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Review

Impact of early life exposure to antiepileptic drugs on neurobehavioral outcomes based on laboratory animal and clinical research

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ABSTRACT

Epilepsy affects approximately 1% of children under the age of 15, making it a very common neurological disorder in the pediatric population (Russ et al., 2012 [1]). In addition, ~0.4–0.8% of all pregnant women have some form of epilepsy (Hauser et al., 1996a,b; Borthen et al., 2009; Krishnamurthy, 2012 [2–5]). Despite the potential deleterious effects of antiepileptic drugs (AEDs) on the developing brain, their use is still required for seizure control in pregnant women (Krishnamurthy, 2012 [5]), and they represent the standard approach for treating children with epilepsy (Chu-Shore and Thiele, 2010; Quach et al., 2010; Verrotti et al., 2011 [6–8]). Even when AEDs are effective, there are potential side effects, including cognitive and affective changes or altered sleep and appetite. The consequences of AED exposure in development have been studied extensively (Canger et al., 1999; Modi et al., 2011a,b; Oguni, 2011 [9–12]). Despite intensive study, there is still debate about the long-term consequences of early life AED exposure. Here, we consider the evidence to date that AED exposure, either prenatally or in early postnatal life, has significant adverse effects on the developing brain and incorporate studies of laboratory animals as well as those of patients. We also note the areas of research where greater clarity seems critical in order to make significant advances. A greater understanding of the impact of AEDs on somatic, cognitive and behavioral development has substantial value because it has the potential to inform clinical practice and guide studies aimed at understanding the genetic and molecular bases of comorbid pathologies associated with common treatment regimens. Understanding these effects has the potential to lead to AEDs with fewer side effects. Such advances would expand treatment options, diminish the risk associated with AED exposure in susceptible populations, and improve the quality of life and health outcomes of children with epilepsy and children born to women who took AEDs during pregnancy.

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1. Introduction

Approximately 0.4 to 0.8% of pregnant women have epilepsy [2–5]. In humans, nearly all AEDs freely cross the placental barrier and can accumulate in the fetus [13–16]. In utero exposure to AEDs in humans has been associated with a variety of effects on somatic, cognitive, and behavioral development. The functional consequences of in utero AED exposure appear to depend upon the type of AED as well as the use of the AED as monotherapy or polytherapy [17,18]. Here, we review the effects of in utero AED exposure on somatic, cognitive and behavioral development using both human and animal data. The effects of in utero exposure are then compared to the effects of exposure in early postnatal life. The focus of the comparison between human and animal research is based on data from the best-studied AEDs: phenytoin, phenobarbital, and valproate.

2. In utero exposure of the fetus to AEDs

2.1. Effects of maternal AED use on somatic development of the newborn

2.1.1. Phenytoin

In the initial studies of prenatal exposure to phenytoin, an association was found between drug exposure and a group of developmental abnormalities that was termed "fetal hydantoin syndrome" [19,20]. This syndrome includes abnormal head and facial development, including microencephaly, short nose, cleft palate, low nasal bridge, and a fold of skin on the upper eyelid (epicanthal fold), abnormal ears, wide mouth and low hairline [20,21]. In general, fetal phenytoin exposure has been associated with a 2–3-fold increase in the likelihood of offspring to develop a congenital anomaly [22,23]. These anomalies include those mentioned above as well as heart defects, and abnormalities of the genitalia [23–28]. In addition, phenytoin exposure has been associated with decreased rate of body growth [27,29]. Despite early reports that showed a strong association between outcome and

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prenatal phenytoin exposure, a number of larger studies that were conducted more recently, in which phenytoin monotherapy was evaluated, did not find a significant association between phenytoin monotherapy and the symptoms previously identified as fetal hydantoin syndrome [30–32]. Nevertheless, concerns remain that phenytoin use in pregnancy could affect the fetus. What seems possible is that the adverse effects of phenytoin monotherapy are not universal because they require genetic predisposition or additional environmental influences to be fully expressed. If so, consideration of genes and environment could explain some of the variability of past studies and potentially lead to genetic or other approaches to more clearly define the risk in mothers taking AEDs. Another issue is that folic acid supplementation, a current standard of care during pregnancy which may diminish some of the adverse effects of phenytoin on somatic and neural development, is somewhat recent and may not have been universal in previous studies of prenatal AEDs.

2.1.2. Phenobarbital

Some of the earliest studies investigating the potential teratogenic effects of phenobarbital demonstrated a possible increase in risk of congenital anomalies [33]; however, many of these studies were single case reports. More recently, better powered studies have found that phenobarbital exposure can lead to a slight but significant increase in the risk of birth defects. Typically, these effects are restricted to an increased risk of cleft palate and cardiovascular anomalies [34–37]. Fetal phenobarbital exposure has also been associated with a decrease in birth weight and a reduced head circumference at birth [38]. Some studies suggest that in utero exposure to phenobarbital can lead to more widespread problems, similar to those reported in fetal hydantoin syndrome [39]. Given the different mechanisms of action of these drugs, it is unclear why in utero exposure to phenytoin and phenobarbital would lead to such similar effects on organ development. One hypothesis is that the epilepsy is teratogenic — not the AED. However, while pregnant women whose seizures are not controlled during pregnancy have an increased risk of premature birth and infants with lower birth weight [5], many of the teratogenic effects on the offspring can be attributed to prenatal exposure to anticonvulsant drugs [40]. In the future, animal models could be valuable to further our understanding of the effects of uncontrolled epilepsy on the developing brain, particularly when epilepsy can be induced without widespread damage to the brain and reproductive system [41]. It is also possible to compare vehicle- and AED-treated groups under better controlled environmental conditions if laboratory animals are used. Recent studies of this kind are elucidating many effects of uncontrolled seizures during pregnancy in female laboratory rats; to date, there is both evidence for and against adverse effects of seizures during pregnancy on development of the offspring [42–45].

2.1.3. Valproate

Prenatal exposure to valproate is associated with a variety of birth defects in humans (effects that occur in approximately 5-10% offspring) [31,46,47,48], a rate that is significantly higher than has been associated with any of other AEDs currently in use. These effects appeared to be dose-dependent, with doses over 1000 mg/day leading to effects in 15-30% children [46,47]. Adverse effects include neural tube defects, decreased brain volume, heart defects, craniofacial dysmorphism (oral cleft), and abnormalities in the urethra in males (hypospadias) [28,46,47,49–60]. Children exposed to valproate in utero also showed intrauterine growth restriction (IUGR), other growth deficiencies, and increased risk of microcephaly [29,50,51]. Based upon the spectrum of effects, children exposed to valproate are said to exhibit "valproate syndrome". Children with valproate syndrome also have facial dysmorphisms which include mid-facial hypoplasia, epicanthal folds, a short nose with a broad ridge, and a thin upper lip [50,51]. Again, the similarity of these effects to those of phenytoin and phenobarbital, AEDs that have distinct mechanisms of action, suggests either a risk inherent to pregnant women with epilepsy or a common teratogenic effect of these drugs that is not currently understood. Understanding a common mechanism – if it exists – deserves attention because it could lead to a treatment to stop adverse effects of AEDs in the fetus.

2.1.4. Other/polytherapy

In addition to the AEDs described above, carbamazepine has been associated with an increased risk of spina bifida, neural tube defects, cardiovascular anomalies, cleft palate, skeletal anomalies, and brain malformations [22,31,47,61–65] leading to the term "carbamazepine syndrome" [66,67]. Fetal carbamazepine exposure is also associated with a decrease in birth weight and premature delivery [68]. Despite a number of published reports showing teratogenic effects of carbamazepine, other studies have failed to replicate these findings [69]. Furthermore, related drugs (oxcarbazepine) have not been associated with a significant increase in birth defects [32,70–72]. However, it should be noted that oxcarbazepine, when used in combination with other AEDs, has been associated with an increased risk of malformations [25,70,73–75]. It has been shown that newer AEDs including lamotrigine have lower rates of major malformations [76–78] that increase when the AED is used in combination with other AEDs [47,79]. To date, detailed studies of newer generations of AEDs (topiramate, tiagabine, and levetiracetam) are still emerging. Rigorous study of the new AEDs is important to clarify whether they reduce risk to the fetus and whether AED effects on the fetus could share common mechanisms — even if the mechanisms that reduce seizures are distinct.

2.2. Effects of maternal AED use on cognition and behavior of the newborn

2.2.1. Phenytoin

Some of the earliest studies to identify a potential effect of AEDs on cognitive function in the offspring come from studies of phenytoin, where it was shown that there was an increased risk to cognitive function following prenatal exposure [19,24]. These findings were, in part, confirmed by follow-up studies in which trends were found toward decreased IQ in children (aged 4, 5, and 7 years) exposed to phenytoin in utero [20,34,80–85]. In a significant proportion of those studies, phenytoin was used as part of a polytherapy, so the direct contribution of phenytoin to cognitive outcomes could not be assessed. Some groups have found that intellectual impairments only occurred in children who were exposed to phenytoin in utero who also presented with clear morphological anomalies [82]. Still, others have failed to find significant impairments in the intellectual abilities of children exposed to phenytoin in utero [86]. In addition to defects in cognitive functioning, some studies have identified delays in motor development in children who were exposed to phenytoin in utero [87,88].

2.2.2. Phenobarbital

In a variety of studies, in utero exposure of the fetus to phenobarbital has been associated with a significantly lower mean IQ score when tested as children [89]. More specifically, phenobarbital exposure is associated with a significant decrease in verbal IQ and verbal functioning [90] when compared with children that were not exposed to phenobarbital in utero. One study that is notable because it was prospective and included controls showed that prenatal exposure to phenobarbital led to worse neurological outcome, which was detected as early as 8 weeks of age [87,91]. Other data suggest the timing of prenatal exposure to phenobarbital is particularly important, because exposure in the third trimester was associated with learning disabilities and decreased cognitive functioning [27], with measurable effects in adulthood [90]. As with phenytoin, some groups report that intellectual impairments presented primarily in those subjects with obvious somatic abnormalities [92]. In contrast