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The treatment of epilepsy in pregnancy: The neurodevelopmental risks associated with exposure to antiepileptic drugs

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ABSTRACT

A number of antiepileptic drugs (AEDs) have been confirmed as teratogens due to their association with an increased malformation rate. The majority of research to date does not find an association between prenatal exposure to monotherapy carbamazepine, lamotrigine or phenytoin and neurodevelopmental outcome in comparison to control children and noted higher abilities in comparison to children exposed to valproate; but further work is needed before conclusions can be drawn. Data for levetiracetam was limited to one study, as was the evidence for topiramate. Sodium valproate exposure appeared to carry a dose dependent risk to the developing brain, with evidence of reduced levels of IQ, poorer verbal abilities and increased rate of autistic spectrum disorder both in comparison to control children and children exposed to other AEDs. The severity of the neurodevelopmental deficits associated with prenatal exposure to valproate highlight the critical need to consider neurodevelopmental outcomes as a central aspect of teratological research.

1. Introduction

The need to optimize seizure control whilst limiting the potential risk to the fetus can be a challenge. Given the nature of the condition pharmacological treatment during pregnancy is typically required and it is estimated that 0.5–2.5% of pregnancies are exposed to antiepileptic drugs (AEDs) for epilepsy and other indications [1–4]. Prescription patterns in women with epilepsy have changed over the last two decades, with a decrease in the older AEDs such as phenytoin, phenobarbital, carbamazepine and valproate, and an increase in 'newer' therapies such as lamotrigine and levetiracetam in women of childbearing age [2,3,5].

The older AEDs have been demonstrated to be associated with a significant increase in risk of major congenital malformation. Valproate is reported as the AED with the highest level of teratogenicity [6] and is associated with neural tube [7–9], cardiac [9,10], orofacial clefts [9,11,12] and skeletal or limb malformations [9,11]; with levels of risk being clearly dose dependent [6,13,14]. Carbamazepine has been associated with an increased risk of major malformation [6], with a higher rate of spina bifida and cardiac malformations reported [6,13,14]. Phenobarbital has been associated with an increased overall rate of malformations [6,15], and specifically with cardiac malformations [6,16] and oral clefts [17]. Finally, phenytoin is also reportedly associated with an increased rate of malformations [15,18].

Prenatal exposure to lamotrigine has been found by the majority of pregnancies registers and population-based studies to not be associated with an increased risk of malformation [16,19–22]. To date no specific pattern of malformations have been reported following exposure to lamotrigine [6]. A previously reported association with oral clefts in data from the North American Pregnancy Register [23] has not been maintained with increased study population [16]. Although the majority of studies have not documented a dose response, the largest study to date does find an association between dose of lamotrigine and prevalence of malformations [6]. Data is more limited pertaining to exposure to levetiracetam. Pregnancy register data from UK, US and Australia failed to find an association with malformation status of the child [16,20,24] as did a population based study [21]. There is consistent evidence of a specific risk of oral clefts following in utero exposure to topiramate

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[25,26]. There is no evidence of an increased rate of malformation in children exposed to gabapentin [21,27], oxcarbazepine [21] or zonisamide [16], however data is too limited for conclusions to be drawn.

There is therefore increased risk to the physical development of the fetus following exposure to certain AEDs. Additionally, there are further risks that should be considered, which convey lifelong impact to the fetus and the later child. Early reports of malformations following prenatal exposure to an AED often also reported neurodevelopmental difficulties [28–32], however it took until the turn of the century to see an increased international interest on neurodevelopment as a primary outcome [33–39] and also the utilization of the already established epilepsy and pregnancy registers for the ascertainment of neurodevelopmental data [38,40–42]. Neurodevelopmental outcomes when affected can be substantial and therefore a comprehensive understanding of any association between a drug exposure and impaired neurodevelopmental outcome should be sought as quickly as possible. Below, the evidence pertaining to the neurodevelopment in children exposed to AEDs is reviewed and the approaches taken to understanding these risks are discussed.

2. Neurodevelopment

With the interchangeable terminology of neurodevelopment, neurobehavioral, intelligence and cognitive development, the term neurodevelopment is utilized here to refer to the functional outputs of the brain ranging from motor performance, intelligence, speed of information processing, social functioning as well as to other cognitive skills. The brain is a complex organ, its functional outcomes diverse and therefore the measurements employed to test cognitive functioning are numerous. The trajectory of neurodevelopment over childhood is dynamic with increasing skill acquisition over time and increasing capacity for processing, reasoning, attending, recalling and communicating. Therefore the outcome 'neurodevelopment' is wide and is constantly evolving as the child ages. Due to this diversity and evolution there are numerous approaches to the measurement of neurodevelopment. Measured most commonly as a global cognitive ability score either as an intelligence quotient (IQ) or by the developmental quotient (DQ) for younger children, these scores provide a summary of global cognitive development or intellectual reasoning respectively. The IQ and the DQ actually measure distinct skills; with the later much more about the emergence of new skills in early childhood (e.g. Bayley Scales of Infant and Toddler Development) [43]. Data is often less for specific cognitive skills such as memory, attention or language functioning or educational measures such as reading proficiency; but the impact of specific deficits in these areas should not be considered minimal. Numerous post-natal environmental influences impact on neurodevelopmental outcomes and should be considered. The hereditary genetic contribution to neurodevelopment, particularly IQ, highlights the need for adjustment for parental IQ in studies investigating neurodevelopmental outcomes in children exposed to AEDs. The impact of parental education, occupation, health variables, age at conception as well as child factors of gestational age at birth, breastfeeding, age at assessment, concomitant medication exposure, access to adequate nutrition and stimulation also require consideration. Additionally, considerations from a teratology point of view are also required when interpreting data in this area. Investigation of a single group of mixed AED exposures will not provide reliable data and outcomes are likely to differ depending on the groups composition. Dose of the AED is also likely to be a key concept as is timing and duration of exposure.

Considering these points, the evidence pertaining to neurodevelopmental outcome is reviewed below for each monotherapy AED, summarizing outcomes in infancy and childhood both for global cognitive measures (IQ and DQ) and specific outcomes.

2.1. Carbamazepine

In infancy, a number of studies have failed to find an association between exposure in utero to carbamazepine and infant neurodevelopment measured by the Bayley Scales of Infant and Toddler Development in comparison to control children representative of the general population [34,36,37,44,45]. However, a significantly poorer level of neurodevelopment was found for the children exposed to carbamazepine (n = 163) in comparison to children born to women with an untreated epilepsy (n = 58, MD (mean difference) −7.22 (95% CI −12.76 to −1.67)) [45]. Numbers of included assessments are relatively small in these comparisons and probably accounts for the contrasting finding across the different control groups.

In school aged children Gaily and colleagues [35] found comparable IQ in children exposed to monotherapy carbamazepine (n = 86) in comparison to general population control children (n = 141) when level of maternal education was taken into account; which is consistent with reports from a UK prospective dataset [46]. In a meta-analysis study combining these two studies with others prospective studies, no significant differences in ability were found for children exposed to carbamazepine in comparison to children born to women without epilepsy (n = 150 vs. n = 552, MD −0.03, 95% CI −3.08 to 3.01) and also children of women with untreated epilepsy (n = 163 vs. n = 87, MD 1.84, 95% CI −2.13 to 5.80) [45]. Consistently, the retrospective study of Adab and colleagues [47] also found no significant difference between the IQ of children exposed to carbamazepine (n = 52) and children born to women with untreated epilepsy (n = 80).

In comparison to other AEDs, carbamazepine exposed children (n = 210) were not different in their early development from 160 valproate exposed children [45]. In older children however, the vast majority of studies find higher IQ scores for children exposed to carbamazepine versus those exposed to valproate [35,46,48], with a meta-analysis demonstrating around a nine point higher mean score (MD 8.69, 95% CI 5.51–11.87) for children exposed to carbamazepine (n = 191) in comparison to valproate exposed children (n = 112)[45]. No difference in the global cognitive development of children exposed to carbamazepine has been noted in comparison to children exposed to lamotrigine either in infancy or in the school-aged years [33,34,40,45,48,49]. In comparison to children exposed to phenytoin a non-significant difference is reported [33,36,45,48]. There is currently no direct comparison to children exposed to levetiracetam, topiramate or other newer AEDs.

There is more limited evidence when it comes to the potential effects of carbamazepine on specific cognitive skills. Rovet et al. [50], Veiby et al. [51] and Nadebaum [52] failed to demonstrate an association between exposure and language development in comparison to control children. In the longitudinal study by Baker, Bromley and colleagues, early language development in the children exposed to carbamazepine was not discernible from control children however, verbal IQ scores at school age were significantly poorer than control children following adjustment for confounding influences [34,41,49]. For child motor development, five studies have failed to find poorer outcomes for carbamazepine exposed children in comparison to control children [34,39,51,53,54], however the NEAD study found a dose related decline in motor skills for the carbamazepine exposed children (n = 61). The adaptive behaviour including communication, daily living and socialisation skills, of children exposed to carbamazepine were reported to be comparable to control children [42]; however, in the NEAD study a small but significant dose-related relationship was demonstrated for carbamazepine [55].