The association between congenital malformations and second generation antiepileptic drugs- retrospective case-controlled study in a Hungarian population

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NEW SZÉCHENYI PLAN

BACKGROUND

Epilepsy is one of the most frequent neurological disorders, with an overall estimated prevalence of 0.5–0.7% in western countries [1]. The prevalence in pregnant women has been estimated to be 0.3–0.5% [2]. At least 25% of people with epilepsy are women of child-bearing age; the majority of them are seizure free with one or more antiepileptic drugs (AEDs) [3]. Seizure type and epilepsy syndrome are the fundamental determinants for the treatment choice in seizure disorders. However, different AEDs are characterized by different side effect and interaction potentials, and individual patients may have different tolerance and pharmacokinetic profiles. Sex, age, genetic profile and co-morbidity are important factors [4–6]; pregnancy represents a unique situation in these respects. All of these elements need to be considered when selecting an AED for the individual patient. The era of the second AED generation started in the 1990s when several new drugs were launched in rapid succession [7,8]. This marked the end of a 20-year long hiatus after the introduction of valproate (VPA), the last of the first-generation AEDs. The second-generation AEDs did not generally prove to be more effective than the first generation, but many of them are better tolerated, less prone to drug interactions and have more predictable pharmacokinetics [9,10]. During the last two decades, much attention has been directed towards problems with the use of first-generation AEDs in women: hormonal and metabolic disturbances, pharmacokinetic interactions with contraceptives and pregnancy-related problems, including adverse reactions in the offspring. VPA, which for many years was a first-choice drug in generalized epilepsy of both sexes, has demonstrated the highest teratogenic potential among the first-generation AEDs [11]. The desire to avoid VPA has led to a wider use of second-generation AEDs in fertile women, particularly the novel broad spectrum drugs in women with generalized epilepsies. New drugs devoid of interactions with hormonal contraceptives are also preferred in fertile women. Lamotrigine (LTG), gabapentin (GBP) and topiramate (TPM) were used to a larger extent in female than in male patients, whereas carbamazepine (CBZ), VPA, phenytoin and oxcarbazepine (OXC) were more frequently used in male patients [12].Recent clinical research has demonstrated that physiological changes during different stages of gestation may change the pharmacokinetics of AEDs significantly and with great interindividual variation [14]. Some second-generation AEDs are more prone to these changes than others. Nevertheless, most of these difficulties can be dealt with, although close, time-consuming clinical and laboratory monitoring may be required. Treatment with AEDs may indeed be complex in females who are, or wish to become, pregnant. The balance between maternal and fetal health risks can be very demanding. Profound knowledge of these issues is necessary, not only to create a rational treatment strategy, but also to provide appropriate information to the woman wishing to conceive while being treated with AEDs.

PURPOSE

Our purposes were three folds: First to explore the relationship between the congenital anomalies and maternal exposure of new generation antiepileptic drugs, and second to analyze the incidence of obstetrical complications among women with epilepsy relative to a neurologically healthy population, and finally to characterize the seizure pattern during pregnancy and after delivery.

PATIENTS AND METHODS

All pregnant patients (n=86) with epilepsy who required obstetrical care at the Department of Obstetrics and Gynecology and were also treated in the Department of Neurology in Szeged, were enrolled in our study between 1 January 2000 and 31 December 2011.The control group, selected by simple random sampling, consisted of 86 age-matched pregnant women with no diagnosis of epilepsy or any other neuro-psychiatric disorder. For comparison of different perinatal parameters were performed χ^2 test and independent sample t-test. Relationships between congenital anomalies and second generation AEDs were examined by non-parametric Kruskal-Wallis analysis. Results were considered significant with a $p < 0.05$.

RESULTS AND CONCLUSIONS

In our 86 pregnant patients with epilepsy, the mean age was 29.4 years ± 5.37, and at the control group it was 30 ± 5.52 years. The mean gestational age was 38.54 ± 2.09 and 38.37 ± 2.16 weeks in the two group ($p > 0.05$). The average body weight of the newborn was 3186.25 ± 563.12 g in women with epilepsy, and 3246.7 ± 574.6 g was in women without epilepsy.

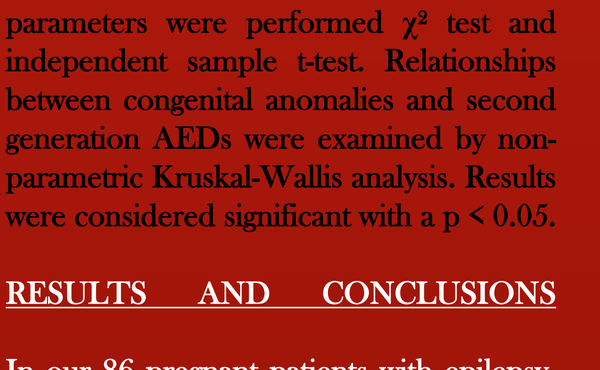
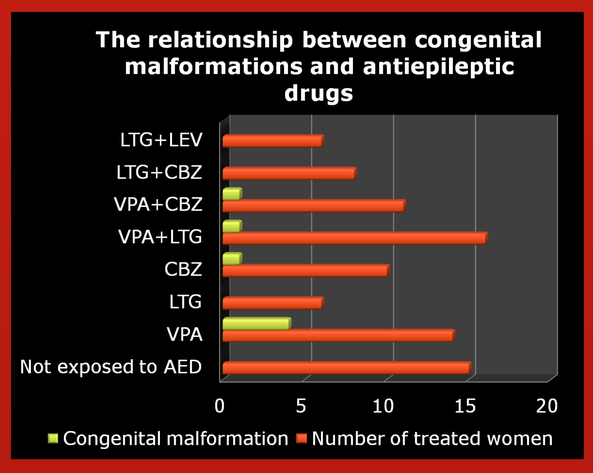


Figure 1. Seizure frequency among women with epilepsy: (0) 60 % of these women with epilepsy had no seizure during this period. (1) Seizure frequency (22%) during pregnancy, (2) at delivery (1%), and (3) in the postpartum period 2%.

The mean malformation rate (MMR) was 9.8% in all AED exposed mother's newborns, which were similar than in the literature described. [13] In our study, the MCM was greater for pregnancies exposed only to valproate compared to all other AED (p=0,054).

Figure 2.



The rate of caesarean sections was significantly different for the two groups (46.51% vs 38.37%, p = 0.014,), these results similar than reported in the literature [14-16].

Table 1.

Comparison of delivery mode and neonatal parameters in the case and control groups

	Women with epilepsy (n=86)		Women without epilepsy (n=86)		p
	n	%	n	%	
Prematurity	12	13.95	9	10.46	N. S.
Intrauterine growth retardation (IUGR)	5	5.81	1	1.16	N. S.
Assisted vaginal delivery	39	45.34	50	58.14	0.026
Caesarean section	40	46.51	33	38.37	N.S.
Missed abortion	6	7	0	0	0.015
Post-term birth	21	24.41	21	24.41	N.S.

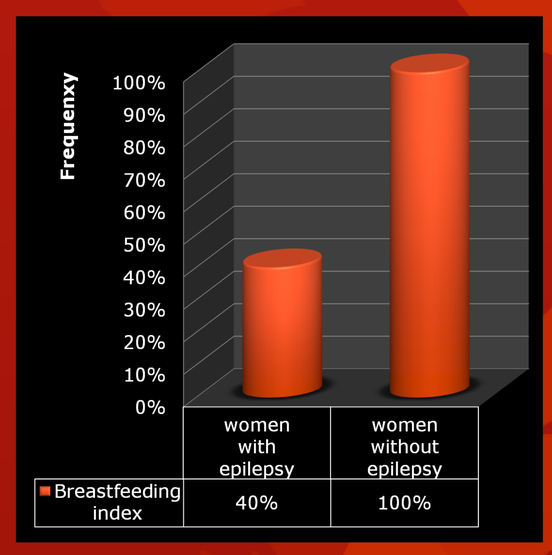
Foetal chest circumference and length were significantly different from those in the control healthy group ($p < 0.001$ and $p < 0.001$).

Umbilical cord blood pH was significantly lower in the epileptic group ($p = 0.028$). 1-minute, 5-minute Apgar scores were significantly lower in newborns of mothers with epilepsy ($p < 0.001$) compared to non-epileptic mother's newborns. Samrén et al. reported a strong correlation between the maternal exposure of AED and significantly lower birth weight, intrauterine growth restriction (IUGR) and smaller head circumference of the newborn [17]

Table 2.

Parameters of neonates women's with and without epilepsy

	Women with epilepsy (n=86)		Women without epilepsy (n=86)		p
	mean	SD	mean	SD	
1 minute Apgar	8.84±1.6		9.73±0.68		<0.001
5 minute Apgar	9.62±0.8		9.8±0.42		<0.001
10 minute Apgar	10.85±8.97		9.94±0.28		N.S.
Chest circumference	32.4±2.5		32.93±1.16		<0.001
Head circumference	33.54±1.68		33.65±1.4		N.S.
Birth length	48.93±2.58		49.64±4.2		<0.001
Umbilical cord blood pH	7.29±0.09		7.28±0.1		0.028



The rate of breastfeeding was relatively low among women with epilepsy, since 40 % of all babies were breastfed.
Breastfeeding is generally thought to be safe for women using antiepileptic medications. Since anticonvulsant drugs are secreted in breast milk, infants may become sleepy and stop feeding prior to satiation.

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