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Developmental and Behavioral Consequences of Intrauterine Anti-Seizure Medication Exposure

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ABSTRACT

Introduction: In this cross-sectional study, whether there is a difference in the prevalence of developmental/behavioral problems in children of those who received mono/polytherapy during pregnancy; How Valproic Acid (VPA) exposure affects developmental/behavioral characteristics compared to other antiseizure medications (ASM) was also investigated.

Method: 64 children of 46 women with epilepsy (WWE) with children aged 0–18 years were included. Ankara Development and Screening Inventory (ADSI) for their children up to the age of six and The Child Behavior Checklist for Ages 4–18-CBCL/4–18 scale was applied for the ages of 6–18. Children exposed to prenatal ASM were divided into two groups as polytherapy and monotherapy. Children exposed to monotherapy were investigated by drug exposure, as well as exposure to VPA and other ASMs. Chi-square test was used to compare qualitative variables.

Results: When monotherapy and polytherapy groups were compared, a significant difference was found in the language cognitive development area of the ADSI (p=0.015) and in terms of the sports activity variable in CBCL/4–18 (p=0.039). When the VPA monotherapy and other ASM monotherapy groups were compared, a significant difference was found in terms of sports activity in CBCL-4–18 (p=0.013).

Conclusion: It was found that language and cognitive development can be delayed, the level of engagement in sports activities can be reduced in children exposed to polytherapy. The rate of doing sports activities in valproic acid monotherapy exposure may decrease.

Keywords: Antiseizure medication, children, epilepsy, neurodevelopment

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INTRODUCTION

It is known that the use of antiseizure medications (ASMs) during pregnancy may cause cognitive, behavioral and developmental problems in the child and adversely affect normal development (1). Despite the known side effects of ASMs, it is necessary to continue the use of ASMs during pregnancy to protect both the mother and the fetus as well as to prevent seizures that may develop during pregnancy (2). There are many studies in the literature comparing the developmental characteristics of the children of women with epilepsy (WWE) who have and have not used ASM during pregnancy. For example, it has been revealed that children of mothers using ASM have difficulties in mental and motor development, communication, peer relations, and social adaptation skills when compared with children of WWE who have not used ASM (3,4). When the studies on the developmental effects of different ASMs used in pregnancy are examined, it is seen that Valproic Acid (VPA) is considered to be the drug with the greatest risk in terms of congenital malformation, cognitive and behavioral problems (5–8). It is known that high doses of maternal VPA negatively affect cognitive functions and may lead to 'attention deficit and hyperactivity disorder (9). It is stated that VPA alone or in combination with other drugs often causes side effects such as neurodevelopmental delay (10). Compared to studies on earlier ASMs, data on the influence of newer ASMs on neurodevelopment appear to be limited. One recent review evaluating the literature on newer ASMs concluded that there is insufficient evidence to make conclusions concerning newer ASMs, except for lamotrigine (11).

Highlights

- **Language and cognitive development can be delayed in children exposed to maternal polytherapy.**
- **Level of engagement in sports activities can be reduced in children exposed to maternal polytherapy.**
- **The rate of doing sports activities can be decreased with the exposure of VPA.**

Although ASMs are known to increase the risk of congenital anomalies 2–4 times, the birth results in a healthy child in most WWE (5,12). Even though no problems are encountered in the neonatal period, the developmental status of the children should be followed up in the long term. For this purpose, in this study, it was investigated whether ASMs, especially VPA, cause long-term effects on the fetus such as

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developmental delay/behavioral problems. To that end, answers to the following questions were sought: Is there any difference in the prevalence of developmental delay/behavioral problems in children of those who received mono/polytherapy during their pregnancy? Do different ASMs (carbamazepine [CBZ], lamotrigine [LTG], levetiracetam [LEV] and oxcarbazepine [OXC]) used by pregnant women affect the severity of developmental retardation/behavioral problems seen in children? Is the frequency of developmental delay/behavioral problems higher in the children of pregnant women using VPA compared to pregnant women using other ASMs? Are the developmental differences in children of pregnant women using different doses of VPA related to the dose used?

METHOD

In this study, we retrospectively evaluated patients who were followed in the epilepsy clinic of Haseki Training and Research Hospital Department of Neurology between January 1997 and November 2021, were diagnosed with epilepsy before pregnancy and had used ASM for at least 6 months prior to pregnancy. Sixty-two WWE were identified in the evaluation, while 26 women couldn't be contacted by telephone. This study included 64 children of 46 WWE with children aged 0 –18. There were 18 pairs of siblings. Children with congenital anomalies or mental retardation were not included in the study. The interviews were conducted in November 2021 by telephone. This study was approved by the Haseki Training and Research Hospital Institutional Review Board committee (approval number: 2021–272). Written consent was obtained from the mothers following a detailed explanation of the study.

Data Collection

From patient charts, epilepsy type, age of onset, epilepsy in family members, consanguineous marriage, number of pregnancies, gestational age, educational status, treatment (without medication, monotherapy, polytherapy, ASM types), seizure frequency during pregnancy and folic acid use of WWE were retrieved. Seizure types and syndromes were determined according to the International League Against Epilepsy, 2017 classification. Children exposed to prenatal ASM were divided into two groups: polytherapy and monotherapy. Children exposed to monotherapy were investigated by drug exposure, as well as exposure to VPA monotherapy and other ASM monotherapies. In the presence of VPA monotherapy exposure, the data were also analyzed in two separate doses, VPA doses of 500 mg/day and below, and VPA doses of 500 mg/day above.

In interviews with mothers, the Ankara Development and Screening Inventory (ADSI) for their children up to the age of six was administered, and for the ages of 6–18, the Child Behavior Checklist for Ages 4–18 (CBCL/4–18) scale was administered. The ADSI is a developmental test used to determine the developmental problems of children between the ages of 0–6. The test consists of 154 items containing "Yes, No, I don't know" answers given by the caregiver to the questions. The child's current developmental status is determined by evaluating in language-cognitive (65 items), fine motor (26 items), gross motor (24 items) and social skills-self-care (39 items) areas. The test results reflect the development of infants and children in the 0–6 age group at the time of evaluation as the four sub-tests mentioned and general development. The CBCL/4–18 was developed in order to evaluate the competence areas and problem behaviors of children and young people aged 4–18 in line with the information obtained from parents. The scale consists of 20 competencies and 118 problem items. Items related to proficiency include sports and non-sports activities in which children and young people are actively involved, and actions they take on inside or outside their houses. The rating is based on the amount and quality of participation. It also determines their functions in social areas. These are functions such as any sports or social organization, club or group membership, friendship, siblings, mother and father relations, playing games or doing business on their own. It reflects the status of success at school, problems concerning school, and the quality and quantity of participation in school activities. A total efficacy score is obtained from the sum of activity, sociability and school subscales. The scale also includes open-ended questions and expressions. They question whether the child or young person has any illness, physical or mental disability, their most admired characteristics, their most concerning characteristics for their parents, and provide a brief medical history from the family, even if it is not scored in the profile. In this study, the competency part of the scale (activation-mobility, social activities and school achievement) was used and total score evaluations were made.

Statistics

The data was analyzed with the SPSS 17 package program. Continuous variables are expressed as mean and standard deviation (SD), and categorical variables are expressed as frequency and percentage. Chi-square test was used to compare qualitative variables. Fisher's Exact Test was used in 2×2 tables where the expected values in the cells didn't have sufficient volume. Pearson Chi-Square analysis was performed on the RxC tables with the use of Monte Carlo Simulation. (Monte Carlo: Chi-square analysis was performed with the help of Monte Carlo Simulation where 20% of the expected values in the cells is less than 5). Subgroup analyses were interpreted with Bonferroni correction. A statistical significance level of alpha was accepted as $p<0.05$. Potential confounding factors that could affect the test results of the children were determined as the type of epilepsy of the mother, the frequency of seizures during pregnancy, the education status of the mother and the consanguinity of the parents. In the case of statistically significant findings, logistic regression analysis was performed to investigate the effects of confounding factors.

RESULTS

A total of 34 children, 17 girls and 17 boys, aged 0–6 years who underwent ADSI (mean age: 3.44 years; STD: 1.93, min-max: 0.30–6.62 years); a total of 30 children, 13 females and 17 males aged 6–18 (mean age: 9.50 years; STD: 3.92, min-max: 6.20–17.82 years) who received CBCL/4–18 were included in the study. Below, in Table 1, clinical and demographic characteristics of the mothers are given and in Table 2, the characteristics of the pregnancies are given. When children of women who used monotherapy and polytherapy during pregnancy were compared, a significant difference was observed in the Language-Cognitive development area of ADSI in the 0–6 age group (p=0.015). Accordingly, while 50% (11/22) of the children

Table 1. Clinical and demographic characteristics of women

	N=46	%	mean ± STD	Min-max
Educational background				
Less than primary	3	6.5		
Primary school	17	37.0		
Middle school	14	30.4		
High school and above	12	26.1		
Epilepsy type				
Focal	13	28.3		
Generalized	31	67.4		
Unclassifiable	2	4.3		
Epilepsy in the family	16	34.8		
Consanguineous marriage	9	19.6		
Age			34.22±16.26	23–56
Epilepsy age of onset (years)			13.98±5.14	4–26
Parity			2.52±1.44	1–9
Average gestational age (years)			26.73±5.40	16–39

Max: maximum; Min: minimum; STD: standard deviation.

Table 2. Characteristics of pregnancies

	0–6 age group		6–18 age group		Total (N=64)	
	(N=34)	%	(N=30)	%		%
Use of folbiol during pregnancy	29	85.3	21	70.0	50	78.1
Treatment						
Without medication	3	8.8	6	20.0	9	14.1
Monotherapy	22	64.7	20	66.7	42	65.6
VPA	10	29.4	10	33.3	20	31.3
CBZ	5	14.7	5	16.7	10	15.6
LEV	4	11.8	0	0.0	4	6.3
LTG	2	5.9	3	10.0	5	7.8
OXC	1	2.9	2	6.7	3	4.7
Polytherapy	9	26.4	4	13.3	13	20.3
VPA+TPM	0	0.0	2	50.0	2	15.4
VPA+LEV	3	33.3	0	0.0	3	23.1
VPA+LTG	1	11.1	0	0.0	1	7.7
CBZ+LEV	2	22.2	1	25.0	3	23.1
CBZ+LTG	1	11.1	1	25.0	2	15.4
LEV+LTG	1	11.1	0	0.0	1	7.7
CBZ+LEV+LTG	1	11.1	0	0.0	1	7.7
Seizure frequency during pregnancy						
Seizure free	21	61.8	15	50.0	36	56.3
Rare	8	23.5	11	36.7	19	29.7
Frequent	5	14.7	4	13.3	9	14.0

CBZ: carbamazepine; LEV: levetiracetam; LTG: lamotrigine; OXC: oxcarbazepine; VPA: valproate.

of women who received monotherapy showed rapid development in the field of language-cognitive development, no rapid development was detected in any (0/9) of the children of women who received polytherapy. In the 6–18 age group, the number of children who do not do any sports activities was significantly higher in the children of women who take polytherapy (3/4, 75%) compared to the children of women who receive monotherapy (3/20, 15%) (p=0.039).

The children of women who used monotherapy during pregnancy were regrouped according to the ASM used: VPA, CBZ, LEV, LTG, TPM, OXC. There were no significant differences in terms of both the ADSI and CBCL/4–18 results (Table 3 and Table 4, respectively) (p>0.05). The children of women who used VPA monotherapy during pregnancy and those of other ASM monotherapies were compared. No significant difference was found in any developmental area in children who underwent ADSI (p>0.05). In the 6–18 age group, there was a significant difference in terms of sports activity (p=0.013). According to this, all children of women using other ASM monotherapy were doing 1 sports activity (10/10), while only 40% of the children of women who used VPA monotherapy performed 1 sports activity (4/10).

Table 3. Children's ADSI results by antiseizure medication type

ADSI	Monotherapy (N=22)					
	VPA (N=10, %)	CBZ (N=5, %)	LEV (N=4, %)	LTG (N=2, %)	OXC (N=1, %)	P value
General development						
Delay	1/10	1/20	0/0	0/0	0/0	
Must be watched	4/40	1/20	1/25	1/50	0/0	0.990
At the expected level	4/40	3/60	2/50	1/50	1/100	
Fast	1/10	0/0	1/25	0/0	0/0	
Language-cognitive						
Delay	2/20	1/20	0/0	0/0	0/0	0.968
Must be watched	4/40	1/20	2/50	1/50	0/0	
At the expected level	4/40	3/60	2/50	1/50	1/100	
Fine motor skills						
Delay	1/10	1/20	1/25	0/0	0/0	
Must be watched	2/20	0/0	1/25	0/0	0/0	0.944
At the expected level	4/40	3/60	2/50	2/100	1/100	
Fast	3/30	1/20	0/0	0/0	0/0	
Gross motor skills						
Delay	2/20	1/20	1/25	0/0	0/0	
Must be watched	4/40	2/40	1/25	1/50	1/100	0.998
At the expected level	3/30	2/40	2/50	1/50	0/0	
Fast	1/10	0/0	0/0	0/0	0/0	
Social skills						
Delay	1/10	1/20	0/0	0/0	0/0	
Must be watched	6/60	1/20	2/50	1/50	0/0	0.885
At the expected level	3/30	2/40	1/25	1/50	1/100	
Fast	0/0	1/20	1/25	0/0	0/0	

ADSI: Ankara development and screening inventory; CBZ: carbamazepine; LEV: levetiracetam; LTG: lamotrigine; OXC: oxcarbazepine; VPA: valproate.

Table 4. Children's CBCL/4–18 results by antiseizure medication type

	Monotherapy (N=20)				
CBCL/4–18	**VPA (N=10, %)**	**CBZ (N=5, %)**	**LTG (N=3, %)**	**OXC (N=2, %)**	**P value**
Sportive activity					
Not doing sports	3/30	0/0	0/0	0/0	0.160
1 Activity	4/40	5/100	3/100	2/100	
2 Activities	3/30	0/0	0/0	0/0	
Non-sports activity					
Not doing sports	3/30	3/60	1/33.3	1/50	0.910
1 Activity	5/50	2/40	1/33.3	1/50	
2 Activities	2/20	0/0	1/33.3	0/0	
Home/away from home work					
1 job	1/10	4/80	1/33.3	0/0	0.094
2 jobs	5/50	1/20	2/66.7	1/50	
3 jobs	4/40	0/0	0/0	1/50	
Close friend					
No friends	0/0	1/20	0/0	0/0	0.580
1 friend	1/10	0/0	0/0	0/0	
2 friends	0/0	0/0	1/33.3	0/0	
3 friends	6/60	3/60	1/33.3	2/100	
4 friends	3/30	1/20	1/33.3	0/0	
Relationship with the parent					
Bad	1/10	0/0	1/33.3	0/0	0.074
Normal	0/0	3/60	0/0	1/50	
Pretty good	9/90	2/40	2/66.7	1/50	
Life science/social					
Unsuccessful	0/0	1/20	1/33.3	0/0	0.296
Middle	1/10	1/20	0/0	1/50	
Successful	7/70	2/40	0/0	1/50	
Very successful	2/20	1/20	2/66.7	0/0	
Arithmetic					
Unsuccessful	1/10	1/20	1/33.3	0/0	0.954
Middle	1/10	1/20	0/0	1/50	
Successful	6/60	2/40	1/33.3	1/50	
Very successful	2/20	1/20	1/33.3	0/0	
Science					
Unsuccessful	0/0	1/20	1/33.3	0/0	0.584
Middle	1/10	1/20	0/0	1/50	
Successful	7/70	2/40	1/33.3	1/50	
Very successful	2/20	1/20	1/33.3	0/0	
Illness/Disability					
No	8/80	1/20	2/66.7	1/50	0.204
Yes	2/20	4/80	1/33.3	1/50	

CBCL/4–18: The Child Behavior Checklist For Ages 4 –18; CBZ: Carbamazepine; LTG: Lamotrigine; OXC: Oxcarbazepine; VPA: Valproate.

The VPA dose of women who used VPA monotherapy during pregnancy was divided into two categories: 500 mg/day and below and over 500 mg/day. A delay in social skills was found in one of two children of women using VPA more than 500 mg/day in the 0–6 age group. No delay was observed in any of the 11 children whose mothers used 500 mg/day or less (p=0.047). However, the interpretation of the results may not be meaningful since there are only two children in the 0–6 age group whose mothers used VPA more than 500 mg/day in their pregnancy. In the 6–18 age group, there was no significant difference in terms of the variables in CBCL/4–18 (p>0.05).

Potential confounding factors that could affect the test results of the children were determined as the type of epilepsy of the mother, the frequency of seizures during pregnancy, the educational status of the mother and the consanguinity of the parents. In the case of statistically significant findings, logistic regression analysis was performed to investigate the effects of confounding factors. According to the results of the logistic regression analysis, it was observed that confounding factors did not affect the test results.

DISCUSSION

In this study, it was investigated whether intrauterine ASM exposure causes developmental problems in children aged 0–18; as well as whether it is possible to obtain evidence about social, physical and academic problems in childhood and adolescence through behavioral problems detected by screening tests. For this purpose, investigations were carried out according to the use of ASM, the type of ASM and the dose of VPA, which is considered the most suspicious drug. There are many studies in the literature on the developmental and neuropsychological consequences of VPA exposure in the intrauterine period. When the neurological, neuropsychological, academic and behavioral characteristics of school-age children exposed to fetal VPA monotherapy were compared with those of WWE children who used the other ASM monotherapy or did not use any ASM, it is stated that behavioral problems are more prevalent in children with VPA exposure (13). Similarly, in a study conducted with 181 children in which the effects of VPA, CBZ, LEV and LMT monotherapies on behavioral and emotional problems were examined, it was found that VPA exposure could cause significant social problems compared to LTG

and LEV; it has also been claimed to cause attention deficit compared to children with LEV exposure (14). In a multicenter study, it was found that the age 6-IQ of children who were exposed to valproate was lower than the IQ of children who were exposed to carbamazepine, phenytoin and lamotrigine (8).

In accordance with the literature, it was observed in this study that the school-age children of women who use VPA monotherapy are less engaged in sports activities than the children of women using other ASM monotherapies. Various studies have demonstrated the effect of prenatal exposure to VPA on gross motor development. Thomas et al. found an impairment in motor development in the VPA-exposed infants compared to the CBZ exposed infants (3). Eighteen-month-old infants as well as school-aged children who have been exposed to VPA had poorer gross motor functions compared to control children (7,15). In comparison with other ASMs, intrapartum VPA exposure also showed significantly poorer outcomes in the motor development of the children (16,17).

The level of engagement in sports activities in children depends on the development of gross motor skills, including locomotor competence, object control and motor coordination, together with a sufficiently developed musculoskeletal system. The development of gross motor skills is affected by many factors such as age, gender, general health status, and environmental conditions (18). It is known that ASMs used in pregnancy affect folate and vitamin B12 levels, which are vital in the development of the nervous system. There is substantial evidence that folate and single-carbon metabolism, including vitamin B12, play a critical role in the closure of the fetal neural tube, the development of the infant's central nervous system, and overall health at all stages of life (19). Valproic acid has a direct inhibitory action on folate and one-carbon metabolism, thus contributing at least in part to the congenital and developmental risks (20). In various animal studies, it has been shown that maternal VPA exposure causes degeneration in cerebellar purkinje cells (21); and changes in the motor, somatosensory and insular cortices (22). In subsequent studies, the gross motor development in children with intrauterine VPA exposure should be investigated in detail.

Another issue addressed in intrauterine ASM exposure is the variety of ASMs mothers use during pregnancy. Studies examining the developmental outcomes in the children of women who received monotherapy and polytherapy reported that polytherapy increases the risk of preterm birth, stillbirth, low birth weight and congenital malformations (23). However, many studies have found the negative effect of maternal polytherapy on cognitive and motor functions (3,7,24–27). Thomas et al. reported that exposure to ASMs, especially exposure to polytherapy, was associated with impaired intellectual and language functions (26). In the present study, in accordance with the literature, it was observed that the children of women who received monotherapy had a faster language-cognitive development compared to the children of women who received polytherapy. In our study, 8 of the 9 children of women who received polytherapy were exposed to VPA or CBZ in combination. This suggests that prenatal polytherapy exposure, especially with old generation ASMs, affects language development. It's crucial to recognize language impairment in children prenatally exposed to ASMs since this could have a significant impact on various aspects of their future lives.

On the other hand, it was found that children of women who took polytherapy in the age group of 6–18 were less engaged in sports activities. Again, in this polytherapy group, all children were exposed to VPA or CBZ in combination. Thomas et al. reported that in the two-drug polytherapy group, impairment of motor and mental development was found to be more pronounced in combinations involving VPA (3). In another study investigating child development, it was found that 55% of the polytherapy exposed group were impaired in more than one domain of development and also had an increased risk of having an abnormal score for gross motor skills (7).

Childhood behavioral problems are associated with genetic, biological and social factors (unemployment, poverty, low education level of parents, conflict between spouses, divorce), as well as inappropriate communication patterns within the family. It is an undeniable fact that the family plays a great role in success in school as well as the social adaptation and personality development of the child (28). The effect of confounding factors such as mother's epilepsy type, frequency of seizures in pregnancy, maternal education status and parental consanguinity, which may affect the development of children with intrauterine ASM exposure, were statistically analyzed in this study, and it was discovered that ASMs caused developmental delay in children. However, we did not include socioeconomic status or maternal IQ as covariates in this study. Also, small sample sizes, lack of objective tests of cognitive performance and lack of blinding and randomization make it difficult to interpret the results of this study. In subsequent studies, the developmental and behavioral consequences of children with intrauterine ASM exposure should be examined in detail, taking into account the biological and physical development of the child, family education and socio-economic status.

CONCLUSION

It has been found that language and cognitive development can be delayed and the level of engagement in sports activities can be reduced compared to monotherapy in children exposed to maternal polytherapy. When VPA monotherapy and other ASM monotherapies are compared in terms of ASM types, the rate of doing sports activities decreases with the use of VPA. Children with maternal ASM exposure should be routinely monitored in terms of physical development, general health and engagement levels in sports activities, as well as developmental delay and emotional-behavioral problems. Another aim of this study was to create a practical functioning routine in order to quickly and briefly scan possible developmental retardation/delays in their children in the follow-up of WWE who were followed in the neurology clinic and who used ASMs during pregnancy. In this way, subclinical developmental/behavioral findings in children with ASM exposure can be detected early and preventive measures can be taken. Subsequent research should be conducted with a larger number of participants; children should be evaluated in comprehensive social, cognitive, behavioral and physical aspects and the effects of the psychosocial and economic status of families on child development should be examined in addition to ASMs.

Ethic Committee Approval: This study was approved by the Haseki Training and Research Hospital Institutional Review Board committee (approval number: 2021–272).

Informed Consent: Written consent was obtained from the mothers following a detailed explanation of the study.

Peer-review: Externally peer-reviewed

Author Contributions: Concept– MAY, ZA, ÖÇ; Design– MAY, ZA, MS; Supervision– MAY; Resources– MAY, ZA; Materials– MAY; Data Collection and/or Processing– MAY, MS; Analysis and/or Interpretation– MAY, MS, SB; Literature Search– MAY, MS; Writing Manuscript– MAY, MS; Critical Review– ÖÇ.

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