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

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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

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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.

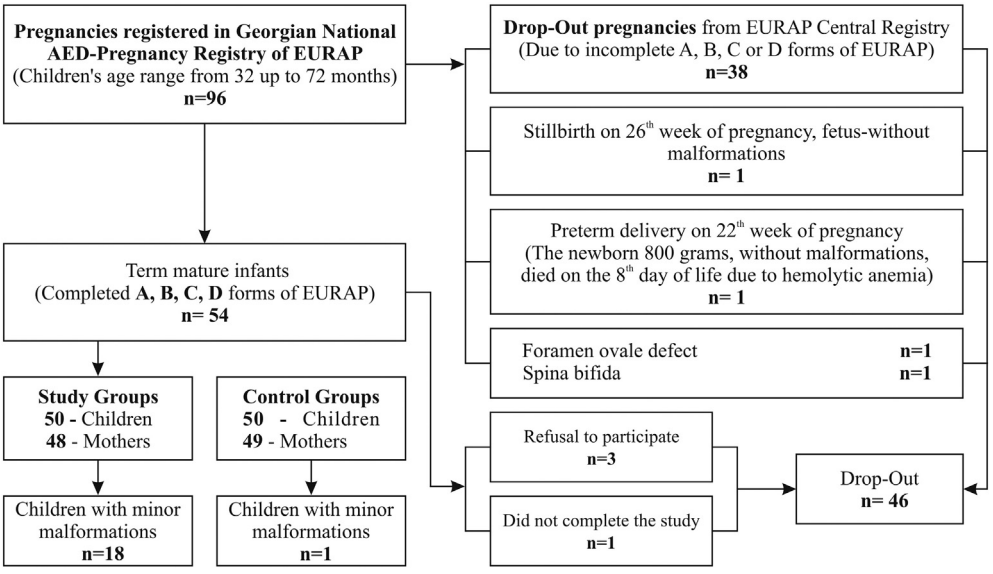
Sixty-one mothers of children who met the study criteria were informed about the study and were invited for the structured interview in the Epilepsy Centre. Of these, 4 mothers declined participation and 57 were interviewed. Of the interviewed mothers, 49 women were selected whose pregnancies and deliveries 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.

Table 1
Socio-demographic and clinical characteristics of mothers and children of study and control groups.

Mothers	Study group $n = 48$	Control group $n = 49$	p-Value
Social status			
University degree, employed	8 (17)	17 (35)	<0.001[c]
University degree, not employed	24 (50)	15 (31)	
Primary school	16 (33)	7 (14)	
Febrile seizures – yes; n (%)	4 (8)	0	0.117[c]
Epilepsy			
Onset age; mean (SD) [min; max]	14.2 (6.5) [1.5; 25]	N/A	N/A
Seizures			
Focal, n (%)	43 (86)	N/A	N/A
Generalised, n (%)	7 (14)	N/A	N/A
Seizure frequency 12 months before pregnancy			
Convulsive			
No seizures	42 (84)	N/A	N/A
Single seizure	6 (12)	N/A	N/A
1–3 seizures per month	2 (4)	N/A	N/A
Non-convulsive			
No seizures	33 (66)	N/A	N/A
Single seizure	4 (8)	N/A	N/A
1–3 seizures per month	13 (26)	N/A	N/A
Reproductive profile			
Menarche Age; median (IQR) [min; max.]	13 (12; 14) [11; 17]	13 (12; 14) [9; 18]	0.849[b]
Menses regularity - regular; n (%)	38 (76)	49 (98)	0.001[c]
Infertility			
Primary, yes; n (%)	10 (20)	1 (2)	0.004[c]
Secondary, yes; n (%)	1 (2)	0 (0)	0.315[c]
Abortion			
Spontaneous	0.2 (0.86) [0; 6]	0.3 (0.87) [0;4]	0.674[b]
Artificial	0.3 (1.6) [0; 11]	0.2 (0.7) [0; 4]	0.496[b]
Pregnancy			
Preconception folate, (yes); n (%)	37 (82)	33 (78)	0.668[c]
Intelligence Quotient (IQ)			
Full scale IQ; mean (SD) [min; max]	81.7 (10.4) [64; 100]	93.9 (12.7) [76; 123]	<0.001[a]
Verbal IQ (VIQ); mean (SD) [min; max]	85.02 (9.7) [66; 104]	94.6 (10.9) [79; 123]	<0.001[a]
Performance IQ (PIQ); mean (SD) [min; max]	80.2 (12.2) [60; 101]	95.1 (15.0) [73; 118]	<0.001[a]

Children	Study group $n = 50$	Control group $n = 50$	p-Value
Newborn			
Breastfeeding (yes); n (%)	37 (74)	47 (94)	0.006[c]
Any congenital anomalies, (yes); n (%)	18 (36)	1 (2)	<0.001[c]
Developmental milestones			
Age at independent sitting (month); mean; (SD)	7.08 (0.98)	6.73 (0.82)	0.058[a]
Age at independent walking (month); mean; (SD)	14.1 (2.44)	12.5 (1.83)	<0.001[a]
Age at first phrases (month); mean; (SD)	25.5 (4.19)	23.9 (4.72)	0.083[a]

N/A - not applicable.
[a] Independent sample *t*-test.
[b] Mann-Whitney *U* test.
[c] Pearson's Chi squared test.

understanding part-whole relationships, attention to visual detail and integrating visual and motor functions), and Full Scale Intelligence Quotient (FSIQ) were calculated for all children.

All tests were performed in the Epilepsy Centre by two (one pediatric, one adult) qualified neuropsychologists. The assessors of the cognitive outcomes were blinded as to whether the child or mother belonged to the case or control group.

2.3. Statistical analysis

A two-sample *t*-test was performed to detect differences between means. A probability of <0.05 was considered as statistically significant. Univariate linear regression was used to examine the relationship between particular predictors and Full-Scale Intelligence Quotient (FSIQ), VCI (Verbal Comprehension Intelligence), and VSI (Visual-Spatial Intelligence) scores of children considered as outcome variables. Specific AEDs (VPA, CBZ or polytherapy in all trimesters); all other AEDs used during pregnancy (PB - three cases, LTG - three cases and LEV - one case) were analysed as one group due to the small number of each) and AED doses were tested. In addition, various other covariates reflecting social, demographic, and medical conditions were used. Variables that showed significant correlation with outcomes in univariate analysis were entered into a multivariate model [where breastfeeding, folate use, abnormalities of reproductive functions, maternal age, employment and education, alcohol and/or tobacco use, seizure frequency, seizure types (convulsive, non-convulsive), gestational age, Apgar score, developmental milestones of children, mother's FSIQ, VIQ and PIQ

Table 2
AED treatment during pregnancy in women with epilepsy (WWE).

AED treatment	N of WWE (%)
CBZ	16 (32)
VPA	18 (38)
Other AEDs in monotherapy (PB - 3; LTG -3; LEV - 1)	7 (14)
Polytherapy	9 (18)
Polytherapy with VPA	*2*

CBZ: carbamazepine; VPA: valproate; PB: phenobarbital; LTG: lamotrigine; LEV: levetiracetam.

Table 3
Mean scores and confidence intervals by AED exposure type across FSIQ, VCI, and VSI[a].

	Full scale IQ	Verbal comprehension (VCI)	Visual-spatial (VSI)
AED exposure type			
Overall AED exposure	84.0 (80.1; 87.9)**	84.4 (80.9; 87.9)**	86.4 (82.6; 90.2)**
CBZ ($n = 16$)	88.2 (82.1; 94.1)*	89.1 (84.2; 94.1)	89.5 (84.1; 94.9)*
VPA ($n = 18$)	82.3 (75.5; 89.2)**	82.6 (75.4; 89.8)**	87.2 (79.4; 94.9)**
VPA more than 800 mg ($n = 12$)	80.3 (72.9; 87.6)**	83.0 (75.2; 90.8)*	85.3 (74.7; 95.8)*
Other AEDs ($n = 7$)[b]	79.6 (62.1; 97.1)**	79.7 (68.4; 91.0)**	79.9 (66.7; 92.9)**
LTG ($n = 3$)	73.7 (44.6; 102.9)*	76.0 (55.7; 96.3)*	77.0 (60.7; 93.3)*
PB ($n = 3$)	75.0 (27.8; 122.2)*	79.0 (37.9; 120.0)*	74.0 (42.9; 105.1)*
Polytherapy ($n = 9$)	84.7 (75.9; 93.6)**	84.0 (76.5; 91.4)*	85.4 (76.3; 94.6)*
Control ($n = 50$)	101.4 (97.6; 105.3)	97.1 (93.8; 100.3)	101.5 (97.6; 105.4)

CBZ: carbamazepine; VPA: valproate; PB: phenobarbital; LTG: lamotrigine.
[a] *p*-Values in all cases indicates comparison vs. control group.
[b] Other AEDs means three cases of LTG exposure, three cases of PB, and one case of exposure with LEV in 2nd and VPA in 1st and 3rd trimesters.
* $p < 0.05$.
** $p < 0.001$.

scores were noted]. Multivariate hierarchical stepwise regression models were used to adjust for covariates. Co-linearity analysis showed that maternal IQ (verbal, performance and total) are problematic, however, standardization of maternal IQ scores improved the problem of co-linearity. The VCI, VSI and full scale IQ of children were included as outcome variables.

An adjusted R-square and non-standardised beta coefficient (B) were calculated. Statistical analyses were performed using SPSS (IBM SPSS Statistics, Version 21.0, Armonk, NY).

3. Results

In total, 100 children aged 36 to 72 months were included in the study. Among them, 50 children (mean age 52.5 months; SD 12.8; min - 33, max - 80) of 48 mothers had been exposed to AEDs in utero (20; 40% male) and the remaining 50 (mean age 54.2 months; SD 14.5; min - 24, max - 81) children of 49 mothers had not (23; 46% male). The age of mothers with (mean age - 30.5; SD - 4.9) and without (mean age - 31.7; SD - 5.2) epilepsy did not differ significantly. It should be noted that the IQ of women with epilepsy (WWE) was significantly lower compared to women without epilepsy in all modalities. In 18 children of WWE, some minor physical disfigurements were observed (hypertelorism, forward position of ears, synophrosys, and widened nasal bridge). The main characteristics of study and control groups are described in Table 1.

The most frequently used AEDs were CBZ and VPA. Only three WWE used phenobarbital (PB) and another three LTG during pregnancy. Eighteen percent of woman with epilepsy (nine cases) were treated with AED polytherapy. Among them, five individuals were switched to polytherapy during the first or second trimester of pregnancy. For more detailed information about AED use, see Table 2.

The cognitive outcomes in relation to exposure are presented in Table 3. These outcomes were, in general, significantly poorer among children exposed to AEDs, regardless of type of treatment. Exposure to VPA was associated with lowest Composite Scores in all modalities, and apparently more so with a daily VPA dose greater than 800 mg ($n = 12$). No particular AED showed significant association with decreased IQ when compared to other AEDs or polytherapy regimen.

Breastfeeding was associated with significantly higher IQ in all modalities compared to formula or mixed feeding (full-scale IQ $p < 0.001$; VCI $p < 0.001$; VSI $p = 0.002$). This trend is retained in AED exposure (FSIQ $p = 0.01$; VCI $p = 0.04$) and control groups (VCI $p = 0.014$). Folic acid supplementation was not associated with Composite Scores in any modality. Frequency of convulsive or non-convulsive seizures within one year prior to delivery was not associated with Composite Scores. For more details see Table 4.

3.1. Regression analysis by IQ domain

Results of the univariate analysis of the relationship of various AED exposure and developmental milestones on IQ domains are provided in Table 5.

3.1.1. Multivariate analysis

3.1.1.1. Full scale IQ. Exposure to VPA (β, −12.04; $p = 0.006$), Other AEDs (β, −16.91; $p = 0.006$), as well as maternal PIQ (β, 6.543; $p < 0.001$) and age at first phrases (months) (β −1.3; $p < 0.001$) were associated with full scale IQ score of children. Adjusted R squared value indicates that nearly 50% of variability of children's full scale IQ could be explained by factors retained in the model.

3.1.1.2. Visual-spatial (VSI). Exposure to other AEDs (β, −17.31; $p = 0.006$), along with maternal PIQ (β, 7.65; $p < 0.001$) and age at first phrases (months) (β, −0.862; $p = 0.014$), were associated with the VSI score of the study subjects. Adjusted R squared indicates that factors retained in the model could explain more than 42% of the variability of children's verbal IQ.

3.1.1.3. Verbal comprehension (VCI). Exposure to VPA (β, −8.89; $p = 0.019$) and other AEDs (β, −12.9; $p = 0.018$), as well as maternal full scale IQ (β, 3.75; $p = 0.019$) and age at first phrases (months)

Table 4
Mean and mean difference scores for Full Scale IQ (FSIQ), Verbal Comprehension Intelligence (VCI), Visual-Spatial Intelligence (VSI) of children by various social and medical factors.

Factors	Full scale IQ	VCI	VSI
Breastfeeding ($n = 84$) vs. artificial; mean, (mean difference)	95.3 (−15.8)**	93.1 (−14.6)**	96.0 (−12.8)*
Preconception folate (yes; $n = 70$) vs. no folate; mean, (mean difference)	95.6 (− 6.2)	92.8 (− 4.2)	95.5 (−3.7)
Any minor congenital anomalies (yes; $n = 19$) vs. no anomaly; mean, (mean difference)	82.3 (12.9)*	83.3 (9.2)*	84.1 (12.2)*
Mother's social status[a] ($n = 25$); mean, (mean difference)	98.9 (−8.2)*	95.0 (−3.2)	99.5 (−8.5)*

[a] Mother's social status was stratified as university degree with employment vs. all others.
* $p < 0.05$.
** $p < 0.001$.

Table 5
Comparisons between the various AED exposure groups and developmental milestones in terms of Full Scale IQ (FSIQ), Verbal Comprehension Intelligence (VCI), Visual-spatial Intelligence (VSI), domains (univariate analysis).

	FSIQ		VSI		VCI	
	Unstandardised coeff. beta	*p*-Value	Unstandardised coeff. beta	*p*-Value	Unstandardised coeff. beta	*p*-Value
AED treatment						
VPA vs. control	−12.87	0.001	−8.385	0.033	−10.063	0.003
CBZ vs. control	−8.18	0.041	−8.313	0.031	−3.910	0.247
VPA vs. CBZ	−3.884	0.358	−0.142	0.974	−5.021	0.221
VPA vs. other AEDs	−0.684	0.905	3.794	0.517	0.852	0.871
LTG vs. control	−19.66	0.039	−17.47	0.054	−15.19	0.054
PB vs. control	−18.29	0.052	−20.57	0.023	−12.09	0.126
Other AEDs vs. control[a]	−10.94	0.032	−11.889	0.016	−10.115	0.018
Polytherapy vs. control	−16.68	0.001	−16.08	0.002	−13.06	0.002
Polytherapy vs. single drug	−6.600	0.420	−10.140	0.82	−0.488	0.916
VPA more than 800 mg vs. control	−14.16	0.004	−9.89	0.032	−8.78	0.033
VPA 800 mg or less vs. control	−7.4	0.242	−3.78	0.536	−9.54	0.07
Developmental milestones						
Age at indep. sitting (month)	−4.32	0.01	−3.13	0.059	−3.98	0.004
Age at indep. walking (month)	−2.33	<0.001	−1.68	0.012	−1.73	0.002
Age at first phrases (month)	−1.46	<0.001	−1.002	0.003	−1.29	<0.001
Breastfeeding vs. artificial	15.76	<0.001	12.81	0.002	14.56	<0.001

CBZ: carbamazepine; VPA: valproate; PB: phenobarbital; LTG: lamotrigine; LEV: levetiracetam.
[a] Other AEDs means three cases of LTG exposure, three cases of PB and one case of exposure with LEV in 2nd and VPA in 1st and 3rd trimesters.

(β −1.27; $p < 0.001$), were associated with the VCI score of study subjects. Adjusted R squared shows that more than 38% of the variability of children's VCI could be explained by factors retained in the model.

Table 6 provides detailed results of the multivariate analysis of associations of various AED exposure and other medical or social factors on the IQ domains of children.

4. Discussion

Multivariate regression showed that VPA was associated with decreased FSIQ and VCI scores. We confirm previous reports from other countries indicating the adverse effects of maternal use of VPA during pregnancy on the cognitive development of the exposed children [6,7,11,22–24]. According to beta values from the multivariate model, exposure to VPA reduces performance on the FSIQ by 12.04 points and VCI by 8.89 points when controlled for confounding variables. This is equivalent to over half a standard deviation of test performance and is likely to present significant difficulties in the children's daily life. These findings are also in line with the review data from Bromley and colleagues [23].

Compared to the control, group exposure to VPA, with doses above 800 mg, was associated with poorer cognitive development, including VCI, VSI, and full scale IQ. Similar results were reported by Meador and colleagues [8]. Also in line with previous findings [12], VPA at lower doses did not have the same association with poor cognitive development. From our data, it appears that the risk associated with VPA is halved with lower doses. This has a direct implication on clinical practice, although more data are needed.

We also found a significant reduction in all IQ modalities in cases exposed to other AED groups, that mainly represent cases exposed to LTG and PB. The association of LTG exposure to impaired cognitive development is scarce [23]; however, exposure to PB, according to some studies, is associated with reduced IQ [24]. In our study it is difficult to discuss the negative effect on cognitive development of LTG or PB exposed children because of the small sample, however, our findings emphasize the need for further research of the cognitive teratogenicity of those AEDs.

The significant difference in IQ between the study mothers with epilepsy and control mothers is important. In fact, this difference between mothers in the study and control group was of the same magnitude as the difference between exposed children and control children. This is a surprising and very important finding, highlighting the need to include an assessment of the cognitive functions of mothers and also demonstrates the difficulties in generalizing results from one study population to other. It should also be noted that fewer WWE had university level of education, and fewer of them were employed. This could be a reflection of the observed differences between WWE and control mothers in various IQ modalities. Many studies have shown that epilepsy leads to difficulties in education and employment due to social stigma [25,26]. Comorbidities may also contribute. In the present

Table 6
Multivariate analysis for association between the various medical and social factors and Full Scale IQ (FSIQ), Verbal Comprehension Intelligence (VCI), and Visual-Spatial Intelligence (VSI) domains of children (variables retained in the final model presented).

	FSIQ		VSI		VCI	
	Unstandardized coeff. Beta	*p*-Value	Unstandardized coeff. beta	*p*-Value	Unstandardized coeff. beta	*p*-Value
AED treatment						
VPA vs. control	−12.04	0.006	–	–	−8.89	0.019
Other AEDs vs. control[a]	−16.91	0.006	−17.31	0.006	−12.9	0.018
Developmental milestones						
Age at first phrases (month)	−1.3	<0.001	−0.862	0.014	−1.27	<0.001
Maternal IQ						
Maternal FSIQ	–	–	–	–	3.75	0.019
Maternal PIQ	6.543	<0.001	7.65	<0.001	–	–
Adjusted R squared for whole model[b]	0.497		0.422		0.387	

PB: phenobarbital; LEV: levetiracetam; VPA: valproate.
[a] Other AEDs means three cases of LTG exposure, three cases of PB and one case of exposure with LEV in 2nd and VPA in 1st and 3rd trimesters.
[b] For interpretation for R squared values see Section 4.1. above.

study, we did not assess stigma level or quality of life; however, our previous study showed considerable stigma and negative attitude towards epilepsy and individuals with epilepsy in Georgia [27], which may contribute to the observed differences between mothers.

Several studies have stressed the benefits of breastfeeding for the children's cognitive performance among those exposed to AEDs [19,20,28,29]. We found a similar effect of breastfeeding on cognitive development among both the exposed and the control group, yet breastfeeding was not retained in the final multivariate model. Further investigation of those factors in terms of cognitive functioning is important as it is linked to a practical recommendation on breastfeeding for WWE.

We tested several confounders that are shown to be strong non-pharmacological correlates for the intellectual abilities of children: We found that exposure to VPA and other AEDs was retained in the model together with the mother's cognitive abilities (full-scale and performance IQ) and early developmental milestone (age at first phrases) as independent risk factors. Our findings are in concordance with other studies where maternal IQ was found to significantly correlate with the cognitive development of children [18,30]. However, we also found that a child's early developmental milestone (age at first phrases), also has a significant effect on predicting cognitive development during childhood. Adjusted R squared scores from 0.40 to 0.50 underlines the reasonably good ability of the regression models to explain the variability of children's IQ with in-utero exposure to AEDs.

We excluded children with major congenital malformations (MCM) from the study. Of course, MCMs are part of the phenotype associated with AED exposure. However, they can also hinder performance of neuropsychological testing and misrepresent results and increase the risk of bias. To avoid this, cases with MCM were excluded from the study. The fact that this study finds an association between VPA exposure and neurodevelopmental outcome in children without MCMs is consistent with the finding of Nadebaum and colleagues [31] and indicates that the impact on neurodevelopment is not limited to children with MCMs.

4.1. Strengths and weaknesses of the study

We conducted multivariate analysis of basic IQ modalities that is unique for this article and gives insight into the effects of fetal AED exposure on verbal comprehension, visual-spatial, and full scale IQ indices. Use of blinded neuropsychological assessments, the use of standardized IQ measures, the consideration of independent AED groups, and the statistical control for confounding variables are additional strengths of the presented study. We also revealed that early developmental milestones are related to cognitive outcome which, to our knowledge, has never been studied in AED-exposed groups before.

However, the study has significant weaknesses that need to be acknowledged. The ascertainment of data regarding pregnancy was prospective but the recruitment of children into this follow-up study was not. This may increase the risk of bias. However, a Cochrane review [23] found similar risk estimates to come from this type of register-based study as from truly prospective studies.

The relatively small sample size of the study should be noted - the statistical power of the study can detect large effect sizes. The small number of LTG and PB cases, as well as combining those AEDs as one variable, makes interpretation of these results difficult.

5. Conclusions

Our data suggests that fetal exposure to VPA could be harmful for cognitive development in childhood. Maternal IQ and age at first phrases are significant confounders for IQ scores of offspring and should be considered during data analysis. The lower cognitive and educational levels of mothers with epilepsy is a general health and educational concern for women with epilepsy in Georgia, and calls for action to clarify the causes as well as to counteract these discrepancies.

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Appendix 1

	Mothers		Children	
	Women with epilepsy	Women without epilepsy	Exposed to AEDs	Not exposed to AEDs
Structured interview	Age/education/profession/employment Age at onset sexual activity Anamnesis of reproductive-endocrine disorders Anamnesis of infertility (primary/secondary) Anamnesis of maternal Febrile Convulsions (FC) Family history of FC Family history of congenital malformations Family history of genetic diseases/epilepsy/other diseases Number of this pregnancy Number of deliveries Number of stillborn offspring Number of malformed offspring Number of neonatal deaths Number of spontaneous abortions Number of induced abortions Number of induced abortions due to fetal malformations Number of normal neonates Age of mother at this pregnancy/age of	Age/education/profession/employment Age at onset sexual activity Anamnesis of reproductive-endocrine disorders Anamnesis of infertility (primary/secondary) Anamnesis of maternal Febrile Convulsions (FC) Family history of FC Family history of congenital malformations Family history of genetic diseases/epilepsy/other diseases Number of this pregnancy Number of deliveries Number of stillborn offspring Number of malformed offspring Number of neonatal deaths Number of spontaneous abortions Number of induced abortions Number of induced abortions due to fetal malformations Number of normal neonates Age of mother at this pregnancy/age of	Date of birth Age in months Gestational age Weight at birth in grams Length at birth in cm's Occipital-frontal head circumference at birth in cm's Apgar score at 1 min/at 5 min Type of nutrition/results of neonatal screening Weight of child at the time of examination Height of child at the time of examination Occipital-frontal head circumference at the time of examination Age at independent sitting Age at independent walking Age at first phrases Listing of stigmatas Heart rate/T/A/cardiac pathology Respiratory date The skin and mucous membranes Lymph nodes	Date of birth Age in months Gestational age Weight at birth in grams Length at birth in cm's Occipital-frontal head circumference at birth in cm's Apgar score at 1 min/at 5 min Type of nutrition/results of neonatal screening Weight of child at the time of examination Height of child at the time of examination Occipital-frontal head circumference at the time of examination Age at independent sitting Age at independent walking Age at first phrases Listing of stigmas Heart rate/T/A/cardiac pathology Respiratory date The skin and mucous membranes Lymph nodes

Appendix (*continued*)

	Mothers		Children	
	Women with epilepsy	Women without epilepsy	Exposed to AEDs	Not exposed to AEDs
	father at birth of child Folic acid use (start date/end date/dosage) Maternal diseases before pregnancy/ at 1st trimester/at 2nd trimester/ at 3rd trimester Results of ultrasound at 1st trimester/ at 2nd trimester/at 3rd trimester Treatment with antibiotics/hormones – 1 year before pregnancy/at 1st trimester/at 2nd trimester/ at 3rd trimester/at delivery Cigarette smoking/alcohol intake/ drug abuse Results of AFP Delivery/number of this delivery/ type of this delivery maternal epilepsy/type of seizures Epilepsy Age of onset maternal epilepsy AEDs and total daily dosage before pregnancy/at 1st trimester/at 2nd trimester/at 3rd trimester Frequency of seizures 1 year before pregnancy/at 1st trimester/at 2nd trimester/at 3rd trimester/at delivery Frequency of GTCS 1 year before pregnancy/at 1st trimester/at 2nd trimester/at 3rd trimester/at delivery Frequency of non-convulsive seizures 1 year before pregnancy/at 1st trimester/at 2nd trimester/at 3rd trimester/at delivery Status epilepticus 1 year before pregnancy/at 1st trimester/at 2nd trimester/at 3rd trimester/at delivery Type of delivery (physiological/ caesarean section/complications) Seizures during delivery	father at birth of child Folic acid use (start date/end date/dosage) Maternal diseases before pregnancy/ at 1st trimester/at 2nd trimester/at 3rd trimester Results of ultrasound at 1st trimester/ at 2nd trimester/at 3rd trimester Treatment with antibiotics/hormones - 1 year before pregnancy/at 1st trimester/ at 2nd trimester/at 3rd trimester/ at delivery Cigarette smoking/alcohol intake/ drug abuse Results of AFP Delivery/number of this delivery/ type of this delivery	Bone and joint system Urinary system Gastro-intestinal system Sight Hearing Chronic diseases Current treatment Morbidity rates during 1 year Past diseases Immunization	Bone and joint system Urinary system Gastro-intestinal system Sight Hearing Chronic diseases Current treatment Morbidity rates during 1 year Past diseases Immunization
Investigations	Neuropsychological testing WAIS-R	Neuropsychological testing - WAIS-R	Neuropsychological testing - WPPSI-4 Standard - EEG	Neuropsychological testing - WPPSI-4 Standard-EEG
Consultations			Neurological Pediatric Psychiatrist	Neurological Pediatric Psychiatrist

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