Fetal anti-epileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study

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At the time of this trial, the teratogenicity of several anti-epileptic drugs (AEDs), specifically valproate (VPA) was well-known, and the US FDA had issued a formal warning regarding the detrimental effect of in utero exposure to VPA on cognitive outcomes in children. For this reason, the goal of this study was to definitively assess the effect of in utero exposure to VPA, vs. other commonly used AEDs, on cognitive outcomes (via IQ scores and other tests of cognitive function) in children by 6 years of age.

Experimental design and statistics: The NEAD study was a prospective observational investigation with masked cognitive assessments. The study authors enrolled pregnant women with epilepsy on AED monotherapy with either carbamazepine (CBZ), phenytoin (PHT), valproate (VPA), or lamotrigine (LTG); enrollment occurred at epilepsy centers across the UK from 1999 - 2004. Exclusion criteria are noted below.[1] A non-exposed control group was not included here. At the start of the study, enrolled women provided their epilepsy history (seizure diary, AED compliance) and serum AED levels were assessed. Masked assessors then performed a range of cognitive tests (including IQ scores) on children of these enrolled women at 2, 3, 4.5, and 6yrs of age; more extensive testing was performed at 6yrs of age, given that cognitive outcomes at this age were most predictive of later school performance. The primary analysis was group differences in IQ in the total enrolled population, while secondary analyses included IQ scores in children completing age-6 testing, scores on additional cognitive testing at 2, 3, 4.5, and 6yrs, and correlations between age-6 IQ testing and AED dosing + maternal IQ. Primary analyses were analyzed via linear regression models, with appropriate adjustments and covariates (including maternal IQ, maternal education, epilepsy type, among others). Additional linear regressions specifically assessed AED drug type, dose, and maternal IQ as specific predictors of child IQ outcome. Cochrane's Q statistics and Fisher's exact tests were also used where appropriate, and the study authors additionally assessed whether baseline differences in the enrolled women (seizure type, etc.) affected the cognitive performances of their children, aside from their AED exposure alone.

Results: A total of 305 women (311 live births) were included in the primary analysis (see **Table 1** for baseline patient characteristics). Across the 4 AED exposure groups, notable differences were found in terms of IQ, standardized AED doses[2], epilepsy type, and ethnic group. In terms of the primary analyses, significant predictors of child IQ (in the total sample) included AED type, AED standardized dose, maternal IQ, and maternal folate use. When assessing IQ scores at 6yrs of age, children exposed to VPA scored significantly lower than children in each of the other 3 AED exposure groups (**Table 2**), and in utero VPA exposure had a dose-dependent effect on IQ scores a 6yrs of age (Pearson's $r = 0.56$, $p<0.001$). This dose-dependent effect was not seen with any other AED (**Figure 1**). Additionally, as in **Tables 3 & 4**, scores of verbal functioning and general memory were also lower in the VPA group vs. all other AED groups, as were scores of executive functioning in children within the VPA vs. the LTG group. As with IQ scores, there was a dose-dependent effect on scores of verbal and non-verbal functioning, general memory, and executive index in the VPA group, but no other AED group. Follow up analyses additionally suggested that any baseline differences inherent to the enrolled women here (i.e., maternal

[1] Exclusion criteria: women on AED polytherapy, women with IQ scores <70 (predictor of poor IQ in offspring), (+) HIV/RPR serology, progressive CNS disease, exposure to other teratogens besides AEDs, poor AED compliance, recent illicit drug use

[2] Given the known differences in routine AED dosing, daily dosing (in mg) was standardized appropriately for adequate comparison

seizure type, chance of being treated with VPA) were not sufficient, alone, to explain the group differences in child IQ scores seen in the dataset. Finally, additional findings in this data set included an overall higher proportion of *non-right handedness* vs. right handedness in the LTG and VPA group (vs. a normative sample of children), with an additional dose-dependent effect seen in all AED groups (higher mean AED doses for non-right handers vs. right handers)

Conclusions: Overall, this study was the first of its scale to demonstrate the detrimental effects of in utero VPA exposure on a wide range of cognitive functions in children, specifically in a dose-dependent fashion and irrespective of maternal IQ. Further, as an additional finding, both VPA and LTG exposure were associated with reduced right-handedness in this sample, suggesting a potential effect of in utero exposure to some AEDs on cerebral lateralization. Otherwise, the authors note several limitations to the study, namely the observational nature of the study (inability to fully control for differences in baseline patient characteristics), the relatively high # of patients lost to follow up, learning and practice effects in cognitive testing due to repeated testing, lack of a control group, and inability to adequately measure changes in AED levels over the course of pregnancy. However, despite these limitations, the data from this study has since strongly argued against the use of VPA during pregnancy. Proposed mechanisms by which in utero VPA may affect neuronal development include enhanced neuronal apoptosis, inhibition of neurogenesis, and/or reduction of neurotrophic support, among others.

Summary created by Elaine Sinclair, D.O.