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Mental development of children from paired mothers with epilepsy: assessing remote teratogenic effects and predictors of developmental disorders

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SUMMARY

Objective: to study teratogenic effect – the long-term pregnant mother-taken antiepileptic drugs (AEDs) related consequences on paired child mental, social and intellectual development.

Material and methods. There were enrolled 80 subjects: 40 children aged 3–9 years and paired mothers suffering from epilepsy for 3 to 35 years. Thirteen and 27 patients had generalized and focal epilepsy, respectively. Seven mothers were in prolonged remission without taking AEDs, 23 were on monotherapy and 10 were on polytherapy. Child research methods: T. Achenbach's clinical CBCL (The Child Behavior Checklist) scales (for children aged under 5 and 6–18 years), a questionnaire for detecting attention deficit hyperactivity disorder and other behavioral disorders modified by N.N. Zavadenko, Wechsler Intelligence Scale for Children (WISC), Luria batteries of neuropsychological tests adapted by J.M. Glozman (for children aged 3–6 and 7–12 years).

Results. Neuropsychological study and assessment of intelligence revealed problems in the development of praxis, speech, gnostic functions and memory, as well as disproportion in the development of verbal and non-verbal structures of intelligence. The most common behavioral disorders in children were impulsivity, distraction, difficulties in controlling and organizing movements. The most affected spheres were praxis (motor awkwardness, fine motor disorders of the hands) and speech.

Conclusion. The proposed hypothesis that the teratogenic effect of taking AEDs may result in unevenness or delay in developing mental functions in a child was confirmed.

KEYWORDS

Epilepsy, pregnancy, antiepileptic therapy, teratogenesis, mental development disorders, neuropsychological syndrome.

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Психическое развитие детей матерей, страдающих эпилепсией: оценка отдаленных тератогенных эффектов и предикторы нарушений развития

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РЕЗЮМЕ

Цель: изучение тератогенного эффекта – отдаленных последствий приема матерями в период беременности антиэпилептических препаратов (АЭП) на психическое, социальное и интеллектуальное развитие ребенка.

Материал и методы. В исследовании приняли участие 80 человек: 40 детей в возрасте 3–9 лет и их матери, страдающие эпилепсией в течение 3–35 лет. Тринадцать пациенток имели генерализованную форму эпилепсии, 27 – фокальную; 7 матерей находились в многолетней ремиссии и не принимали АЭП, 23 были на монотерапии и 10 – на политерапии. Методы исследования ребенка: клинические шкалы Т. Ахенбаха (англ. The Child Behavior Checklist, CBCL) (для детей до 5 лет и 6–18 лет), анкета для выявления синдрома дефицита внимания и гиперактивности и других поведенческих расстройств в модификации Н.Н. Заваденко, метод исследования интеллекта Д. Векслера (англ. Wechsler Intelligence Scale for Children, WISC), Луриевские батареи нейропсихологических тестов в адаптации Ж.М. Глозман (для детей 3–6 лет и 7–12 лет).

Результаты. Нейропсихологическое исследование и оценка интеллекта выявили у детей проблемы в развитии праксиса, речи, гностических функций и памяти, а также диспропорциональность в формировании вербальной и невербальной структур интеллекта. Чаще всего встречающимися нарушениями поведения у детей были импульсивность, отвлекаемость, трудности контроля и организации движений. Наиболее пострадавшими оказались праксис (моторная неловкость, нарушения мелкой моторики рук) и речевая сфера.

Заключение. Гипотеза исследования о том, что тератогенный эффект от приема АЭП может привести к неравномерности или задержке развития психических функций у ребенка, подтвердилась.

КЛЮЧЕВЫЕ СЛОВА

Эпилепсия, беременность, антиэпилептическая терапия, тератогенез, нарушения психического развития, нейропсихологический синдром.

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INTRODUCTION / ВВЕДЕНИЕ

Epilepsy is one of chronic diseases in which constant medication is vital, even during pregnancy period [1]. Taking antiepileptic drugs (AEDs) entails various risks to a child, which include intrauterine growth restrictions, congenital malformations, negative effects on cognitive function, and an increased risk of developing nervous system disorders [2]. V.A. Karlov et al. [1] explain the pathological effect of AEDs on the fetus by altered pharmacokinetics, immunological, allergic reactions, as well as direct toxic effects. Hence, in most studies, taking AEDs by mothers is considered as one of the key factors in subsequent developmental disorders in paired child.

The effect of each of the drugs separately has been studied for a long time, but the results of such studies remain ambiguous and often contradict each other. The most studied is the effect of valproic acid (VA). Numerous reports confirm that for children whose mothers took VC during pregnancy, cognitive impairments were much more likely to be detected, mostly affecting verbal intelligence [3, 4].

The data on the effect of carbamazepine (CBZ) are contradictory – in some studies, no differences in development were found between children whose mothers took CBZ and those from control group [5]. However, other studies [6] observed a definite effect on the general intelligence (IQ) in children exposed to CBZ.

A.E. Scheuerle et al. [7] found no effect of taking levetiracetam (LTC) on fetal development. However, the results from the majority of the studies assessing effects of LTC and topiramate (TPM) also turned out to be rather contradictory [8].

Now, the effect of lamotrigine (LTD) on child development has been well examined due to the growing tendency to assess it and the lack of evidence about any teratogenic effects related to it, it is currently the most common drug used during pregnancy [4, 9].

A.A. Veroniki et al. [10] in an extensive literature review note the absence of convincing evidence for a link between the intake of CBZ, LTD, phenytoin and neurological as well as neuropsychological disorders in children. No data were found about the effects of clonazepam, oxcarbazepine, gabapentin and pregabalin. Nevertheless, despite the number of studies confirming the relative safety of taking AEDs during pregnancy, the incidence of developmental disorders in children from paired mothers with epilepsy is significantly higher than its average level in the population, which indicates that this issue is not well understood. It is also important to note that the majority of the studies were conducted with drawbacks (small and non-randomized samples), and resulted in errors in data interpretation.

In addition to the difference in teratogenic effects of diverse AEDs, the effect of mono- or polytherapy has also been investigated. Studies on long-term AEDs effects on the cognitive development in children showed that in case of polytherapy, child intelligence was significantly lower than the age-related norm [11], as was in the case of mothers taking VA and CBZ [12]. A number of other international studies [11, 13] confirmed this issue – in case of polytherapy vs. monotherapy during pregnancy, a risk of potential cognitive impairments in child was higher. Primarily, it affected the general level of intellectual development, verbal intelligence and psychological maturity of the child.

T.T. Kispayeva and A.S. Nurakhmetova [14] note an increased risk of malformations, as well as cognitive impairment of children, if mother takes several drugs. They established a dose-dependent effect: the higher the drug dosage mother required, the higher was likelihood of developing malformations in the future. The effect of drug dosage on the cognitive development of children has been proven if mothers took VA [3, 5, 9]. However, for other AEDs, this effect was not found [3].

Undoubtedly, the choice of AEDs is accounted for by type of epileptic seizures, and generalized tonic-clonic seizures are the most dangerous during pregnancy due to the risk of trauma to both mother and child (in utero) [15]. Upon that, most common are generalized seizures [16]. Especially dangerous is tonic-clonic status epilepticus, which prevalence comprises 3%, and may cause premature birth, hypoxia, or even fetal death [17].

Other seizures may not be as dangerous, but uncontrolled astatic, myoclonic, and complex focal seizures during pregnancy can also lead to trauma if mother falls or intrauterine fetal trauma, as well as to delayed fetal development and the risk of premature birth [18].

The presence of seizures could also cause the development of cognitive impairments – children who had 5 or more maternal seizures in utero had lower verbal scores, deteriorated speech understanding, motor skills and coordination [5].

Thus, patients with epilepsy face a dilemma. On the one hand, AEDs refusal can cause recurrence of epileptic seizures, which is extremely dangerous for maternal life and health as well as intrauterine child development. On the other hand, due to toxicity, taking AEDs poses risks for de-

veloping fetus and can negatively affect its subsequent development. Therefore, in case of inability to achieve remission before conception, the main task for medical doctors in managing pregnancy is to find a balance between the risks associated with seizures and exposure to AEDs [1].

The problems noted above confirm the high practical importance of preparing and managing pregnancy in women with epilepsy, however, in Russia, studies on the long-term effects from mothers taking AEDs on cognitive development of paired children are still rare. For instance, A.B. Kozhokaru et al. [19] found that the indicator of general intellectual development in such children was lowered compared to control group, but no significant differences in the level of verbal and non-verbal intelligence were observed. The data obtained can be accounted for by the specifics of the applied methodological tools. First, the psychometric method – the Wechsler Intelligence Scale for Children (WISC) evaluates integral parameters of intelligence, and not individual mental functions, based on which they are formed. Each subtest reflects the level of development for several basic child functions, and, accordingly, if something "falls behind", then it will not be that obvious within the overall parameter. Secondly, this test was proposed in 1940s for Russian cohort and standardized in 1973. And now it should be revised because part of the test tasks (both verbal and non-verbal) became outdated over decades and irrelevant to current reality, so that the test material presented to children today is simply not identified by them (e.g., an image of corded telephone) or has a completely different meaning. Hence, the test material and age norms, which psychologists rely on while assessing level of intellectual development, need to be revised [20].

No studies on children from paired mothers with epilepsy were conducted by using neuropsychological methods which are most sensitive to even minor impairments of individual mental functions and, therefore, providing more differentiated assessment of the "sliced" child mental underdevelopment. In this regard, this study is relevant and highly demanded both in scientific and practical terms.

Objective: to study teratogenic effect – the long-term pregnant mother-taken AED-related consequences on paired child mental, social and intellectual development.

MATERIAL AND METHODS / МАТЕРИАЛ И МЕТОДЫ

The specific objectives of the study were as follows: assessing parameters of mental, social and intellectual development, neuropsychological syndromes of impaired child development, depending on the form of epilepsy in paired mother, observed remission, the type and number of mother-taken AEDs, the preparedness for delivery and complications of pregnancy (toxicosis, anemia, ARVI), routes of delivery and type of feeding; searching for predictors of mental development disorders in children with paired mothers suffered from epilepsy.

Study design / Дизайн исследования

The interventional study was conducted in a controlled environment: while mothers were filling out the methods, the researcher conducted neuropsychological tests and subtests from the WISC battery with children in person in a playful manner, following the recommended breaks and switching activities. Since standardized methods were used, the results were compared with age norms, which made it possible not to recruit a control group.

Ethical aspects / Этические аспекты

Patients (mothers) signed an informed consent in a medical institution, where they were constantly observed. The study of the child's mental development took place in the presence of the mother or other legal representative.

Patients / Пациенты

There were enrolled 80 subjects: 40 children aged 3–9 years and paired mothers with epilepsy. The duration of the epilepsy disease varied from 3 to 35 years and averaged 15 years. The age of epilepsy onset was 4–36 years, with an average of 14 years. Mothers were observed at the Russian Polenov Neurosurgical Institute – the branch of the Almazov National Medical Research Center and the City Epileptological Center (CEC) of St. Petersburg. Neurologists of the Russian Polenov Neurosurgery Institute and CEC carried out clinical diagnostics of patients with epilepsy, collected disease anamnesis (experience, frequency of seizures, type of therapy, treatment plan) and other medical data regarding the course of pregnancy, delivery, and early child development.

Mothers

Duration, age of disease onset, forms and activity of epilepsy

The average age at which mothers gave birth was 27 years old and ranged from 18 to 41 years. The duration of epilepsy history varied from 3 to 35 years and averaged 15 years. The age of onset of epilepsy was 4–36 years (on average 14 years).

According to International League Against Epilepsy classification (1991), 13 (33%) and 27 (67%) patients had generalized and focal epilepsy, respectively.

Twenty five (62%) mothers were in remission – had no seizures for more than 4 years before the onset of pregnancy. The remaining subjects had rare seizures of epilepsy.

Antiepileptic drug therapy

At the time of delivery 7 mothers did not take any AEDs, 23 were on monotherapy and 10 – on polytherapy. Of those who took the drugs, 15 mothers were taking the

first-generation AEDs, and 18 were taking the next and new generation agents.

Complications of pregnancy

In 26 (65%) mothers, pregnancy proceeded without toxicosis, whereas others were noted to have early and late gestosis: toxicosis, anemia, exacerbated chronic diseases (pyelonephritis, cholecystitis, etc.).

Pre-gravidar preparation and routes of delivery

The gestation age ranged from 35 to 42 weeks; 21 (52%) of deliveries were prepared and 19 (48%) were unprepared.

All deliveries were urgent, babies were born full-term after gestational age of 35 weeks; 22 (55%) women gave birth to a child naturally, 18 (45%) – by caesarean section.

Children

Sex and age

There were enrolled 22 girls and 18 boys aged 3 years 1 month to 9 years 9 months, the average age was 5 years 5 months. All children attended preschool educational institutions or school.

Body mass

The birth body mass of the children ranged within 2345–4276 g.

Feeding type in the first year of life

Eighteen (45%) children were artificially fed, 22 (55%) were breastfed.

Methods of child examination / Методы исследования ребенка

The following child examination methods were used:

– questionnaire with medical data on child development;

– T. Achenbach's Child Behavior Checklist (CBCL) was assessed by the mother, depending on child age, 2 variants were used: for age to 5 years, and for ages from 6 to 18 years;

– the questionnaire for identifying symptoms of attention deficit hyperactivity disorder (ADHD) and other behavioral disorders modified by N.N. Zavadenko (from 5 years of age and older) was assessed by the mother;

– Wechsler Intelligence Scale for Children (WISC) – from 5 years of age and older;

– two Luria batteries of neuropsychological tests adapted by J.M. Glozman (2018) for preschool (3–6 years old) and school children (7–12 years old).

All methods were standardized.

Methods of statistical analysis / Методы статистического анализа

Statistical data processing was carried out by using the SPSS Statistics (IBM, USA) software. The groups were compared by using nonparametric Mann–Whitney U test, one-way analysis of variance (ANOVA, Bonferroni) as well as correlation and regression analysis.

RESULTS AND DISCUSSION / РЕЗУЛЬТАТЫ И ОБСУЖДЕНИЕ

Assessing children's mental and intellectual development level / Оценка уровня психического и интеллектуального развития детей

While assessing the level of intellectual development using the WISC, we obtained the data similar to those by A.B. Kozhokaru et al. [19] – the average score of general intellectual development (M total IQ) corresponded to the age norm and comprised 122.04 points (M verbal IQ = 118.92; M non-verbal IQ = 121.46). However, more than half of the children showed a disproportionate development of intellectual functions: 28% had verbal intelligence higher than non-verbal by more than 10 points due to uneven development or delayed development of some higher mental functions, and 36% had the non-verbal parameter significantly exceeded the verbal level, which can be due to delayed speech development or pedagogical neglect. The data obtained on other clinical scales (CBCL and N.N. Zavadenko's ADHD questionnaire) also indirectly suggested altered development of motor and cognitive spheres in children. The results obtained using neuropsychological diagnostics have objectively confirmed this premise. Hence, it repeatedly demonstrates that the Wechsler method (WISC) should not be used alone and requires additional tools while assessing level of child mental development .

Adjusted by mother epilepsy form

Differences in mental and intellectual development were found between children with paired mothers suffered from various forms of epilepsy (**Table 1**). In particular, for children with paired mothers suffered from focal epilepsy, attention and behavior problems, psychosomatic and emotional-volitional disorders, speech disorders, symptoms of hyperactivity and attention deficit, motor awkwardness were more prominent. Moreover, child behavior was less adequate during examination and less able to deal with tasks to derive analogies. They had less short-term and working memory, but they coped better with the similarity subtest, which requires a certain level of developed abstract-logical verbal thinking, than children from paired mothers with generalized form of seizures. It may infer that children from paired mothers with focal epilepsy are also cognitively impaired, similar to adults with focal seizures, probably due to the exposure to AED.

Correlation analysis

These patterns were also confirmed by the results of a correlation analysis (**Fig. 1**): the focal form of

Table 1. Disorders of child mental development. abilities and intelligence. neuropsychological symptoms coupled to the form of epilepsy in paired mother

Таблица 1. Нарушения психического развития. способностей и интеллекта. нейропсихологические симптомы у ребенка в зависимости от формы эпилепсии у матери

Parameters of development / Параметры развития	Middle rank / Средний ранг		Significance of the Mann–Whitney U test / Значимость критерия U Манна–Уитни
	Generalized form of epilepsy / Генерализованная форма эпилепсии	Focal form of epilepsy / Фокальная форма эпилепсии	
Mental development disorders / Нарушения психического развития	*n=13*	*n=27*	
Attention problems / Проблемы внимания	14.5	**23.39**	0.023
Indicators of ability and mental development / Показатели способностей и психического развития	*n=9*	*n=20*	
Psychosomatic disorders / Психосоматические нарушения	10.94	**16.23**	0.085 (tendency / тенденция)
Motor awkwardness / Моторная неловкость	9.26	**17.40**	0.023
Hyperactivity / Гиперактивность	9.06	**17.68**	0.010
Speaking disorders / Нарушения устной речи	9.06	**17.68**	0.010
Attention deficit / Дефицит внимания	7.56	**18.35**	0.001
Emotional volitional disorders / Эмоционально-волевые нарушения	9.33	**17.55**	0.015
Behavior problems / Проблемы поведения	9.56	**17.45**	0.020
Neuropsychological tests / Нейропсихологические пробы	*n=13*	*n=26*	
General characteristic – adequacy / Общая характеристика – адекватность	14.81	22.60	0.043
Intelligence – analogies / Интеллект – аналогии	9.00	14.88	0.066 (tendency / тенденция)
Intelligence subtests / Интеллектуальные субтесты	*n=9*	*n=18*	
Similarity / Сходство	**19.11**	**11.44**	0.017
Digit repetition / Повторение цифр	8.83	**16.58**	0.015

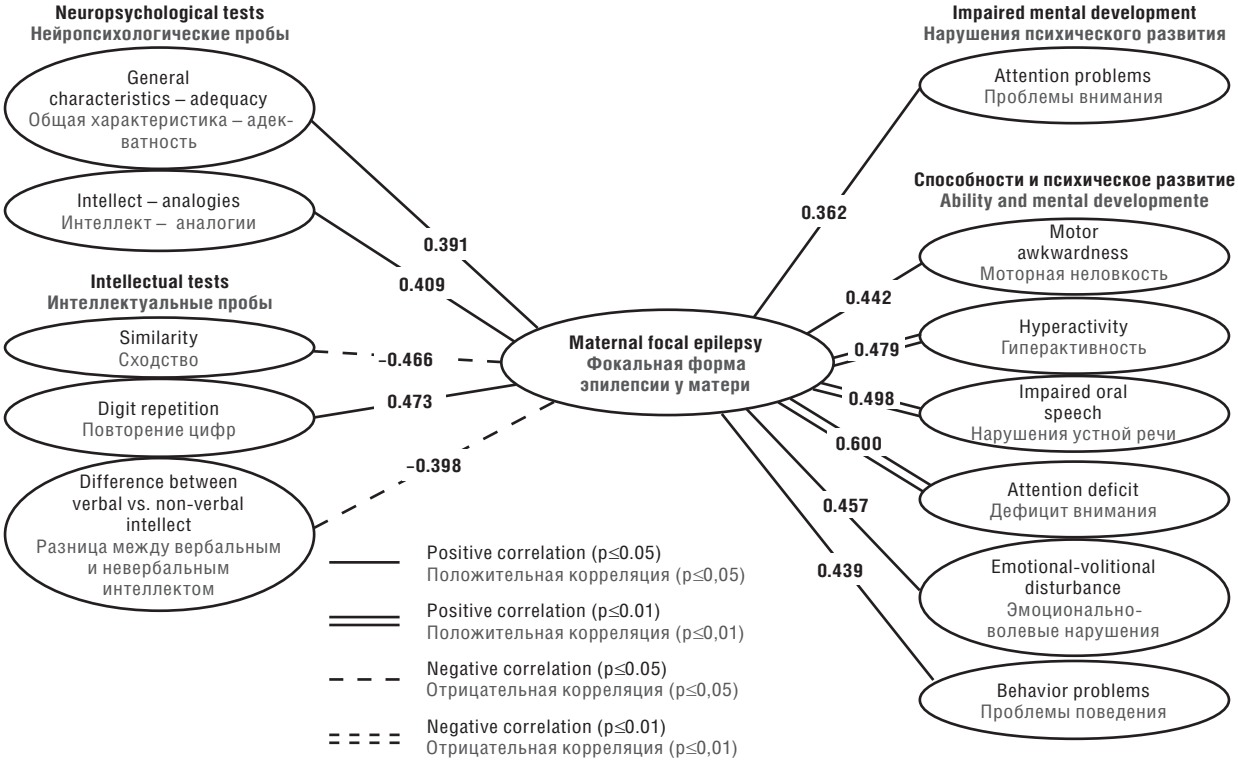

Figure 1. The correlation Pleiad 1: correlations between developmental disorders and maternal focal epilepsy

Рисунок 1. Корреляционная плеяда 1: корреляции между нарушениями развития и фокальной формой эпилепсии у матери

mother's epilepsy was associated with such developmental disorders in a paired child such as hyperactivity, attention deficit, impaired oral speech, motor awkwardness, attention and behavior problems, etc., the maternal focal epilepsy correlated with the disproportionate development of intelligence in paired children (a large difference between verbal and non-verbal intelligence).

Adjusted by current/lacking maternal disease remission

Differences in development were revealed between children from paired pregnant mothers in disease remission (no seizures for at least 1 year before the onset of pregnancy) and paired children with continuing seizures (**Table 2**).

Absolutely all the data indicate that the state of remission at the time of pregnancy is the key parameter to the favorable child development in the future.

Children of mothers who failed in achieving remission were more anxious, had problems with socialization, thinking and attention. They had more internalization problems (withdrawal, somatic complaints, anxiety), and the overall (total) parameter of developmental disorders was higher, which indicates a greater number of identified developmental disorders. They were more likely to have psychosomatic disorders, fears, hyperactivity, attention deficit, speech disorders and motor awkwardness.

Children whose mothers were in remission during pregnancy were better oriented in surrounding environment and behaved more adequately in the survey situation.

Correlation analysis

The patterns found above were also confirmed in the correlation analysis (**Fig. 2**). In addition, remission was negatively correlated with externalization problems (de-

Table 2. Disorders of mental development. abilities and intelligence in children. depending on the presence or absence of disease remission in paired mothers

Таблица 2. Нарушения психического развития. способностей и интеллекта у детей в зависимости от отсутствия или наличия ремиссии у матери

Parameters of development / Параметры развития ребенка	Middle rank / Средний ранг		Significance of the Mann–Whitney U test / Значимость критерия U Манна–Уитни
	Remission / Ремиссия	No remission / Нет ремиссии	
Mental development disorders / Нарушения психического развития	*n=25*	*n=14*	
Anxiety / Тревожность	16.16	**26.86**	0.004
Socialization disorders / Нарушения социализации	16.14	**26.86**	0.004
Thinking problems / Проблемы мышления	16.48	**26.29**	0.009
Attention problems / Проблемы внимания	16.52	**26.21**	0.010
Internalization problems / Интернализационные проблемы	16.90	**25.54**	0.022
General indicator / Общий показатель	16.58	**26.11**	0.011
Indicators of ability and mental development / Показатели способностей и психического развития	*n=16*	*n=11*	
Psychosomatic disorders / Психосоматические нарушения	11.41	**18.63**	0.020
Psychosomatic disorders / Тревожность. страхи. навязчивость	11.78	**18.13**	0.042
Motor awkwardness / Моторная неловкость	10.88	**19.33**	0.006
Hyperactivity / Гиперактивность	11.75	**18.17**	0.042
Speaking disorders / Нарушения устной речи	12.28	**17.46**	0.100 (tendency / тенденция)
Attention deficit / Дефицит внимания	11.91	**17.96**	0.053 (tendency / тенденция)
Neuropsychological tests / Нейропсихологические пробы	*n=25*	*n=13*	
General characteristics – orientation / Общая характеристика – ориентировка	17.26	**23.81**	0.085 (tendency / тенденция)
General characteristic – adequacy / Общая характеристика – адекватность	16.82	**24.65**	0.038

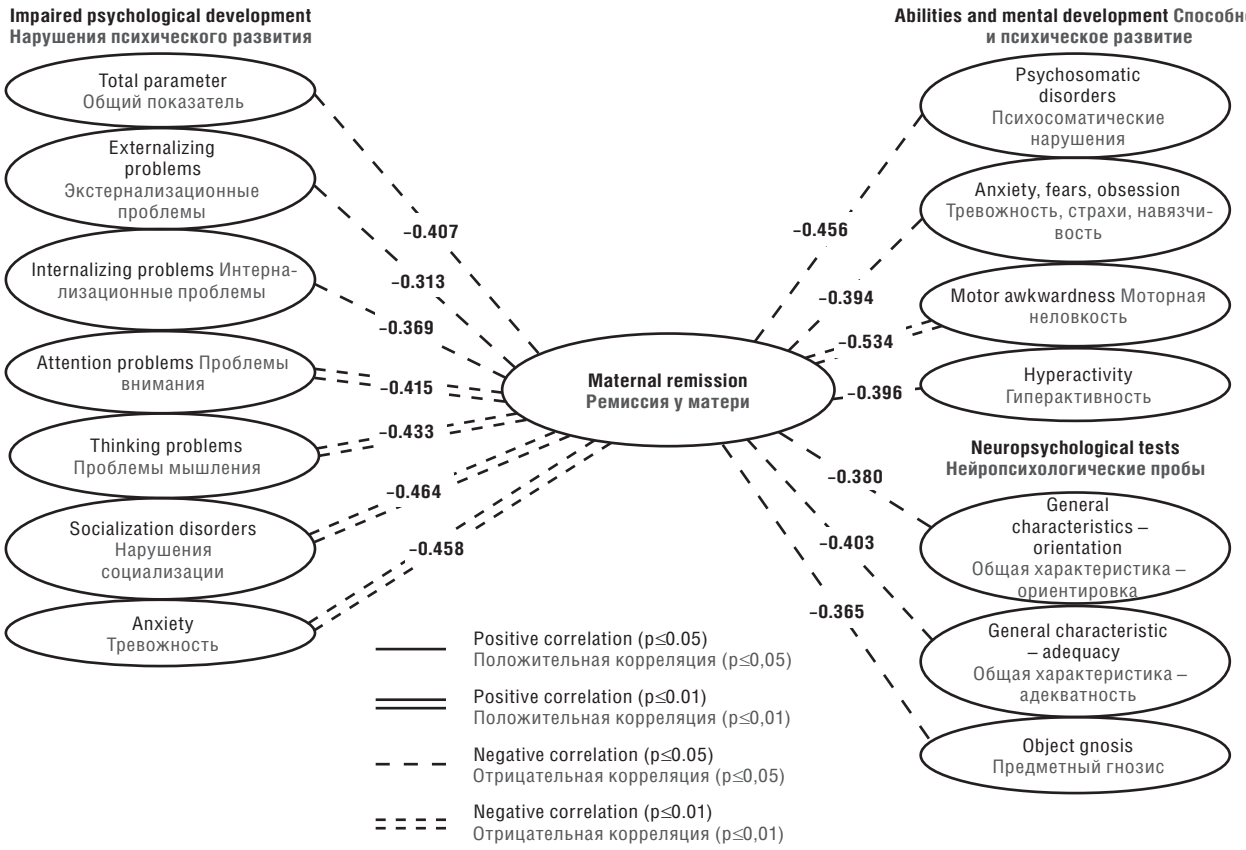

Figure 2. A correlation Pleiad 2: correlations between child developmental disorders and maternal remission during pregnancy

Рисунок 2. Корреляционная плеяда 2: корреляции между нарушениями развития у ребенка и ремиссией в период беременности у матери

linquent, aggressive behavior) and mental development disorders, as well as with the child's subject gnosis. It suggests about importance of achieving maternal disease remission for the further mental child development. Perhaps this is due to lower doses of AEDs or their withdrawal during the period of stable disease remission, which reduces the risks of teratogenicity.

Adjusted to maternal therapy type

Differences in the development of children were revealed depending on the therapy used for treating paired mother (mono or polytherapy). The ANOVA data (**Table 3**) confirm an increase in the teratogenic effect on child mental development, depending on increased AED amount applied to paired mother.

Children of paired mothers not taking vs. taking AEDs in remission showed a higher development of logical processes (according to the "Comprehensibility", "Sequential pictures" subtests).

They were also better at recognizing emotions and testing for conditioned selection responses as well as reproduction of rhythmic structures.

Children of mothers receiving monotherapy dealt better with tests for emotional gnosis, conditioned selection reactions, and reproduction of rhythmic structures from the sphere of praxis than children of mothers taking multiple AEDs. However, with neuropsychological tests (for emotional gnosis, conditioned reactions of choice and reproduction of rhythmic structures), children of paired mothers taking no AEDs also dealt less efficiently than those from paired mothers who did not take AEDs. Taking into account the small size of the sample, these data require additional verification on a larger number of subjects. Nevertheless, ANOVA data showed that increasing the number of drugs exerted negative effect.

Correlation analysis

These patterns were confirmed by the data of correlation analysis. In addition to emotional gnosis, polytherapy was associated with altered child oral praxis, i.e. the more AEDs were taken by the mother, the more pronounced such disorders were observed in paired child.

Adjusted to generation of drugs taken by paired mother

Differences in the development of children adjusted to novelty of AEDs used by paired mother were also found. The results of variance ANOVA analysis (**Table 4**) also confirm an increase in the teratogenic effect on the child mental development, depending on the toxicity of the select AED.

Children of paired mothers taking no AEDs were highlighted by a higher development of logical processes

Table 3. Disorders of mental development, abilities and intelligence in children, depending on the type of therapy for the mother

Таблица 3. Нарушения психического развития, способностей и интеллекта у детей в зависимости от от вида терапии матери

Parameters of development / Параметры психического развития ребенка	Maternal type of therapy / Вид терапии матери						Significance of differences / Достоверность различий		
	No AEDs (I) / Без АЭП (I)		Monotherapy (II) / Монотерапия (II)		Polytherapy (III) / Политерапия (III)		ANOVA		Bonferroni
	M	S(M)	M	S(M)	M	S(M)	F	P	P
Intelligence subtests / Интеллектуальные субтесты									
Comprehensibility / Понятливость	**19.00**	1.000	13.65	3.372	12.43	6.503	2.585	0.096 (tendency / тенденция)	–
Consecutive pictures / Последовательные картинки	**15.33**	1.155	12.53	1.807	14.33	3.724	2.673	0.090 (tendency / тенденция)	–
Нейропсихологические пробы / Neuropsychological tests									
Emotional gnosis / Эмоциональный гнозис	0.33	0.577	**0.03**	0.121	0.50	0.775	3.151	0.062 (tendency / тенденция)	p II–III = 0.074 (tendency / тенденция)
Praxis – conditioned choice responses / Праксис – условные реакции выбора	1.00	0.000	**0.26**	0.452	0.50	0.500	2.687	0.089 (tendency / тенденция)	–
Praxis – reproduction of rhythmic structures / Праксис – воспроизведение ритмических структур	2.50	0.707	**0.36**	0.479	0.67	0.876	11.552	0.001	p I–II < 0.001 p I–III = 0.003

Note. AED – anti-epileptic drugs; M – mean; S(M) – mean square; F – Fisher criterion value; P – significance level.

Примечание. АЭП – антиэпилептические препараты; M – среднее; S(M) – средний квадрат; F – значение критерия Фишера; P – уровень значимости.

("Comprehensibility" subtest) than those from paired mothers taking AEDs. They also behaved more appropriately in the survey situation.

The novelty (generation) of AEDs taken by paired mother during pregnancy was also important for the further child development: children of paired mothers who took the first-generation drugs (VA, CBZ, phenytoin, phenobarbital, ethosuximide) did less efficient tasks for naming objects, their speech was less smooth and detailed and, in general, less developed than those with paired mothers taking the next-generation drugs (LTD, LTC, TPM, oxcarbazepine, zonisamide, lacosamide). They also understood grammatical constructions worse than children from paired mothers taking none of AEDs. Children whose paired mothers taking the new generation drugs, and worse, children from paired mothers taking former generation drugs exerted peak efficiency in the task on conditioned responses of choice.

According to neuropsychological diagnostics, child mental retardation was most prominent in the group with paired mothers taking former generation drugs and the least significant in the group of the next generation drugs. Children with paired mothers taking former (old) generation drugs also showed greater motor awkwardness and more pronounced delinquent behavior than those from paired mothers taking the next (second) generation drugs.

Even though the subject samples were very small and require to be further tested on a larger number of subjects, ANOVA showed that the novelty (generation) of the drugs (and hence its toxicity), as well as the number of AEDs used by paired mother (mono/polytherapy), affects the child mental development. In addition, the differences revealed between AED generations are not sufficient to identify a drug with the greatest teratogenic effect, because even among the next-generation drugs there were identified those exerting lower and greater toxicity. To identify a drug with the peak teratogenic effect, it is necessary to compare groups with larger number of subjects with paired mothers receiving monotherapy. Due to the small size of our sample, division into subgroups (for specific drugs) for statistical analysis was inappropriate.

Correlation analysis

Nevertheless, correlations (**Table 5**) between maternal former generation AED taking and the child developmental disorders noted above such as problems of socialization, disorders of speech development (spontaneity, understanding, naming of objects, understanding of logic and grammar) were found.

For children whose mothers took drugs of the new generation, socialization disorders, delinquent behavior, motor awkwardness, speech disorders in general, and spontaneous speech were less common.

Table 4. Disorders of mental development, abilities and intelligence in children, depending on the generation of the drug taken by paired mother

Таблица 4. Нарушения психического развития, способностей и интеллекта у детей в зависимости от поколения препарата, принимаемого матерью

Parameters of development / Параметры психического развития ребенка	AEDs generation / Поколение АЭП						Significance of differences / Достоверность различий		
	No AEDs (I) / Без АЭП (I)		First generation (II) / Первое поколение (II)		Second generation (III) / Второе поколение (III)		ANOVA		Bonferroni
	M	S(M)	M	S(M)	M	S(M)	F	P	P
Intelligence subtests / Интеллектуальные субтесты									
Comprehensibility / Понятливость	17.50	3.391	**12.63**	4.897	13.08	4.153	2.763	0.083 (tendency / тенденция)	
Neuropsychological tests / Нейропсихологические пробы									
Impaired mental function / Задержка психического развития	2.20	1.418	**3.32**	2.926	1.61	1.037	2.939	0.066 (tendency / тенденция)	p II–III = 0.062 (tendency / тенденция)
General characteristic – adequacy / Общая характеристика – адекватность	0.15	0.338	**0.77**	1.148	0.22	0.492	2.61	0.087 (tendency / тенденция)	
Spontaneous speech / Спонтанная речь	0.50	0.707	**0.91**	1.221	0.11	0.274	3.831	0.031	p II–III = 0.082 (tendency / тенденция)
Speech – naming / Речь – называние	0.10	0.316	**0.64**	1.206	0	0	3.395	0.045	p II–III = 0.047
Understanding grammar / Понимание грамматики	0	0	**0.80**	0.837	0	0	5.107	0.023	p I–II = 0.070
Speech / Речь	0.20	0.350	**0.82**	1.189	0.060	0.236	4.591	0.017	p II–III = 0.016
Praxis – conditioned choice responses / Праксис – условные реакции выбора	**0.80**	0.274	**0.29**	0.488	0.25	0.470	2.936	0.073 (tendency / тенденция)	p I–III = 0.081 (tendency / тенденция)
Mental development disorders / Нарушения психического развития									
Delinquent behavior / Делинквентное поведение	2.30	1.703	**2.42**	2.234	1.17	1.098	2.598	0.088 (tendency / тенденция)	
Indicators of ability and mental development / Показатели способностей и психического развития									
Motor awkwardness / Моторная неловкость	2.67	2.503	**4.11**	2.619	1.43	2.311	3.307	0.053 (tendency / тенденция)	p II–III = 0.049

Note.AED – anti-epileptic drugs; M – mean; S(M) – mean square; F – Fisher criterion value; P – significance level.

Примечание.АЭП – антиэпилептические препараты; M – среднее; S(M) – средний квадрат; F – значение критерия Фишера; P – уровень значимости.

Table 5. Correlations between disorders of mental development, abilities and intelligence and novelty (generation) of antiepileptic drugs

Таблица 5. Корреляции между нарушениями психического развития, способностей и интеллекта и поколением антиэпилептических препаратов

Parameters of development / Параметры развития	Spearman's correlation coefficients / Коэффициенты корреляции Спирмена	
	Old AEDs / Старые АЭП	New AEDs / Новые АЭП
Mental development disorders / Нарушения психического развития		
Socialization disorders / Нарушения социализации	0.319*	–0.397*
Delinquent behavior / Делинквентное поведение	–	–0.335*
Indicators of ability and mental development / Показатели способностей и психического развития		
Motor awkwardness / Моторная неловкость	–	–0.422*
Neuropsychological tests / Нейропсихологические пробы		
Spontaneous speech / Спонтанная речь	0.357*	–0.339*
Speech – naming of objects / Речь – называние предметов	0.333*	–
Understanding speech / Понимание речи	0.349*	–
Speech – understanding logic / Речь – понимание логики	0.358*	–
Speech – understanding grammar / Речь – понимание грамматики	0.709**	–
Speech / Речь	0.462**	–0.381*
Motor memory / Двигательная память	–0.416*	–

*Note. * Correlation is significant at 0.05 level (two-sided). ** Correlation is significant at the 0.01 level (two-sided).AEDs – antiepileptic drugs.*

*Примечание. * Корреляция значима на уровне 0,05 (двухсторонняя). ** Корреляция значима на уровне 0,01 (двухсторонняя). АЭП – антиэпилептические препараты.*

Regression analysis / Регрессионный анализ

The regression analysis also confirmed the influence of prenatal and perinatal factors associated with maternal epilepsy on the further mental development of paired children.

The admission of the maternal first-generation AEDs during pregnancy led to delayed development of spontaneous speech and object gnosis (naming of objects) in paired children, and also negatively affected entire development of the speech sphere (**Fig. 3**);

Children whose mothers were undergoing polytherapy during pregnancy performed worse at recognizing emotions, and this pattern was more characteristic of children of young mothers (**Fig. 4**).

Children from paired mothers suffered from seizures in the 2nd trimester of pregnancy had the least development of overall gnosis (R=0.400, R^2=0.160, β=0.400);

Maternal anemia during pregnancy was a predictor of subsequent child difficulties in understanding of addressed speech (R=0.471, R^2=0.222, β=0.471), and the severe acute respiratory syndrome (SARS) – a predictor

Figure 3. Predictors of child speech disorders, spontaneous speech and object gnosis.
AEDs – antiepileptic drugs

Рисунок 3. Предикторы нарушений в речевой сфере, спонтанной речи и предметном гнозисе у ребенка.
АЭП – антиэпилептические препараты

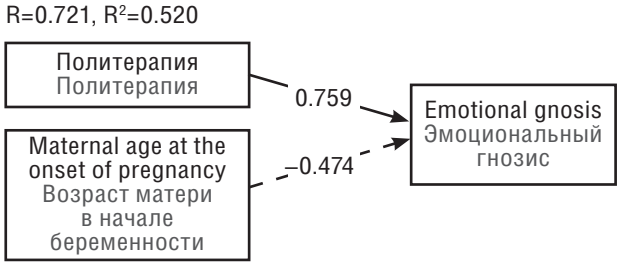

Figure 4. Predictors of emotional gnosis disorders in a child

Рисунок 4. Предикторы нарушений эмоционального гнозиса у ребенка

of the child poor ability to automated speech (R=0.558, R^2=0.312, β=0.558).

Anemia and toxicosis during pregnancy became the predictors of later poor object gnosis (difficulties in recognizing objects) in paired children, but not in the case of artificial feeding in the first year of life (**Fig. 5**).

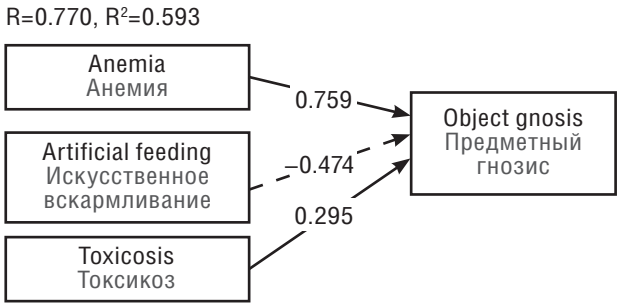

Figure 5. Predictors of object gnosis disorder

Рисунок 5. Предикторы нарушений предметного гнозиса

Analytical abilities (derivation of analogies) were worse in those children whose mothers suffered from anemia during pregnancy, but this pattern was less typical for children of mothers with generalized epilepsy (**Fig. 6**).

Of all the maternal pregnancy complications, the most destructive effect on the general level of child neuropsychological development, despite the absence of the threat to pregnancy termination, was anemia. The paired children experienced the greatest difficulty in performing neuropsychological tests – i.e. demonstrated a greater number of problems in various areas of mental development (**Fig. 7**).

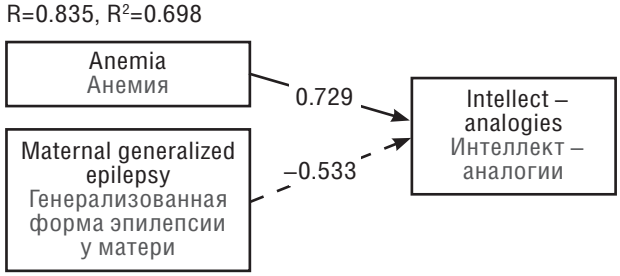

Figure 6. Predictors of altered child logical operations (analogies)

Рисунок 6. Предикторы нарушения логических операций (аналогий) у ребенка

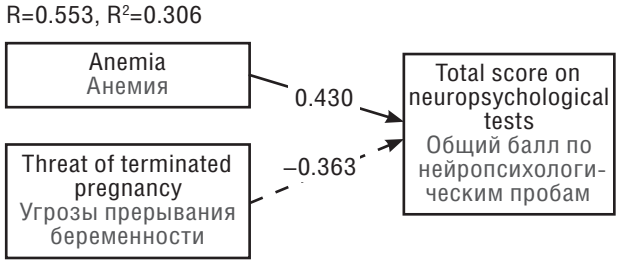

Figure 7. Predictors of the general level of neuropsychological development

Рисунок 7. Предикторы общего уровня нейропсихологического развития

Predictors of subsequent poor mechanical memorization in paired children were associated with the maternal focal epilepsy, seizures in the 2nd trimester of pregnancy, independent refusal to take AEDs, even despite the preparedness of delivery. It can be noted that with the maternal focal epilepsy, the paired children also suffer from poor mnestic processes (memory), which may be due to the long-term use of certain drugs that form cognitive deficits (**Fig. 8**).

The longer mothers suffered from epilepsy, especially in the absence of seizure control, the more often the paired children suffered from semantic memory (remembering a story). Conversely, children whose paired mothers had a short history of the disease and were in remis-

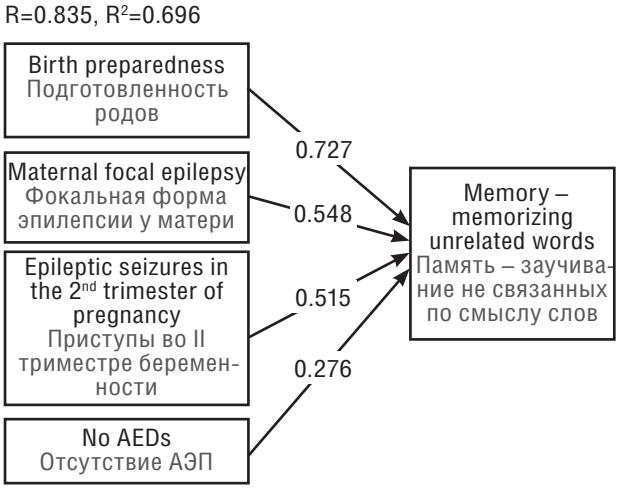

Figure 8. Predictors of child mnestic processes (rote memorization).
AEDs – antiepileptic drugs

Рисунок 8. Предикторы мнестических процессов (механическое запоминание) у ребенка.
АЭП – антиэпилептические препараты

sion were able to better remember the semantic elements of stories (**Fig. 9**).

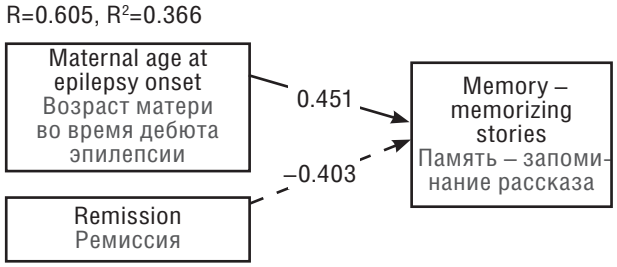

Figure 9. Predictors of child mnestic processes (semantic memorization)

Рисунок 9. Предикторы мнестических процессов (смысловое запоминание) у ребенка

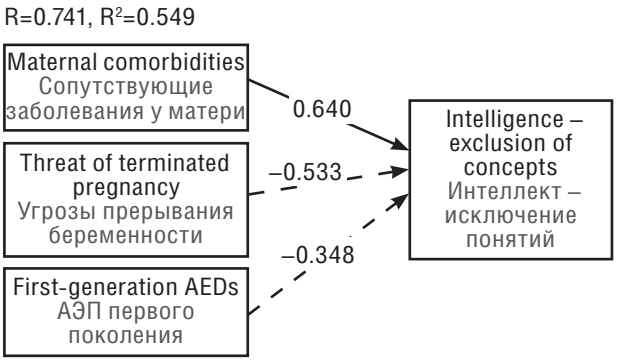

Figure 10. Predictors of child intelligence (concept exclusion). AEDs – antiepileptic drugs

Рисунок 10. Предикторы интеллекта (исключение понятий) у ребенка
АЭП – антиэпилептические препараты

Logical operations (excluding concepts) were less performed by those children whose paired mothers, in addition to epilepsy, suffered from other concomitant diseases. This pattern was not typical for mothers taking no first-generation AEDs and had no threat of termination of pregnancy. For this category of children, comorbid diseases of paired mothers had no such a destructive effect on relevant intellectual abilities (**Fig. 10**).

CONCLUSION / ЗАКЛЮЧЕНИЕ

After analyzing multiple regressions, we can conclude that the predictors, which were most often encountered in them and had the peak predictive power (having high values of R, R^2 and β coefficients), were of paramanout significance for the child mental development. In particular, they included maternal epileptic seizures in the 2nd trimester of pregnancy, complicated course of pregnancy (anemia, toxicosis, acute respiratory viral infections, comorbidity), lack of disease remission and maternal preparation of pregnancy. It was also influenced by the form of maternal epilepsy (child cognitive deficit was most pronounced in the focal form) and the route of delivery (caesarean section increased the risks of negative consequences for child central nervous system).

Thus, to reduce the teratogenic fetal effects from AEDs during pregnancy and avoid a negative effect on child mental development in the future, it is necessary to aspire to maternal disease remission while applying monotherapy with new generation AEDs.

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