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Antiepileptic Drugs and Neurodevelopment: An Update

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Abstract

In utero exposure to some antiepileptic drugs (AEDs) is associated with an increased risk of impaired cognitive development. Specifically, valproate and polytherapy exposure are each associated with an increased risk of cognitive impairment in children compared with other antiepileptic medications. The data regarding the risk to neurocognitive development imposed by maternal use of other AEDs are conflicting or insufficient at this time to draw definitive conclusions. Behavioral dysfunction including autistic spectrum disorder is also associated with maternal use of AEDs during pregnancy. Whether treatment with AEDs during childhood permanently affects cognitive neurodevelopment is yet to be determined.

Keywords

Antiepileptic drugs; Cognition; Neurodevelopment; Epilepsy; Pregnancy

Introduction

That antiepileptic drugs (AEDs) can influence neurodevelopment has been known for several years. The relationship between maternal use of AEDs during pregnancy and major anatomic congenital malformations was first recognized as early as the 1960s [1]. Data collected over the past 15 years from several pregnancy registries indicate the risk of major congenital anatomic malformations in children born to women with epilepsy treated with AEDs during pregnancy to be two to three times higher than in the general population. Valproate has been found to be associated with a higher risk of malformations than other AEDs, particularly neural tube defects [2]. The impact of fetal exposure to maternal AEDs on cognitive and behavioral development has recently emerged as an area of interest and research. The evidence from research efforts thus far suggests that maternal use of some AEDs during pregnancy may negatively impact cognition in the infants of these women with epilepsy. Because in utero exposure to AEDs can affect a child's cognitive development, the

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question arises as to whether treatment with AEDs during childhood can have a similar impact. This has become a growing area of interest.

In Utero Exposure to AEDs and Cognition

Reports of the effects on cognition in children from maternal use of AEDs during pregnancy date to the 1970s [3,4]. Since then, a number of studies have been performed and many have reported an increased risk of cognitive impairment in the children of women with epilepsy exposed in utero to AEDs [3–9]. Some have shown certain AEDs to pose a greater risk than others, including phenobarbital [5, 8, 9] and phenytoin [4, 9]. Yet other studies have shown no significant difference in measures of cognition between exposed and nonexposed children [10, 11]. These conflicting results are due in part to limitations in study methodologies, including marked variability between studies in the number of participants (sample size was typically small); ages of children included; and tools used to measure developmental outcomes. These issues have been described in detail in a literature review of published studies by Nicolai et al. [12•].

Another source of conflict in results is that cognitive development may be influenced by a number of factors aside from fetal AED exposure. These include number of seizures during pregnancy, seizure type, parental IQ, and socioeconomic factors. Thus, parsing out the independent effect of AEDs on cognitive development is complicated. This is illustrated in a literature review by Adab etal. [13] that included 31 studies of cognition and AEDs published between 1974 and 2002. The review highlights these and other confounding factors that were not accounted for in data collection that may have contributed to the differences in study results.

Two large prospective studies that included analysis of these potentially confounding factors have been recently published and revealed similar results. Cognitive outcomes in 309 children at 3 years of age exposed in utero to monotherapy with carbamazepine, lamotrigine, phenytoin, or valproate were assessed in the NEAD (Neurodevelopmental Effects of Antiepileptic Drugs) study [14••]. Analyses controlled for maternal IQ, maternal age, seizure type, number of convulsions during pregnancy, AED dose, gestational age at birth, and preconception use of folate, among multiple other factors. Mean IQ for children exposed to carbamazepine, lamotrigine, or phenytoin ranged from 98 to 101 with no statistical difference between drugs. In contrast, the average IQ for those exposed to valproate was significantly lower than that for each of the other three AEDs. In a separate study from the Liverpool and Manchester Neurodevelopment Group (LMNDG), cognition was assessed in 2-year-old children exposed in utero to AEDs and compared with a control group of children representative of the general population [15]. This study controlled for similar covariants as the NEAD study. Monotherapy exposure to carbamazepine or lamotrigine was not associated with impaired development. Valproate exposure was associated with lower overall developmental scores than scores in children in the control group. Lower scores were also reported for children exposed to topiramate, gabapentin, vigabatrin, oxcarbazepine, and polytherapy, but numbers were too small to reach statistical significance. None of the factors assessed were found to confound the data when included in analysis.

Other studies have also shown an increased risk for cognitive impairment in children with in utero exposure to valproate [16–18]. Thus, there is good evidence that maternal valproate use during pregnancy poses a risk for impaired cognitive development in the exposed fetus, similar to its increased risk of anatomical congenital malformations. If possible, treatment with valproate should be avoided in pregnant women with epilepsy.

There is not enough evidence at this time to confidently determine the risk to cognition with the use of newer AEDs in monotherapy during pregnancy. However, polytherapy treatment, which includes these AEDs during pregnancy, has been found to have adverse effects on cognitive development in children born to this subset of mothers with epilepsy in several studies [17–19].

For the clinician treating pregnant women with epilepsy, it is prudent to avoid the use of valproate, either as monotherapy or in polytherapy, as well as polytherapy with any AEDs if possible. However, the risks to cognitive development must be weighed against the risk of recurrent seizures in the mother and the complications that may occur as a result of either stopping or changing drug treatment.

In Utero Exposure to AEDs and Behavior

The potential for behavioral dysfunction in children exposed to AEDs in utero has been an area of study largely neglected. In a study from the United Kingdom, 110 children exposed to monotherapy with valproate, carbama-zepine, or phenytoin, and 52 exposed to polytherapy were tested with two tools to measure behavioral dysfunction [20••]. Children exposed to valproate as monotherapy or in polytherapy were classified as having lower adaptability, especially in skills of daily living and socialization. In particular, scores were higher on scales measuring demandingness, problems adapting to changes in routine, distractibility, and unhappy mood, leading to higher scores on scales of parental stress. These behavioral changes were independent of child IQ. These findings are supported by two earlier studies [21, 22].

In utero exposure to AEDs has also been linked with autistic spectrum disorder (ASD). In one study, autism was associated primarily with exposure to carbamazepine or valproate compared with phenobarbital, phenytoin, primidone, ethosuximide, and gabapentin [21]. Another study from the United Kingdom found 8.9% of children exposed in utero to valproate to meet *Diagnostic and Statistical Manual of Mental Disorders IV* criteria for ASD with prevalence more than eight times higher than in the general population [23]. Similarly, the LMNDG study found that 6.3% of children exposed to valproate monotherapy in utero had ASD, seven times higher than the control group [24].

Thus, there is early evidence that in utero exposure to some AEDs, particularly valproate, may be associated with adverse behavioral effects in children. Further investigation into this area is clearly needed.

Pathophysiology

The underlying etiology of the adverse effects of in utero exposure to AEDs on cognitive development is unknown. Animal studies suggest several possible mechanisms including altered neuronal proliferation and migration, synaptogenesis, and apoptosis. It is important to note that each of these processes is crucial to normal brain development and occur throughout gestation. In fact, synaptogenesis and apoptosis are seen most prominently during the third trimester. Thus, unlike congenital anatomical malformations that are associated with in utero AED exposure primarily during the first trimester, functional brain development may be adversely affected by drug exposure at any time during the pregnancy of a woman with epilepsy and may be particularly susceptible to third trimester exposure.

Neuronal Proliferation and Migration

The mechanism of action of AEDs is primarily alteration in neurotransmitter systems. Glutamate binding at *N*-methyl-D-aspartate (NMDA) receptors is the primary excitatory influence on neuronal activity and cell proliferation, whereas γ-aminobutyric acid (GABA) has strong inhibitory influence. Multiple AEDs inhibit glutamate action including felbamate and topiramate, whereas GABA agonists include phenobarbital, benzodiazepines, and valproate. The neurotransmitter milieu in the developing brain is largely responsible for regulation of neuronal differentiation and migration. In animal studies, blockade of NMDA receptors or enhanced GABA inhibition impairs neurogenesis and cell migration [25, 26], resulting in decreased brain volume and cortical dysplasias. These cellular changes may account at least in part for impaired cognition in children exposed in utero to such drug-induced neurotransmitter changes.

Synaptogenesis

Normal neuronal networks develop by proliferation of synaptic connections followed by pruning to refine the network. Like neurogenesis, this complicated process is regulated by neurotransmitters. There is evidence that drug-induced inhibition of NMDA receptor activity [27] or enhanced GABA activity [28] can disrupt this process.

Apoptosis

Initially during brain development, an excess number of cells proliferate. Apoptosis, or programmed cell death, reduces the number of cells to the newborn population. This process is mediated by growth factors, cytokines, and neurotransmitters and is critical to development of normal cognitive function. Excessive apoptosis in developing brains of neonatal rats exposed to benzodiazepines, phenobarbital, phenytoin, vigabatrin, and valproate has been reported [25, 29]. The AED-induced apoptosis was related to antagonism of neurotropins and cell growth signal proteins. Apoptosis was not seen in studies of carbamazepine, lamotrigine, levetiracetam, or topiramate, although most of these AEDs were shown to enhance apoptotic effects of the above AEDs [30, 31].

Cognitive Effects of AED Use in Childhood

Impaired cognition affects a child's ability to learn, which may impose limits to academic achievement and later, accomplishment of life goals. There are numerous reports of impaired cognition in children taking AEDs.

Older AEDs

Phenobarbital use in children with epilepsy is associated with lower scores on cognitive tests than in controls or children treated with other AEDs [32–34]. Reports of the effects of phenytoin are more variable. In one study, children treated with phenytoin had poorer reading skills than those treated with other AEDs [35]. Conflicting results have been found when the cognitive affects of carbamazepine have been investigated. This is due at least in part to differences between studies in the tools used as a cognitive measure. Impairment in memory was found in one study [36], whereas improved performance on a psychomotor task was reported for moderate to high carbamazepine doses in another study [37]. Inconsistent results in academic achievement variables have also been reported [38]. Cognitive effects of valproic acid treatment in children have been compared with other AEDs in several studies. Scores on varying tests of neuropsychological function were better when compared to treatment with phenobarbital [33], and no different compared with carbamazepine [39].

New AEDs

There are very few studies that have examined the effect of treatment with newer AEDs on cognition in children with epilepsy. Children treated with oxcarbazepine for 6 months had similar scores on cognitive tests to those treated with either carbamazepine or valproate in one study [39]. One double-blind placebo-controlled study revealed no significant difference in cognitive measures in children taking lamotrigine treatment versus controls [40]. Levetiracetam has been reported to have no significant adverse cognitive effects on children in two studies [41, 42]. Adverse cognitive side effects from topiramate use have been well described in adults. The same effect has been reported in children [43–45]. The results of these studies must be interpreted with caution. All included small numbers of patients and short follow-up periods. In addition, comparator groups varied as did study design. Finally, most studies did not account for the confounding factor of seizure control. Cognition was likely to be better in children who achieved a significant reduction in seizure frequency with drug treatment, but this variable was not considered in analysis of study results. There are no published studies addressing cognitive side effects in children of treatment with lacosamide, pregabalin, rufinamide, vigabatrin, or zonisamide.

Overall, there is some evidence to indicate that treatment with phenobarbital or topiramate may be associated with cognitive slowing in children. But is this effect reversible once the medication is stopped, or is neurodevelopment affected permanently in these children, leading to long-term cognitive impairment? The answer to this important question is as yet unknown. Observational experience would lead most practitioners to the conclusion that cognition improves after the suspect AED is discontinued. However, in a long-term study of a cohort of children with febrile seizures treated with phenobarbital, scores on achievement tests were significantly lower for the treated group compared with placebo when tested 6

months [32] and again 5 years [46] after phenobarbital had been discontinued. These findings suggest that treatment with phenobarbital during childhood may have long-term con-sequences on cognition by inducing changes in brain development that produce permanent changes in plasticity. Further investigation into the long-term consequences on cognition of childhood exposure to AEDs is clearly needed.

Conclusions

Women with epilepsy are very concerned about AED use during pregnancy and the consequent health of the child. Most rely on their physician to provide information about these concerns, but many feel that they are not provided sufficient information regarding their concerns [47]. Many patients and clinicians are familiar with the association between in utero exposure to AEDs and major anatomical malformations. The potential consequences of maternal AED exposure during pregnancy on cognition and behavior in the offspring are not as well known. It is important for physicians caring for women with epilepsy to understand these risks so that they can provide their patients with the accurate information and counsel them appropriately.

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