per Child

	0	1	2	3	4	5	6	7	8	9	Total
DPH	3	0	2	6	4	5	5	2	2	2	139
DPH control	12	6	1	3	8	1	2	1	—	—	73
CBZ	1	9	1	0	2	6	7	6	2	—	149
CBZ control	15	5	2	0	2	3	2	3	3	—	89

TABLE IV. Type of Anomalies

Anomalies	DPH[a] Study no.	DPH Control no.	DPH P	DPH RR	CBZ Study no.	CBZ Control no.	CBZ P	CBZ RR
High forehead	22	15	0.05	1.665	22	14	0.03	1.722
Frontal bossing	21	13	0.04	1.647	21	14	0.03	1.699
Malar hypoplasia	22	9	0.001	2.258	19	10	0.02	1.778
Toe-finger-nail dysplasia	17	9	0.02		15	7	0.02	
Micrognathia	7	2	NS		15	4	0.02	2.105
Epicanthal folds	15	7	0.03	1.667	11	8	NS	
Depressed nasal bridge	6	2	NS		2	3	NS	
Long philtrum	12	9	NS		20	14	NS	
Toe-finger abn.	6	2	NS		4	0	0.05	
Narrow upper lip	7	5	NS		12	10	NS	
Strabismus	1	1	NS		0	1	NS	
High arched palate	2	1	NS		3	1	NS	

[a] NS, not significant; RR, relative risk.

TABLE V. Intercanthal Index (Mean + SD)

	DPH Study 8/31	DPH Study %	DPH Controls 4/32	DPH Controls %	CBZ Study 2/30	CBZ Study %	CBZ Controls 3/36	CBZ Controls %
Severe	1	3.2	0	—	0	—	1	2.7
Moderate	6	19.2	1	3.1	1	3.3	1	2.7
Mild	1	3.2	3	9.3	1	3.3	1	2.7

nonepileptics exposed to DPH. Craniofacial and digital anomalies previously reported as typical of the fetal hydantoin syndrome [Hansen and Smith, 1975] were included in our minor anomaly checklist. As expected, we found that epicanthal fold and hypertelorism were associated with DPH treatment; however, malar hypoplasia and micrognathia occurred more commonly also among offspring of nontreated epileptics. Conversely, high forehead, frontal bossing and malar hypoplasia were associated with untreated epilepsy, as well as with DPH and CBZ treatment. This suggests that different features of anomalies may be caused by the epilepsy than those caused by these drugs. Furthermore, a synergistic effect of drug and epilepsy may give rise to different malformations.

Hypertelorism has been reported in 23% to 52% of exposed children [Hansen et al., 1976; Rating et al., 1982]. However, in previous studies the data were collected by unblinded clinical observation and could be affected by observer bias. Using precise anthropometric methods of measuring of the intercanthal distance, we found a 25% rate of hypertelorism among children in the DPH group versus 11% in their controls; severe and moderate cases were significantly more common in the DPH group.

In summary, the present study is unique in separating the effects of epilepsy from the two most commonly used AEDs. Because most women with epilepsy are treated with these drugs, the "untreated" epileptic group was relatively small, as were the groups of nonepileptics treated by DPH and CBZ. While larger numbers in these groups would make the conclusions stronger, the effect size on some morphologic finding was large enough to allow the conclusion that the drugs and the epilepsy have independent effects on the developing fetus. DPH appears to be more teratogenic than CBZ as related to minor anomalies. Our previous analysis of neurotoxicity reveals DPH to be also substantially more teratogenic to the developing brain [Scolnik et al., 1993].

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REFERENCES

Burdick AB, Bixler D, Puckett CL (1985): Genetic analysis in families with van der Woude syndrome. J Craniofac Genet Dev Biol 5: 181–208.

Cohen MM (1982): Malformations, deformations, and disruptions. In Cohen MM (ed): "The Child With Multiple Birth Defects, Chap. 1." New York: Raven Press, pp 1–26.

Eurocat Working Group (1991): Surveillance of congenital anomalies, 1980–1988. Brussels: Eurocat Working Group.

Farkas LG et al. (1989): Orbital measurements in 63 hyperteloric patients. Differences between the anthropometric and cephalometric findings. J Cranio-Max, Fac Surg 17:249–254.

Gaily EK, Granstrom ML, Miilesmaa VK, Ali M, Bardy AM (1990): Head circumference in children of epileptic mothers: Contributions of drug-exposure and genetic background. Epilepsy Res 5: 217–222.

Hanson JW, Smith DW (1975): The fetal hydantoin syndrome. J Pediatr 87:285–290.

Hanson JW, Myrainthopoulos NC, Sedgwick HMA, Smith DW (1976): Risks to the offspring of women treated with hydantoin anticonvulsants, with emphasis on the fetal hydantoin syndrome. J Pediatr 89:662–688.

Heinonen OP, Slone D, Shapiro S (1977): "Birth Defects and Drugs in Pregnancy." Littleton, Massachusetts: Publishing Sciences Group.

Janz D (1982): On major malformations and minor anomalies in the offspring of parents with epilepsy: Review of the literature. In: Jayz D, Dam M, Richeus A, Bossi L, Helge M, Schmidt D (eds): "Epilepsy, Pregnancy, and the Child." New York: Raven Press, pp 211–222.

Kaneko S (1991): Antiepileptic drug therapy and reproductive consequences; functional and morphologic effects. Reprod Toxicol 5: 179–198.

Kelly TE, Edwards P, Rein M, Miller JQ, Dreifuss FE (1984): Teratogenicity of anticonvulsant drugs. II. A prospective study. Am J Med Genet 19:435–443.

Margcurgos PJ, Post DM, Patel J, Zauder K, Pharma A, Weiss S (1983): Specific and potent inter-action of carb with brain adenosine receptors. Eur J Pharmacol 93:175–182.

Olpe HR, Jones RSG (1983): The action of anticonvulsant drugs on the firing of neurons: selective, activating effect of carbamazepine. Eur J Pharmacol 91:107–110.

Rating D, Jager-Roman E, Koch S, Gopfert-Geyer I, Helge H (1982): Minor anomalies in the offspring of epileptic parents. In Janz D, Dam M, Richeus A, Bossi L, Helge H, Schmidt D (eds): "Epilepsy, Pregnancy and the Child." New York: Raven Press, pp 283–288.

Schardein J (1985): Chemically Induced Birth Defects." New York, NY: Marcel Dekker Inc., pp 142–189.

Scolnik D et al. (1993): Neurodevelopment of children exposed *in utero* to phenytoin and carbamazepine monotherapy. JAMA 271:767–770.

Sells CJ (1977): Microcephaly in a normal school population. Pediatrics 59:262–265.

Shapiro S, Slone D, Hartz SC, Rosenberg L, Siskind V, Monson RR, Mitchell AA, Heinonen OP (1976): Anticonvulsants and parental epilepsy in the development of birth defects. Lancet 1:272–275.

Smith DW (1982): "Recognizable Patterns of Human Malformations, 3rd ed." Philadelphia: W.B. Saunders, p 573.

Spranger J, Benirschke K, Hall JG, et al. (1982): Errors of morphogenesis: Concepts and terms. J Pediatr 100:160–165.

Sulik KK, Johnston MC (1985): Embryonic origin of halopronencephaly: Interrelationships of the developing brain and face. Scan Microsc 1:309–322.

Sulik KK, Cook CS, Webster WS (1988): Teratogens and craniofacial malformations: Relationship to cell death. Development 103 (Suppl): 213–231.

Vert P, Deblay MF, Andre M (1982): Follow-up study on growth and neurologic development of children born to epileptic mothers. In Janz D, Dam M, Richens A, Bossi L, Helge H, Schmidt D (eds): "Epilepsy, Pregnancy and the Child." New York: Raven Press, pp 433–436.