Seizure 28 (2015) 46–50

Contents lists available at ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

Review

Major congenital malformations in children of women with epilepsy

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ARTICLE INFO

Article history:
Received 9 October 2014
Received in revised form 11 February 2015
Accepted 12 February 2015

Keywords:
Epilepsy
Pregnancy
Congenital malformation
Abnormality
Anticonvulsant
Antiepileptic drug

ABSTRACT

It has been long known that the risk of major congenital malformations is increased among children of mothers with epilepsy. This is mainly due to the teratogenic effects of antiepileptic drugs although other factors, such as genetically determined individual susceptibility, are likely to contribute. Recent large scale prospective epilepsy and pregnancy registries have indicated that the rate of major congenital malformations may be at most two-fold higher than expected with exposure in utero to the presently most frequently used antiepileptic drugs such as carbamazepine or lamotrigine. Higher rates are consistently reported with exposure to valproate. The risk of teratogenic effects appears to be dose dependent and the lowest effective dose should thus be established before pregnancy regardless of which antiepileptic drug the woman is taking. Major changes such as switches between drugs should be avoided when pregnancy is established.

1. Introduction and background

In 1968 Meadow reported oro-facial clefts and other abnormalities among babies of mothers who received primidone, phenytoin, or phenobarbital [1]. Over the more than 50 years since this first report of birth defects in children exposed in utero to antiepileptic drugs (AEDs), subsequent studies have confirmed higher birth defects rates among children of mothers with epilepsy [2,3]. Research since the initial report have also demonstrated a broader picture of developmental toxicity of AEDs, which in addition to major congenital malformations (MCM) includes potential adverse effects on intrauterine growth [4], on cognitive development of the exposed child [5], and on the behavioral development [6]. The reasons for the increased risks are multifactorial and may include genetic factors, the maternal epilepsy and seizures during pregnancy, socio-economic status, but accumulating data strongly suggest that AEDs are the main reason for the increased risks [7]. A pooled analysis of data from 26 studies reported an MCM rate of 6.1% in offspring that had been exposed to AEDs compared to 2.8% in children of untreated women with epilepsy, and 2.2% in offspring of mothers without epilepsy [8]. Similar results were reported in a formal meta-analysis of 10 studies. The offspring of women with epilepsy who received AEDs had higher prevalence of MCM than controls (odds ratio (OR) 3.26; 95% CI 2.15–4.93), while the risk for MCM in the offspring of women with untreated epilepsy was not significantly higher than among non-epilepsy controls (OR 1.92; 95% CI 0.92–4.00) [9].

The present review will focus on the risk of MCM in offspring of women with epilepsy and in particular the role of AEDs and possible differences between drugs in their potential to cause MCM. The topic has been covered in previous reviews and guidelines [2,7], so emphasis in the present article will be on the more recent publications.

2. Methodological considerations

Studies aiming at assessment of the risk of MCMs in children exposed to AEDs in utero face many challenges in particular when the objective is to compare risks associated with different AEDs. For obvious ethical reasons randomized studies are not possible. We are restricted to observational studies with the potential problems of confounding by other risk factors than the AEDs, e.g. impact of seizures, type of epilepsy and related or unrelated genetic factors, and socio-economic circumstances. Second, fortunately the vast majority of pregnancies in the general population as well as in women with epilepsy result in healthy offspring without MCMs. As a consequence large numbers are needed for meaningful analyses where adjustments can be made for potential confounding factors. Even larger studies are necessary

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http://dx.doi.org/10.1016/j.seizure.2015.02.019
1059-1311/

for assessment of individual specific MCMs. Avoiding selection or reporting bias is another challenge. It is more likely that adverse pregnancy outcomes are reported compared with normal outcomes. It is therefore essential that information on exposure, i.e. the AED treatment, is obtained, and enrollment achieved, before outcome of the pregnancy is known. This is best accomplished in prospective registries where pregnancies are enrolled in early pregnancy before any information on outcome is available. This is becoming more and more difficult as prenatal diagnostic tests are used earlier in pregnancy. Yet another challenge is the question of a comparison or control group. Some studies are restricted to internal comparisons between different AEDs, whereas others compare MCM rates among AED exposed with pregnancy outcomes in the general population, or in offspring of untreated women with epilepsy. The identification of MCMs depends on the vigilance of the observer as well as the time window of observation. It is therefore essential that exposed cases and unexposed controls are followed in an identical way.

Traditionally, the first suspicion of associations between drug use in pregnancy and occurrence of MCM has come from spontaneous reporting to manufacturers or regulators, or from retrospective case reports. These provide signals that need to be confirmed or refuted in epidemiological studies, with case–control or a cohort design. In case–control studies, cases with a birth defect are compared with controls, children without the defect, with regard to exposure to AEDs. Such studies are particularly useful when the event of interest is rare, such as a specific uncommon birth defect. A problem with many case–control studies is that the information on AED use is obtained after the pregnancy outcome is known, with an inherent risk of recall bias, and an over-estimation of risks. In addition, while providing a measure of the association between exposure to a specific AED and birth defects, case–control studies do not provide information on the frequency of the malformations in children exposed to the particular treatment or to comparators.

Cohort studies can be used to evaluate outcome of pregnancies with a certain drug. Ideally, information on exposure is obtained and enrollment in prospective cohort studies completed before outcome is known, thus avoiding recall bias. Some countries, e.g. in Scandinavia, have National Medical Birth Registers where information on maternal drug intake is recorded in early pregnancy and outcome of pregnancy obtained through other linked national registers. Such Medical Birth Registers have been used to assess risks for MCM in association with maternal use of AEDs [4,10]. They have the advantage of being population-based, and thus representative, and also to provide the outcome in the general population as control. There are also limitations: they lack information on the type of epilepsy (the Swedish Medical Birth Registry in fact does not specify the indication for the treatment), occurrence of seizures during pregnancy, details about drug dose, and many other potentially relevant risk factors. Pregnancies ending in induced abortions (due to detected MCM or for other reasons) are excluded in some [10], which underestimates the risk.

Epilepsy/antiepileptic drug and pregnancy registers were established in different countries some 15 years ago. These prospective observational studies have the specific objective to assess and compare risks for MCM with maternal use of different AEDs during pregnancy [11] and have by now each collected thousands of pregnancies with AED use. These registers are not population-based, but they contain much more detailed information on AED exposure, types of epilepsy, seizure frequency during pregnancy, and several other risk factors that are not available in the Scandinavian Medical Birth Registers. Although the basic principles of the epilepsy and pregnancy registers are similar, they differ slightly in some regards, e.g. methods for enrollment, exclusions, outcome criteria and time window for assessment of outcome. Their results are thus not immediately comparable [11].

The North American AED Pregnancy Registry (NAAPR) enrolls pregnant women from the US and Canada. The UK and Ireland Epilepsy and Pregnancy Register includes pregnancies from the UK and Ireland. EURAP is an international registry enrolling pregnant women from more than 40 countries world-wide. The Australian Pregnancy Register and the Kerala Registry of Epilepsy and Pregnancy in India are part of the EURAP collaboration but also publish independently [11]. These observational studies have provided much information in recent years that has had a direct impact on clinical practice, and the results will be summarized in the present review.

A different type of antiepileptic drugs and pregnancy registers are those organized by a pharmaceutical company, where the GlaxoSmithKline International Lamotrigine Register is the most established example [12]. A major drawback of these registers is that they only include pregnancies with the companies' own product, one specific antiepileptic drug, without comparators. This makes it difficult to draw meaningful conclusions since MCM rates, for reasons discussed above, cannot be compared across registers.

3. Different types of MCMs

Malformations among offspring of women with epilepsy are not unique but generally follow a pattern similar to what is seen in the general population with cardiac defects being the most common followed by facial clefts, and hypospadias, but with some variation between different AEDs. A pooled analysis of data from 21 prospective studies looked at four different groups of MCMs (cardiac, neural tube defects, oro-facial clefts, and hypospadias) associated with monotherapy exposure to the five most commonly used AEDs in these studies [2]. Cardiac malformations were the most frequent of the four MCMs for carbamazepine, lamotrigine, barbiturates, and phenytoin, whereas neural tube defects were the most common for valproate. Cardiac malformations appeared more frequently with barbiturates than with any of the other AEDs, whereas neural tube defects and hypospadias were more prevalent with valproate than with the other AEDs.

NAAPR reported a prevalence of oral clefts of 7.3/1000 infants exposed to lamotrigine monotherapy, a 10-fold increased rate compared to unexposed infants [13]. The prevalence of oral clefts among lamotrigine exposed was lower, 2.5/1000, in five other registries [13.] A population-based European case–control study found no evidence for a specific increased risk of orofacial clefts versus other malformations due to lamotrigine, but the study was not designed to assess whether there is a general increased risk of malformations with lamotrigine [14]. NAAPR has also observed a 10-fold increase in the rate of oro-facial clefts among infants exposed to topiramate monotherapy compared to unexposed [15]. A multi-database cohort study recently reported a prevalence of non-syndromic oral clefts 5.4 times higher among children exposed to topiramate in utero compared to unexposed children [16].

Case–control studies based on EUROCAT data have investigated the risks for specific MCMs with valproate exposure compared with no use of an AED. Valproate was associated with increased risks for spina bifida OR 12.7 (95% CI 7.7–20.7), atrial septal defect 2.5 (95% CI 1.4–4.4), cleft palate 5.2 (95% CI 2.8–9.9), hypospadias 4.8 (95% CI 2.9–8.1), polydactyly 2.2 (95% CI 1.0–4.5), and craniosynostosis 6.8 (95% CI 1.8–18.8) [17]. In a similar case–control study the only specific malformation associated with exposure to carbamazepine monotherapy was spina bifida, OR 2.6 (95% CI 1.2–5.3) compared with no AED [18]. Although these data can inform about associations between a particular AED and specific malformations, they rarely provide the direct comparison