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SEIZURES IN INFANCY IN THE OFFSPRING OF WOMEN WITH EPILEPSY

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Abstract

Objectives: To assess (i) the incidence of seizures in the first year of life in infants born to mothers with epilepsy, and (ii) factors that might contribute to the seizure incidence.

Materials & Methods: Analysis of data collected in the Australian Register of Antiepileptic Drugs in Pregnancy during and at the end of the year after pregnancy.

Results: By the end of a year following pregnancy, seizures had occurred in the progeny of 47 pregnancies (2.40%), including febrile seizures in 18 (0.92%), the latter rate being higher than the 0.40% and 0.59% rates for the same situation in the general population reported in the recent literature. Seizures in infancy were more likely in the offspring of mothers with generalised as compared with focal epilepsies (3.65% v. 1.56%; R.R.= 2.332; $P < .05$), and within the generalised epilepsy mothers in those who were not seizure-free during pregnancy (4.83% v. 2.89%). Seizures were also more likely in infants

with foetal malformations, especially ones not discovered until after the first post-natal month.

Conclusions: These findings may help in advising mothers with epilepsy regarding the chance of their offspring experiencing seizures in the first year of life; they also suggest the desirability of achieving maternal seizure control throughout pregnancy.

Key Words: focal epilepsy, generalised epilepsy, infants, mothers, pregnancy, seizures.

Introduction

For some 20 years the Australian Register of Antiepileptic Drugs in Pregnancy (APR) has been collecting data on the relationships between foetal malformations and intrauterine exposure to the drugs used in treating epilepsy during pregnancy. Its policy has been little unusual in that, it has maintained contact with those enrolled in it beyond the immediate post-natal period and up to the end of the first post-natal year. Over that initial year of extra-uterine life it has also collected information about the occurrence of epileptic seizures in the offspring of the pregnancies that have been followed. Up to the present time, this information regarding seizures in early infancy has not been analysed. The present paper attempts such an analysis in what has proved to be a larger collection of pregnancies than others in the literature dealing with related topics.

Materials and Methods

The APR collects information on the course and outcomes of pregnancies in informed-consenting Australian women with epilepsy (WWE) who volunteer to participate. Details of their pregnancies are recorded, after they become aware of its existence and activities. The Register is based in Melbourne, and all contact with it is by means of telephone. Women are interviewed at recruitment, at 7 months of pregnancy, during the month after giving birth and finally at one-year post-partum. As far as possible, details provided by the women are checked with their treating doctors, but APR personnel play no part in the actual management

of the pregnancies. Additional details of the register's recruitment policies and practices have been published elsewhere. (1, 2) Relevant data items were extracted from the APR database and analysed by simple statistical methods, logistic regression and confidence interval analysis.

The study was approved by the Melbourne Health Human Research and Ethics Committee. Written informed consent was obtained from all participants.

Results

At the end of 2018, the APR contained records of 1958 pregnancies of WWE, which had resulted in live births (including 39 sets of twins) and in which contact with the women involved could be maintained to the 12-month postnatal interview. Because the interest of the present paper lies in seizures in infancy and none of the 39 sets of twins had experienced seizures in their post-natal year, in what follows seizure rates and factors potentially involved in infantile seizure occurrence have been related to the 1958 pregnancies rather than to the offspring numbers.

Of the 1958 pregnancies, 47 had produced offspring who had experienced seizures of various types in the first postnatal year (2.40%). In 18 of the 47, the seizures were recorded as febrile ones (38%). The recorded descriptions of the remainder with seizures included three instances of generalised convulsing, one instance of seizures during meningitis, one of infantile spasms, at least one of episodes termed myoclonic, 21 in which there was episodic disturbed consciousness with or without other features, and two that lacked any recorded description.

Logistic regression was used to detect statistically significant associations between (i) infancy seizures of any type, and (ii) febrile seizures only, and various recorded data items that applied for the pregnancies and the pregnant women. The factors considered were: number of previous pregnancies, pre-pregnancy folate use, duration of labour, caesarean section, otherwise assisted delivery, offspring gender, breast feeding, maternal epilepsy type (generalised, focal), family history of epilepsy, seizure occurrence in (i) the pre-pregnancy year (ii) during pregnancy (iii) in labour, any intrauterine exposure to carbamazepine, to valproate, to lamotrigine, to levetiracetam, to topiramate, the presence of foetal malformations. The only variables that showed statistically significant relationships in the regression for infantile seizure of any type were (i) maternal generalised epilepsy ($P =$

0.0027) and (ii) the presence of foetal malformation ($P=0.0084$). In the regression for febrile seizures only, the relationship with generalised epilepsy had a P value of 0.0557, with the relationship for foetal malformation being non-significant statistically.

Table 1 shows the calculated relative risk values for the above variables that were statistically significant, or approached statistical significance, in relation to the occurrence of (i) any seizures in infancy and (ii) febrile seizures in infancy. While most of the foetal malformations had been recognised by birth or in the first post-natal month, some had not been recognised until later in the first year of life, and these two malformation sub-groups were also included in the analysis shown in the Table. In relation to all seizures in infancy, each parameter that was considered was associated with a higher risk of infancy seizures, the risks being at least doubled for maternal generalised epilepsy and foetal malformation, but more than 5-fold increased for late recognised foetal malformation. In relation to febrile seizures, where the numbers involved were smaller, the only statistically significant association was with late recognised foetal malformation, though the trends were generally similar to those that applied in relation to seizures overall.

There was a statistically significant increased hazard of infancy seizures in the offspring of women with generalised epilepsy, and also a non-statistically significant increased seizure occurrence hazard in infants of mothers who had seizures during pregnancy, the latter seizure situation being a potentially preventable one. The seizure-affected infant occurrence rate was 4.83% in 331 offspring of women with generalised epilepsy who had seizure-affected pregnancies, but 2.89% in 519 pregnancies in women with generalised epilepsy who had seizure free pregnancies (Relative Risk = 1.67, 95% C.I. 0.838, 3.357). For febrile seizures the corresponding rates were lower, and reasonably similar, viz. 1.52% and 1.35%.

Because of the association found between seizure-affected infants and late-recognised foetal malformations, the types of these malformation that had occurred in the infants with seizures were ascertained. There were two infants with febrile seizures, one with a trigger thumb, the other with blepharophimosis, and a further two with other types of infancy seizures, one having delayed brain myelination and a ventricular septal defect, the other periventricular nodular hyperplasia.

Although regression analysis showed no statistically significant association in the present material between birth weight and hazard of seizures in infancy, because of the reported association between prematurity and epilepsy in childhood (3, 4) seizure rates were

calculated for infants born with birth weights below 2500 grams (118 infants) and 3000 grams (401 infants) and their respective heavier counterparts. The seizure rates were 3.39% and 2.34% (Odds Ratio 1.547, 95% C.I. 0.549, 4.305%) for the comparison for birth weights below and above 2500 grams, and 3.24% and 2.19% (Odds Ratio 1.500; 95% C.I. 0.784, 2.870%) for those below and above 3000 grams.

Discussion

No appropriately matched group of pregnancies was available within the APR material as a comparator that would have allowed assessment regarding whether maternal epilepsy had affected the rate of giving birth to infants who would experience seizures in their first year of life. In the literature there are the potentially suitable comparator studies of Verity et al (5) and Visser et al (6). The data of Verity et al (5) show that 0.40% of their population of 13,135 British infants had experienced febrile seizures by one year of age while Visser et al (6) reported a febrile seizure-affected rate of 0.59% and a total epileptic seizure rate of 0.66% in the first year of life in the offspring of 2860 pregnancies. Those febrile seizure rates are below the 0.92% rate found in the APR material, and the total seizure rate in the Visser et al (6) population was notably below the 2.40% rate found in the present study, though the differences in the latter rates may to an extent be explained by different definitions of epilepsy that may have been adopted. Nevertheless, it may be prudent to regard the higher seizure affected infant rates in the present study cautiously.

Earlier sometimes cited published data exist concerning the rates of occurrence of epilepsy in the offspring of WWE, but these involve longer periods of observation. For instance, Annegers et al (7) and Ottman et al (8) found that the offspring of mothers with epilepsy were more likely to suffer from the disorder than the offspring of fathers with epilepsy. Annegers et al (7) calculated that the hazard in relation to the affected mothers was increased some 3.2 times. The Annegers et al (7) offspring were followed into adolescence and early adult life and the diagnosis of epilepsy required the occurrence of at least two unprovoked seizures, while the present material dealt only with infants up to one year of age, and included febrile and other provoked seizures.

The present study found that there was a notably increased hazard of having a seizure-affected offspring when the infant has a malformation that was not detected in the first few weeks after birth, but was found later. This finding in contrast to when a malformation was detected soon after birth, is not easily explained. Intuitively, the hazard might have been

expected to be greater if the infant was affected by the generally more severe types of malformation that are more readily detected early in postnatal life. The present finding raises the possibility having a seizure in infancy may lead to careful physical examination of the infant which reveals comparatively mild foetal malformations that might otherwise have not been noticed or, if noticed, not seemed worth reporting to the APR. There seems no way of assessing that possibility in the material contained in the APR. As well, the earlier finding of such milder malformations might not be of much predictive value in the individual infant.

The at least doubled hazard of having seizures in infancy in the offspring of women with genetic (primary) generalised epilepsy in the APR data might be explained by the belief that this type of epilepsy has a genetic basis. The risk of an individual offspring having such seizures is low, under 4% in the present study, but mothers with genetic generalised epilepsy should be made aware of it, and also of the lesser hazard if a mothers epilepsy has a focal cerebral origin. Although the evidence from the present study is not statistically significant, the higher relative hazard found (by a factor of 1.67 times) if women with generalised epilepsy have seizures during pregnancy may further encourage attempts at achieving full seizure control in these women before and throughout pregnancy.

Because in the Australian Register some of the dates of the last menstrual period before pregnancy are suspect (which is a limitation of the study), more accurate birth weight data were used to investigate whether the known association between premature birth and seizures in infancy (3, 4) might have contributed to the seizure-affected infancy rate in the present data. There was a trend for low birth weight (below 2500 and 3000 grams) to have done so, though not to a statistically significant extent in the available material.

Thus, analysis of the present Australian data, suggests that the offspring of women with epilepsy, particularly women with genetic generalised epilepsies and with incompletely controlled seizure disorders, appear at increased hazard of seizures in their first year of life, with their hazard being further increased if they also have a foetal malformation.

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Disclosure of conflict of interest

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C M Lander, JE Graham, AA Hitchcock and M J Eadie have no relevant conflicts of interest to declare. No personal funding from outside bodies has been involved in their roles in this paper.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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	Seizure rate	%	R.R.	95% C.I.
ALL SEIZURES				
Seizures in pre-pregnancy year	25/827	3.02	1.554	0.883, 2.737
Seizure free pre-pregnancy year	22/1131	1.95		
Focal epilepsies	15/959	1.56	2.332	1.277, 4.289
Generalised epilepsies	31/850	3.65		
Seizures in pregnancy	26/887	2.93	1.495	0.847, 2.239
Seizure free pregnancy	21/1071	1.96		
Family history of epilepsy	20/630	3.17	1.561	0.883, 2.762
No family history of epilepsy	27/1323	2.04		
Taking AEDs throughout pregnancy	45/1789	2.52	2.113	0.517, 8.633
Not taking AEDs in early pregnancy	2/168	1.19		
Taking AEDs in pregnancy	47/1924	2.44	Diff =	7.72%, - 3.23%
Not taking AEDs in whole pregnancy	0/34	0	2.44%	
Foetal malformation present	8/132	6.06	2.838	1.354, 5.947
Foetal malformation absent	39/1826	2.14		
Foetal malformation present at birth	4/95	4.215	1.824	0.669, 4.977
Foetal malformation absent at birth	43/1863	2.31		
Foetal malformation found late	5/42	11.90	5.574	2.314, 13.429
Foetal malformation absent	39/1826	2.14		
Offspring male	25/974	2.67	1.148	0.652, 2.022
Offspring female	22/981	2.24		
FEBRILE SEIZURES				
Seizures in pre-pregnancy year	6/827	0.73	0.664	0.258, 1.814
Seizure free pre-pregnancy year	12/1131	1.06		
Focal epilepsies	6/959	0.63	2.257	0.851, 5.986
Generalised epilepsies	12/850	1.41		
Seizures in pregnancy	8/887	0.90	0.966	0.383, 2.437
Seizure free pregnancy	10/1071	0.93		
Family history of epilepsy	6/630	0.95	1.054	0.397, 2.795
No family history of epilepsy	12/1328	0.90		
Taking AEDs throughout pregnancy	1/168	0.60	1.569	0.214, 11.922
Not taking AEDs in early pregnancy	17/1789	0.95		
Taking AEDs in pregnancy	18/1924	0.94	Diff=	-1.47, 9.22%
Not taking AEDs in whole pregnancy	0/34	0	0.94%	

Foetal malformation present	2/132	1.52		
Foetal malformation absent	16/1826	0.88	1.729	0.402, 7.441
Foetal malformation present at birth	0/95	0	Diff=	
Foetal malformation absent at birth	18/1863	0.97	- 0.97%	-2.94, 1.01%
Foetal malformation found late	2/42	4.76	5.435	1.290, 22.887
Foetal malformation absent	16/1826	0.88		
Offspring male	10/974	1.03		
Offspring female	8/984	0.81	1.263	0.501, 3.186

Table 1: Comparisons of certain properties relating to the mother and to the infant with any type of seizure, and infants with febrile seizures only.

Statistically significant Relative Risk values are in bold type.

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