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BRIEF COMMUNICATION

Valproate teratogenicity and epilepsy syndrome

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Summary

Maternal valproate (VPA) use is associated with a significant risk for congenital malformations in the exposed fetus. Since VPA is commonly used in epilepsy syndromes with a presumed genetic cause (idiopathic epilepsies), it is possible that maternal genetic background contributes to this outcome. We reviewed responses to telephone questionnaires and medical records, when available, of enrollees in the North American Antiepileptic Drug Pregnancy Registry, classifying reason for treatment as idiopathic generalized epilepsy (IGE), partial epilepsy (PE), nonclassifiable epilepsy (NCE), or not epilepsy (NE). Of 284 VPA-exposed pregnancies, 30 (11.0%) were associated with malformations: IGE = 15/126 (12%), PE = 4/28 (14%), NCE = 9/105 (9%), NE = 2/25 (8%) ($p > 0.7$ for all comparisons). There was a trend toward increased malformation risk with higher VPA doses ($p = 0.07$). VPA, and not the underlying genetic syndrome, seems to be associated with the elevated risk for malformations in the drug-exposed fetus.

KEY WORDS: Antiepileptic drug, Idiopathic generalized epilepsy, Birth defects, Teratogenicity.

There is controversy as to whether epilepsy itself contributes to antiepileptic drug teratogenicity (Holmes et al., 2001). If specific epilepsy syndromes, particularly those thought to have a strong genetic basis, were associated with a higher risk of congenital malformations, then the underlying disease could confound the teratogenic risk of a drug used to treat such conditions. Some of the idiopathic generalized epilepsies (IGEs), such as juvenile myoclonic or juvenile absence epilepsy, do not typically remit before the patient reaches childbearing age and are often treated with valproic acid (VPA) (Beghi et al., 2006). Multiple studies suggest that this drug carries an elevated risk of teratogenicity, which may be dose-related (Mawer et al., 2002; Wide et al., 2004; Alsdorf & Wyszynski, 2005; Artama et al., 2005; Wyszynski et al., 2005; Meador et al., 2006; Morrow et al., 2006; Vajda et al., 2006). We therefore sought to determine, from answers to questionnaires and medical records collected by the North American Antiepileptic Drug Pregnancy Registry, whether there is an association between IGE and the presence of major congenital malformations in offspring of women exposed to VPA.

Methods

The method of data collection and identification of congenital malformations utilized by the North American Antiepileptic Drug Pregnancy Registry has been described previously (Wyszynski et al., 2005). Thecurrent data set consisted of a telephone-administered questionnaire and, when available, the medical records of mothers exposed to VPA as monotherapy in the first trimester of gestation. Data were collected between September 1997 and January 2007. The questionnaire included items pertaining to age at epilepsy onset, presumed etiology, and seizure manifestations, including tonic–clonic convulsions, staring spells (either absence or complex partial seizures), myoclonic jerks, and seizure auras. Medical records were reviewed to confirm this information and also results of neuroimaging and electroencephalographic (EEG) studies and, when available, syndrome diagnosis as determined by the treating neurologist.

Two board-certified neurologist-epileptologists (E.B.B. and B.A.D.) reviewed independently all questionnaires and medical records and classified each subject as

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follows: IGE, partial epilepsy (PE), nonclassifiable epilepsy (NCE), nonepilepsy (NE; e.g., migraine, psychiatric diagnosis). Because of missing data, firm rules could not be applied universally to these classifications. An IGE diagnosis required typically an age of onset between ages 3 and 25 years, an unknown or hereditary etiology, tonic-clonic seizures, and at least one of the following: myoclonic jerks while awake, an EEG showing generalized discharges, or a specific syndrome diagnosis by an epileptologist, identified as a neurologist with membership in the American Epilepsy Society or working at a Comprehensive Epilepsy Center. Disagreements between the raters were resolved by consensus, with doubtful cases assigned the NCE classification.

The primary outcome data were categorical classifications regarding the presence or absence of major congenital malformations in relation to diagnosis. Statistical significance was analyzed by means of Fisher's exact test, with a significance criterion of $p < 0.05$, two-tailed. We also analyzed daily VPA doses during the first trimester, most at the time of last menstrual period, using the unpaired Student's t-test and nonparametric Median Test to compare doses between the mothers of children with and without malformations and Fisher's exact test to compare malformation risks at various dose thresholds. Consistently obtained serum concentrations of VPA were not available on many patients.

Results

VPA-exposed pregnancies (284) were identified, of which 30 (11.0%, including one set of dizygotic twins, which counted as a single pregnancy) were associated with major congenital malformations, as previously defined (Wyszynski et al., 2005). Interrater agreement on diagnostic classification exceeded 80%. The final diagnoses were: IGE = 126, PE = 28, NCE = 125, NE = 25. Medical records were available on 47.1% (134/284) of the women; the others did not provide written permission to send records. The records obtained varied in completeness. The women with medical records available were more likely to be classified as IGE ($p < 0.0001$). Those without records were more likely to be classified as NCE ($p < 0.0001$) or NE ($p = 0.01$).

Among the group of mothers with IGE, 15/126 (12%) had children with malformations, as opposed to 4/28 (14%) with PE, 9/105 (9%) with NCE, and 2 (8%) without epilepsy (NE) (Table 1). Comparisons between IGE and PE ($p = 0.75$) and between all epilepsy groups and NE ($p = 1.00$) showed no differences. For the comparison between IGE and PE, the ratio of malformation risk was 0.83, with a 95% confidence interval of 0.30–2.32.

First trimester VPA doses were available for 30/30 pregnancies resulting in malformations, and for 252/254 pregnancies without malformations. Median daily dose across all groups was 750 mg, and mean daily doses were 1075 (±518) mg in the malformation group and 902 (±497) mg in the no malformation group; this difference trended toward significance on parametric testing ($t = 1.795$, $df = 280$, $p \leq 0.07$) and reached significance on the Median Test ($p \leq 0.04$). Of note is that the specific preparation used was recorded for only 46 subjects, fewer than one-fifth of the total, and Depakote-ER, which has only approximately 90% bioavailability compared to other preparations, was specified in 7 (4 IGE and 3 NCE).

Table 1. Number (percentage) of pregnancies with major congenital malformations for each maternal diagnosis

Type of epilepsy	Malformation		Total pregnancies
	Yes	No	
Idiopathic generalized epilepsy	15[a] (12)	111 (88)	126
Partial epilepsy	4 (14)	24 (86)	28
Nonclassifiable epilepsy	9 (9)	96 (91)	105
Nonepilepsy	2 (8)	23 (92)	25
Totals	30	254	284

[a]There were 16 offspring, including a set of twins.

For each diagnostic group, mean (±SD) daily VPA doses in milligrams were: IGE 920 (±477), PE 1042 (±645), NCE 895 (±482), and NE 894 (±543). These values were not significantly different from each other by one-way analysis of variance (ANOVA) ($p = 0.60$), and the PE values by unpaired Student's t-tests were not significantly different from the IGE group ($p = 0.26$) or from the other three groups combined ($p = 0.19$). Median daily doses were 750 mg for the IGE, NCE, and NE groups and 875 mg for the PE subjects. No threshold dose at which risk significantly increased could be identified, although there was a strong trend toward lower risk at <750 mg/day (5.5% versus 15.1% for doses ≥750 mg/day, $p = 0.063$). The risk at doses above 1100 mg/day was 16% versus 9% for lower doses ($p = 0.11$).

Discussion

The proportion of pregnancies resulting in malformations did not differ in relation to epilepsy syndrome. Although the Registry was not designed to address this question, the frequency of malformations was actually lower in patients with IGE, where genetic factors are likely to play a major role, than in those with PE, where environmental factors are considered more likely. Furthermore, our confidence interval argues that maternal IGE would be very unlikely to increase the risk of malformations more than twofold over PE, although many more cases would be required to exclude a smaller effect. In fact, assuming a 4.5 ratio of IGE to PE cases, as seen in our sample, 2086 IGE and 459 PE

subjects would be required to detect malformation risks of 15% in the IGE group and 10% in the PE group with 80% power. Similar to several previous studies (Mawer et al., 2002; Alsdorf & Wyszynski, 2005; Wyszynski et al., 2005; Meador et al., 2006; Morrow et al., 2006; Vajda et al., 2006), there was a suggestion of a dose-dependent effect; the high frequency of malformations in the PE group may in part be explained by the finding that this group also had the highest mean daily VPA dose, although this difference did not reach statistical significance.

It is likely that genetic factors do play a role in teratogenicity of VPA, as well as other drugs; alterations in genes for histone deacetylase, placental drug transport proteins, or methylenetetrahydrofolate reductase have been proposed (Atkinson et al., 2007; Dean et al., 2007). Research is needed to identify the genetic differences related to the susceptibility of the fetus to VPA and the other anticonvulsant drugs. Such studies may determine whether or not these differences are more common in women with IGE, PE, or other medical conditions. In any case, the present data reinforce the recent recommendations of some authorities to avoid VPA in women of childbearing age whenever possible, and if VPA is needed to control convulsive seizures, to use the lowest effective dose (Meador et al., 2006)—regardless of underlying epilepsy syndrome.

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