Epilepsy & Behavior 66 (2017) 105–112

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Cognitive functions in children exposed to antiepileptic drugs in utero - Study in Georgia

Sofia Kasradze [a], Nino Gogatishvili [a], Giorgi Lomidze [a,*], Tamar Ediberidze [a], Marine Lazariashvili [a], Ketevan Khomeriki [a], Shorena Mamukadze [a,b], Mariam Metreveli [a,b], Tamar Gagoshidze [a,b], Nino Tatishvili [c], Torbjörn Tomson [d]

[a] Epilepsy Prevention and Control Centre, Institute of Neurology and Neuropsychology, 83/11, Vazha-Pshavela Ave. 0186, Tbilisi, Georgia
[b] Iv. Javakhishvili Tbilisi State University, 1, I. Chavchavadze Ave. 0179, Tbilisi, Georgia
[c] Department of Neuroscience of the Central Children Hospital, 2/6, Lubliana Str. 0159, Tbilisi, Georgia
[d] Department of Clinical Neuroscience, Karolinska Institutet, 18A, Tomtebodavägen, 17177 Stockholm, Sweden

ARTICLE INFO

Article history:
Received 17 June 2016
Revised 7 September 2016
Accepted 8 October 2016
Available online xxxx

Keywords:
Fetal AED exposure
Cognitive teratogenicity
Multivariate analysis

ABSTRACT

Objective: The cognitive teratogenicity of antiepileptic drugs (AEDs) has gained increasing attention in the last decade. The objective of the current study was to assess the effects of AED fetal exposure on the cognitive development of children of mothers with epilepsy from Georgia in a controlled study taking into consideration major confounding factors.
Methods: A prospective cohort group was formed from children and mothers registered in the Georgian National AED-Pregnancy Registry. The study group's age- and gender-matched control children without fetal AED exposure were selected retrospectively. The Intelligence Quotient (IQ) using the Wechsler Adult Intelligence Scale – revised (WAIS-R) was assessed in mothers. The Wechsler Preschool and Primary Scale of Intelligence (WPPSI-4) were used to assess intellectual functioning for children of both study and control groups. Linear regression analysis was performed to detect association of AED exposure on the cognitive performance of children.
Results: In total, 100 children aged 36 to 72 months were evaluated. The IQ of WWE was significantly lower compared to women without epilepsy in all modalities. Exposure to valproate (VPA) ($n = 18$) was associated with lowest cognitive performance regarding Full Scale IQ (FSIQ) (β, −12.04; $p = 0.006$) and verbal comprehension (VCI) (β, −8.89; $p = 0.019$). Maternal FSIQ, maternal performance IQ (PIQ), and child's age at first phrases were independent factors associated with the cognitive development of children.
Conclusions: Multivariate analysis showed VPA to be an independent predictor for decreased cognitive performance. Maternal FSIQ, PIQ, and child developmental achievements were significant confounders for cognitive performance in children.

1. Introduction

Women with epilepsy require long-term treatment with antiepileptic drugs (AEDs), including during the childbearing period and pregnancy, to maintain adequate control of their seizures [1]. It is well known that AEDs are associated with an increased risk of major congenital malformations [2–4], while the cognitive teratogenicity of AEDs has been more in focus the last decade [5]. There is increasing evidence that fetal exposure to valproic acid (VPA) is associated with decreased verbal and full-scale intelligence quotients (IQ) [6–10] and that verbal IQ is significantly lower in VPA-exposed children compared to unexposed or other monotherapy groups including carbamazepine (CBZ) or phenytoin [11]; and that the adverse effects of VPA are dose dependent [8–10,12]. Data about cognitive impairment with CBZ fetal exposure are more uncertain. Adab [11] and Wide et al. [13] did not find any difference in children exposed to CBZ compared to a control group, however; more specific influence on cognitive skills has been suggested by some [14]. (See Box 1.)

Newer-generation AEDs are less well studied. Fetal exposure to levetiracetram (LEV) was not associated with an increased risk of delayed cognitive development under the age of two years, but data are scarce and more investigations are needed due to this limited evidence [14,15]. In utero exposure to lamotrigine (LTG) has been studied more, and does not seem to be associated with a significant detrimental effect on neurodevelopment [8,9,12,16].

There are many factors in addition to AED exposure that can affect the cognitive development of the exposed child. Possible confounding

* Corresponding author.
E-mail addresses: sofiakas@gmail.com (S. Kasradze), nino_gogat@yahoo.com (N. Gogatishvili), lomidzegiorgi@yahoo.com (G. Lomidze), ediberidzet@yahoo.com (T. Ediberidze), lazariashvilimari@ymail.com (M. Lazariashvili), kkhomeriki@yahoo.com (K. Khomeriki), sh.mamukadze@gmail.com (S. Mamukadze), metrmari01@gmail.com (M. Metreveli), gagoshidzet@gmail.com (T. Gagoshidze), n_tatishvili@hotmail.com (N. Tatishvili), torbjorn.tomson@karolinska.se (T. Tomson).

http://dx.doi.org/10.1016/j.yebeh.2016.10.014
1525-5050/

factors include maternal IQ [17,18], socio-economic status, gestational age, and breastfeeding. Breastfeeding seems to be a factor associated with better cognitive development of children [17]. Meador and colleagues measured cognitive ability in children with various AED in-utero exposure and found breastfeeding to be associated with higher IQ and enhanced verbal abilities [19,20].

Most previous studies on the neurodevelopment of children exposed to AEDs in utero come from North America, Northern Europe or Australia. Given the importance of the confounding factors discussed above, it is important to analyze similar data from other parts of the world. The current study attempts to estimate the effects of AED fetal exposure on the cognitive development of children of mothers from Georgia in a prospective study taking into consideration major confounding factors.

2. Material and methods

2.1. Participants

2.1.1. Study groups

2.1.1.1. Children with fetal AED exposure and their mothers. A study with prospective ascertainment of pregnancy-related information was conducted with a group formed from children and mothers registered in the Georgian National AED-Pregnancy Registry that opened in 2001 at the Epilepsy Prevention and Control Centre of the Institute of Neurology and Neuropsychology (INN) in Tbilisi, Georgia. Since its establishment this has been the Georgian branch of the International Registry of Antiepileptic Drugs and Pregnancy (EURAP).

All women with epilepsy registered in the Georgian Antiepileptic Drugs and Pregnancy Register are managed by epileptologists at INN.

From all pregnancies registered in the Georgian registry of EURAP, we selected women with epilepsy whose children had reached ages from 36 to 72 months at the time of the study.

Children with major congenital malformations were excluded from the study (see Box 1 for flow chart).

All mothers with epilepsy of recruited children were invited and informed about the study. After obtaining informed consent from the mothers, they and their children were included in the study group and investigated according to the study protocol.

2.1.2. Control group

Children without fetal AED exposure (and without major congenital malformations, genetic or chromosomal abnormalities, and any somatic diseases) and their mothers (without epilepsy, with no AED or other drug treatment during pregnancy) were selected as a control group. Children from the control group were age and gender-matched with those from the study group. Control group representatives were selected at admittance to the planned consultation or for prophylactic vaccination in three independent Primary Healthcare Centres, located in different districts of Tbilisi, Georgia.

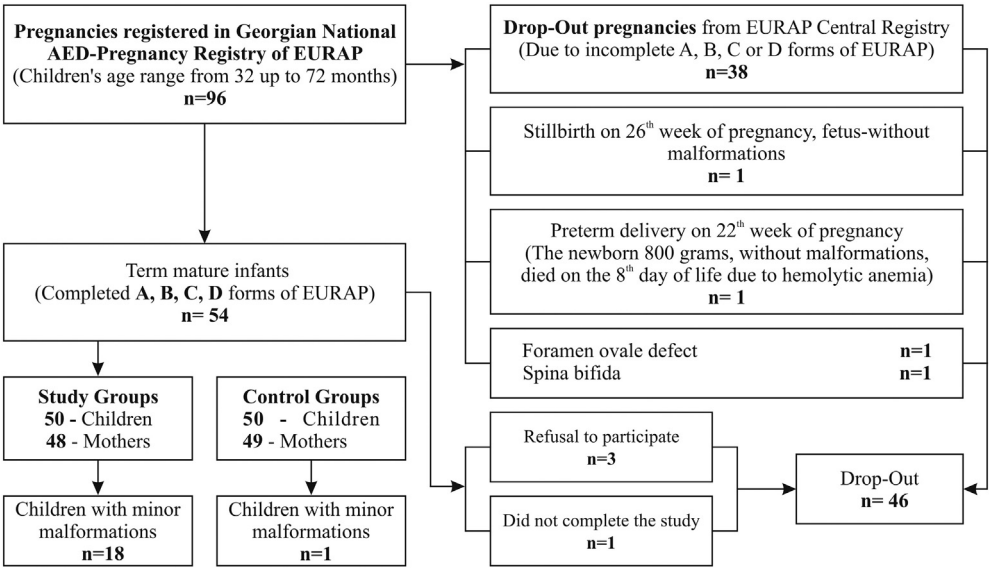
Sixty-one mothers of children who met the study criteria were informed about the study and were invited for the structured interview in the Epilepsy Centre. Of these, 4 mothers declined participation and 57 were interviewed. Of the interviewed mothers, 49 women were selected whose pregnancies and deliveries were under medical and gynecological surveillance and had complete data about anthropologic and medical measurements of their new-borns as well as the course of pregnancy. After obtaining informed consent, the mothers and their children were included in the control group and investigated according to the study protocol. Study data were obtained through a structured questionnaire (see Appendix 1).

Among other data, developmental milestones were assessed retrospectively during the mother's structured interview as indices expressed in months: age at independent sitting, age at independent walking, and age at first phrases. This assessment was made for children in both groups by two non-blinded child neurologists. For detailed information about the structured questionnaire used, see Appendix 1.

2.2. Neuropsychological assessment

The Intelligence Quotient (IQ) using the Wechsler Adult Intelligence Scale – revised (WAIS-R) [21] was assessed in mothers of both study and control groups. Scores for Verbal IQ (VIQ), Performance IQ (PIQ), and Full Scale IQ (FSIQ) were calculated.

The Wechsler Preschool and Primary Scale of Intelligence (WPPSI-4) [22] were used to assess intellectual functioning for children of both the study and control groups. Two forms of WPPSI-4 were used: for children aged 2.6–3.1 years and for children aged 4.0–7.7 years. Composite scores of Verbal Comprehension Intelligence (VCI - Knowledge acquired from child's environment, verbal concept formation and verbal reasoning), Visual-Spatial Intelligence (VSI - Organising visual information,



Box 1. Flow chart showing recruitment of study and control groups.