

# A Paper on Cognitive Development in Children

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**ABSTRACT:** *The early cognitive performance of children born to mothers with epilepsy (n = 198) has been tested in this longitudinal analysis and compared to a group of children comprising the general population (n = 230). Children were evaluated using the Griffiths Mental Development Scales at a younger age than 2 years, either in their local participating hospital or in their home. An evaluator who was blinded to whether the mother of the boy had seizures as to the type of antiepileptic treatment performed the tests. Children exposed to sodium valproate had a statistically significant elevated risk of delayed early growth in contrast to the control children. Linear regression research revealed a statistically meaningful impact of sodium valproate toxicity on the child's average developmental stage that was not compensated for by confounding variables. For children within an ad hoc group of less widely used antiepileptic medications, delayed early development is also observed, but conclusions should not be made because of the size of this group (n = 13). In children exposed to either carbamazepine or lamotrigine in utero, their overall developmental ability did not differ significantly. Differences observed in particular developmental areas for these two classes were not statistically important after the control for confounders such as social status and maternal IQ. Women with epilepsy should be aware of the dangers present to their future offspring prior to birth to allow for informed choices about treatment. Throughout infancy, infants subjected in utero to antiepileptic medications should be controlled to allow for early intervention if appropriate.*

**KEYWORDS:** *Carbamazepine (CBZ), Sodium Valproate (VPA), lamotrigine (LTG), Polytherapy Treatments.*

## INTRODUCTION

There is evidence that in utero exposure to antiepileptic drugs (AEDs) poses an increased risk of poorer cognitive abilities. The largest risk appears to be associated with exposure to sodium valproate, consistent with findings regarding the incidence of malformation [1]. Despite the fact that several studies aim to address the relative risks of the various AEDs, due to methodological flaws, firm conclusions are lacking. The numbers of children enrolled and the control of confounding variables are key methodological limitations. The effects of confounding variables such as socioeconomic status, maternal IQ ability, and gestational age at birth are of paramount importance in any research involving children. Unreliable conclusions are probable without statistical control over such influences [2]. Children's evaluation at school age allows for more reliable conclusions, but research often focuses on preschool children. The development of children exposed to carbamazepine (CBZ), sodium valproate (VPA), lamotrigine (LTG), or polytherapy from early childhood to school age has not been prospectively documented in any study to date, compared to a control group representative of the general population [3]. A prospective study was set up in 2000 by the Liverpool and Manchester Neurodevelopment Group to document the long-term development of children exposed to utero AEDs. This cohort's early cognitive development is reported here in children younger than 24 months of age.

## METHODOLOGY

### *Prospective recruitment*

Detailed information has been published elsewhere on the induction of mothers into this cohort. This cohort contains a sample that is prospectively defined, which varies from the previously recorded cohort of our party. Between 2000 and 2006, women were hired from maternity clinics at 11 separate Public Health Service hospitals in Merseyside and Greater Manchester, UK. The related ethics committees within the local area gave ethical consent [4]. Epilepsy-free monitoring women were drawn from the same antenatal clinics. The women with epilepsy (WWE) were matched for age, within a 5-year band, and for parity. This was an independent analysis with no clinical management role being played by the authors. The seizure type, syndrome diagnosis,

current seizure frequency, and AED regimen were determined by an epilepsy specialist (GM). The epilepsy syndrome was classified as generalized, or unclassified, focal (localization-related), idiopathic. The dose of AED was reported during pre-conception and during pregnancy. There was an analysis of both the pre-conceptual dose and the cumulative dose over the whole gestation. No specific information was available about the AED prescription.

### *Neuropsychological evaluation until 2 years of age*

The mothers involved in the study were given an appointment between the ages of 4 months and 2 years for the first examination of their infant. Owing to personnel availability, children employed at the Manchester sites were also seen earlier than those recruited at the Liverpool sites. Originally, this consultation was given by letter and then a follow-up phone call. A further letter was submitted by non-responders. Every child was tested at either a local hospital or their home using the Griffiths Mental Health Scales [5]. The National Adult Reading Test, a standardized instrument used to notify maternal intellectual capacity, was asked to be performed by each mother. An assistant psychologist tested the children blinded to not only what AED the infant may have been subjected to, but whether they were born to a WWE. The families were provided with guidance on the progress of the infant, and referrals to professional facilities were made where appropriate [6]. Additional evidence on growth parameters and dysmorphic characteristics has also been obtained and will be published in forthcoming publications. Differences between the classes and then individually by the number of children dropping below the normal range is evaluated as the outcomes of the Griffiths Behavioral Growth Scales [7].

## RESULTS

This first neuropsychological examination was performed by 428 children in all, comprising 73 percent of children whose mothers were successfully participating in this study during pregnancy ( $n = 592$ ). The first neuropsychological examination was not performed by twenty-seven percent of the patients for the following reasons: 80 percent could not be contacted; 15 percent attended the appointment, but the evaluation could not be completed; and 5 percent no longer chose to participate [8]. The mothers who took their child for the first evaluation were slightly older ( $p = 0.005$ ) than those who did not attend, but there were no statistically meaningful socio-economic class differences. Of the 428 children examined, 198 were children born to WWE and 230 were born to epilepsy-free mothers. Due to coexisting disorders likely to impair cognitive capacity, four children out of the 198 children born to WWE were omitted from this analysis: respectively, Di George syndrome; Down syndrome; spina bifida with hydrocephalus; and neonatal meningitis with complications [9]. No infants born to manipulate women will need to be omitted. Therefore, the study involves 424 children: 194 children born to WWE and 230 children born to women in charge. From this point forward, all the figures, percentages, and study findings recorded are without the data from the excluded children and their mothers. 167 children (86 percent) were exposed to AEDs in utero and 27 (14 percent) were not exposed in the category of 194 children born to WWE. Of the infants exposed to utero AEDs, 137 were mono-therapy-exposed and 30 were poly-therapy exposed (17 including VPA). Of the mono-therapy community, 48 were exposed to CBZ, 42 to VPA, 34 to LTG, and the remaining 13 were exposed to mono-therapy [10].

## DISCUSSIONS

In this report, 73 percent of women enrolled during pregnancy, when less than 24 months of age, brought their child for examination. The social status of the group of women attending this first appointment was comparable to that of women not attending, although there was a gap in maternal age. This may be attributed, in part, to a lack of encouragement and a sense of competence. The British Public Health Service, reported shame young mothers experience. Results here suggest that infants exposed to VPA in utero were at an elevated risk of lower, global growth across early developmental areas. 29 percent of children exposed to VPA in utero fell below

normal for general growth. The absence of impact in the composite dose study needs consideration of broader cohorts.

Larger cohorts would allow cumulative research to evaluate the dose effects independently over various trimesters, most especially the third trimester when neuronal activity is plentiful. The children were shown to have an elevated risk at a level comparable to the VPA-exposed children in the 'other mono-therapy' community (relative risk of 3.5). With this party, however, vigilance is appropriate because of its size ( $n = 13$ ). Such a small group size may have resulted in an erroneous inflation of results below average. Alternatively, within this ad hoc community there might be legitimate fears about the kids. Within this category, the presence of a variety of AEDs implies that assumptions cannot be made. More than half of the patients in this group, however, have been exposed to PHT in utero, an AED associated with worse cognitive outcomes. Study into the cognitive ability of children subjected to newer AEDs is urgently needed, as no studies on the damage to a child's cognitive ability have been released to date.

### CONCLUSION

This research found that children subject to in utero VPA mono-therapy are at elevated risk of delayed early childhood growth, with 29 percent of children displaying clinical deficiency levels. The children exposed to CBZ and LTG also displayed distinct regions of lower results, but this could not be directly related to the drug exposures in the linear regression study. For both WWE and their neurologists, the results of this research have consequences. Effective pre-conceptual therapy should be provided to prospective mothers with epilepsy, advising them of an elevated likelihood of adverse early growth.

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