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

Mikhailova N.F.¹, Krasko A.S.¹, Odintsova G.V.², Larina I.V.³, Mikhailov V.A.⁴

1 Saint Petersburg State University (7-9 Universitetskaya Qy, Saint Petersburg 199034, Russia)
2 Russian Polenov Neurosurgical Institute – branch of Almazov National Medical Research Center (12 Mayakovskiy Str., Saint Petersburg 191014, Russia)
3 City Epileptology Center, City Psychiatric Hospital No. 6 (hospital with dispensary) (9 lit. A Obvodnoy Channel Qy, Saint Petersburg 192029, Russia)
4 Bekhterev National Medical Research Center for Psychiatry and Neurology (3 Bekhterev Str., Saint Petersburg 192019, Russia)

Corresponding author: Nadezhda F. Mikhailova, e-mail: mail.mikhailova@gmail.com

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.

Received: 24.08.2021; in the revised form: 13.09.2021; accepted: 30.09.2021

Conflict of interests
The authors declare no conflict of interest regarding this publication.

Authors’ contribution
All authors contributed equally to this article.
Психическое развитие детей матерей, страдающих эпилепсией: оценка отдаленных тератогенных эффектов и предикторы нарушений развития

Михайлова Н.Ф.1, Краско А.С.1, Одинцова Г.В.2, Ларина И.В.3, Михайлов В.А.4

1 Федеральное государственное бюджетное образовательное учреждение высшего образования «Санкт-Петербургский государственный университет» (Университетская наб., д. 7-9, Санкт-Петербург 199034, Россия)
2 Российский научно-исследовательский нейрохирургический институт им. проф. А.Л. Поленова – филиал Федерального государственного бюджетного учреждения «Национальный медицинский исследовательский центр им. В.А. Алмазова» Министерства здравоохранения Российской Федерации (ул. Маяковского, д. 12, Санкт-Петербург 191014, Россия)
3 Городской эпилептологический центр Санкт-Петербургского государственного казенного учреждения здравоохранения «Городская психиатрическая больница № 6 (станционар с диспансером)» (наб. Обводного канала, д. 9, лит. А, Санкт-Петербург 192029, Россия)
4 Федеральное государственное бюджетное учреждение «Национальный медицинский исследовательский центр психиатрии и неврологии им. В.М. Бехтерева» Министерства здравоохранения Российской Федерации (ул. Бехтерева, д. 3, Санкт-Петербург 192019, Россия)

Для контактов: Михайлова Надежда Федоровна, e-mail: mail.mikhailova@gmail.com

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.

Статья поступила: 24.08.2021 г.; в доработанном виде: 13.09.2021 г.; принята к печати: 30.09.2021 г.

Конфликт интересов

Авторы заявляют об отсутствии необходимости раскрытия конфликта интересов в отношении данной публикации.

Вклад авторов

Авторы сделали эквивалентный вклад в подготовку публикации.
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 VA 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-
Developing 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-gravida 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, psycosomatic 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

| Parameters of development / Параметры развития | Middle rank / Средний ранг | Focal form of epilepsy / Фокальная форма эпилепсии | Generalized form of epilepsy / Генерализованная форма эпилепсии | Significance of the Mann–Whitney U test / Значимость критерия U Манна–Уитни |
|-----------------------------------------------|-----------------------------|-----------------------------------------------|-------------------------------------------------|---------------------------------|
| 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) |
| 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) |
| 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
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

| Parameters of development / Параметры развития ребенка | Middle rank / Средний ранг | Significance of the Mann-Whitney U test / Значимость критерия U Манна-Уитни |
|---------------------------------------------------------|----------------------------|--------------------------------------------------------------------------------|
| **Mental development disorders / Нарушения психического развития** |                           |                                                                               |
| Anxiety / Тревожность                                   | n=25                       | 16.16                                                                          | 26.86 | 0.004       |
| Socialization disorders / Нарушения социализации        | n=14                       | 16.14                                                                         | 26.86 | 0.004       |
| Thinking problems / Проблемы мышления                   | n=25                       | 16.48                                                                         | 26.29 | 0.009       |
| Attention problems / Проблемы внимания                 | n=14                       | 16.52                                                                         | 26.21 | 0.009       |
| Internalization problems / Интернализационные проблемы  | n=25                       | 16.90                                                                         | 25.54 | 0.022       |
| General indicator / Общий показатель                    | n=16                       | 16.58                                                                         | 26.11 | 0.011       |
| **Indicators of ability and mental development / Показатели способностей и психического развития** |                           |                                                                               |
| Psychosomatic disorders / Психосоматические нарушения   | n=16                       | 11.41                                                                         | 18.63 | 0.020       |
| Psychosomatic disorders / Тревожность, страхи, навязчивость | n=11                       | 11.78                                                                         | 18.13 | 0.042       |
| Motor awkwardness / Моторная неловкость                 | n=25                       | 10.88                                                                         | 19.33 | 0.006       |
| Hyperactivity / Гиперактивность                          | n=13                       | 11.75                                                                         | 18.17 | 0.042       |
| Speaking disorders / Нарушения устной речи              | n=25                       | 12.28                                                                         | 17.46 | 0.100 (tendency / тенденция) |
| Attention deficit / Дефицит внимания                    | n=13                       | 11.91                                                                         | 17.96 | 0.053 (tendency / тенденция) |
| **Neuropsychological tests / Нейропсихологические пробы** |                           |                                                                               |
| General characteristics – orientation / Общая характеристика – ориентировка | n=25                     | 17.26                                                                         | 23.81 | 0.085 (tendency / тенденция) |
| General characteristic – adequacy / Общая характеристика – адекватность | n=13                     | 16.82                                                                         | 24.65 | 0.038       |
Figure 2. A correlation Pleiad 2: correlations between child developmental disorders and maternal remission during pregnancy

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

Inquent, 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.

| 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) |
| | M | S(M) | F | P | ANOVA | Bonferroni |
| Comprehensibility / Понятливость | 19.00 | 1.000 | 13.65 | 3.372 | 12.43 | 6.503 | 2.585 | 0.096 (tendency / тенденция) | – |
| Consecutive pictures / Последовательные картины | 15.33 | 1.155 | 12.53 | 1.807 | 14.33 | 3.724 | 2.673 | 0.090 (tendency / тенденция) | – |

Neuropsychological tests / 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.

Понятливость / Emotional gnosis / Эмоциональный гнозис – тест понятливости.

Verbal reasoning / Способности говорить.

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 / Корреляционный анализ.

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

| Parameters of development / Параметры психического развития ребёнка | 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 / Нейropsychологические 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 |
| Speech – naming / Речь – называние | 0.10 | 0.316 | 0.64 | 1.206 | 0 | 0 | 3.395 | 0.045 |
| Understanding grammar / Понимание грамматики | 0 | 0 | 0.80 | 0.837 | 0 | 0 | 5.107 | 0.023 |
| 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–II = 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 – Fisber criterion value; P – significance level.

Примечание. АЭП – антиэпилептические препараты; М – 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* |
| 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 / Перрессионный 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 gnosia (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 gnosia (R=0.400, R²=0.160, β=0.400); Maternal anemia during pregnancy was a predictor of subsequent child difficulties in understanding of addressed speech (R=0.471, R²=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 gnosia.

Рисунок 3. Предикторы нарушений в речевой сфере, спонтанной речи и предметном гnosизе у ребенка.

AEDs – antiepileptic drugs

AЭП – антиэпилептические препараты
R=0.721, R²=0.520

Политерапия Политерапия

0.759

Emotional gnosис Эмоциональный гнонис

Maternal age at the onset of pregnancy Возраст матери в начале беременности

-0.474

Figure 4. Predictors of emotional gnosис disorders in a child

Рисунок 4. Предикторы нарушений эмоционального гнониса у ребенка

of the child poor ability to automated speech (R=0.558, R²=0.312, β=0.558).

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

R=0.721, R²=0.520

Anemia

0.759

Object gnosис Предметный гнонис

Artificial feeding Искусственное вскармливание

-0.474

Toxicosis Токсикоз

0.295

Figure 5. Predictors of object gnosис disorder

Рисунок 5. Предикторы нарушений предметного гнониса

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).

R=0.553, R²=0.306

Anemia

0.430

Threat of terminated pregnancy Угрозы прерывания беременности

-0.363

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-
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, R² and β coefficients), were of paramount 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 (cesarean 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.

REFERENCES:

1. Karlov V.A., Vlasov P.N., Petrukhin V.A., et al. Epilepsy and pregnancy. In: Karlov V.A. Epilepsy in children and adult women and men. A guide for doctors. 2nd ed. Moscow: BINOM, 2019: 896 p. (in Russ.).
2. Kozhokar A.B., Karlov V.A., Zhidkova I.A., Serkina A.V. Dysembryogenetic stigmata and physical development in children born to epileptic mothers. Epilepsia i paroksizmal'nye zabolevания / Epilepsy and Paroxysmal Conditions. 2010; 2 (2): 25–31 (in Russ.).
3. Gailly E., Kantola-Sorsa E., Hillesmaa V., et al. Normal intelligence in children with prenatal exposure to carbamazepine. Neurology. 2004; 62 (1): 28–32. https://doi.org/10.1212/wnl.62.1.28.
4. Meador K.J., Baker G.A., Browning N., et al. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. Lancet Neurol. 2013; 12 (3): 244–52. https://doi.org/10.1016/S1474-4422(12)70323-X.
5. Adab N., Kini U., Vrenti J., et al. The longer term outcome of children born to mothers with epilepsy. J Neurol Neurosurg Psychiatry. 2004; 75 (11): 1575–83. https://doi.org/10.1136/jnnp.2003.029132.
6. McCorry D., Bromley R. Does in utero exposure of antiepileptic drugs lead to failure to reach full cognitive potential? Seizure. 2015; 28: 51–6. https://doi.org/10.1016/j.seizure.2015.01.019.
7. Scheuerle A.E., Holmes L.B., Albano J.D., et al. Levetiracetam Pregnancy Registry: final results and a review of the impact of registry methodology and definitions on the prevalence of major congenital malformations. Birth Defects Res. 2019; 111 (13): 872–87. https://doi.org/10.1002/bdr2.1526.
8. Blotière P., Miranda S., Weill A., et al. Risk of early neurodevelopmental outcomes associated with prenatal exposure to the antiepileptic drugs most commonly used during pregnancy: a French nationwide population-based cohort study. BMJ Open. 2020; 10 (6): e034829. https://doi.org/10.1136/bmjopen-2019-034829.
9. Baker G.A., Bromley R.L., Briggs M., et al. IQ at 6 years after in utero exposure to antiepileptic drugs: a controlled cohort study. Neurology. 2015; 84 (4): 382–90. https://doi.org/10.1212/wnl.0000000000001882.
10. Veroniki A.A., Rios P., Cogo E., et al. Comparative safety of antiepileptic drugs for neurodevelopmental outcome in children exposed during pregnancy and breast feeding: a systematic review and network meta-analysis. BMJ Open. 2017; 7 (7): e017248. https://doi.org/10.1136/bmjopen-2017-017248.
11. Koch S., Titze K., Zimmermann R.B., et al. Long-term neuropsychological consequences of maternal epilepsy and anticonvulsant treatment during pregnancy for school-age children and adolescents. Epilepsia. 1999; 40 (9): 1237–43. https://doi.org/10.1111/j.1528-1157.1999.tb00852.x.
12. Banach R., Boskovic R., Einarson T., Koren G. Long-term developmental outcome of children of women with epilepsy, unexposed or exposed prenatally to antiepileptic drugs: a meta-analysis of cohort studies. Drug Saf. 2010; 33 (1): 73–9. https://doi.org/10.2165/11317640-00000000-0000.
13. Morrow J., Russell A., Guthrie E., et al. Malformations of antiepileptic drugs in pregnancy: a prospective study from the UK Epilepsy and Pregnancy Register. J Neurol Neurosurg Psychiatry. 2006; 77 (2): 193–8. https://doi.org/10.1136/jnnp.2005.074203.

14. Kispayeva T.T., Nurakhmetova A.S. Modern aspects of antiepileptic therapy during pregnancy. S.S. Korsakov Journal of Neurology and Psychiatry. 2018; 118 (7): 101–3 (in Russ.). https://doi.org/10.17116/jnv201811871101.

15. Vlasov P.N., Petruhin V.A., Gasparyan N.D. Epilepsy and pregnancy. In: Logutova L.S. (Ed.) Extragential pathology and pregnancy. Moscow: Litterra; 2012: 485–533 (in Russ.).

16. AlSheikh M.H. Prevalence of epilepsy in Saudi pregnant women and possible effects of anti-epileptic drugs on pregnancy outcomes. Neurosciences (Riyadh). 2020; 25 (1): 32–7. https://doi.org/10.17112/nsj.2020.1.20190077.

ЛИТЕРАТУРА:
1. Карпов В.А., Власов П.Н., Петрухин В.А. и др. Эпилепсия и беременность. В кн.: Карпов В.А. Эпилепсия у детей и взрослых женщин. Руководство для врачей. 2-е изд. М.: БИНОМ; 2019: 896 с.
2. Коможару А.Б., Карлов В.А., Жидкова И.А., Серкина А.В. Стigma дизэмбриогенеза и физическое развитие у детей, рожденных от матерей, страдающих эпилепсией, Эпилепсия и пароксизмальные состояния. 2010; 2 (2): 25–31.
3. Gally E., Kantola-Sorsa E., Hillesmaa V., et al. Normal intelligence in children with prenatal exposure to carbamazepine. Neurology. 2004; 62 (1): 28–32. https://doi.org/10.1212/wnl.62.1.28.
4. Meador K.J., Baker G.A., Browning N., et al. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 (NEAD) study: a prospective observational study. Lancet Neurol. 2013; 12 (3): 244–52. https://doi.org/10.1016/S1474-4422(12)70323-X.
5. Adab N., Kini U., Vinten J., et al. The longer term outcome of children born to mothers with epilepsy. J Neurol Neurosurg Psychiatry. 2004; 75 (11): 1575–83. https://doi.org/10.1136/jnnp.2003.029132.
6. McCorry D., Bromley R. Does in utero exposure of antiepileptic drugs lead to failure to reach full cognitive potential? Seizure. 2015; 28: 51–6. https://doi.org/10.1016/j.seizure.2015.01.019.
7. Scheuerle A.E., Holmes L.B., Albano J.D., et al. Levetiracetam monotherapy during pregnancy. A population-based cohort study. BMJ Open. 2020; 10 (6): e034829. https://doi.org/10.1136/bmjopen-2019-034829.
8. Baker G.A., Bromley R.L., Briggs M., et al. IQ at 6 years after in utero exposure to antiepileptic drugs: a controlled cohort study. Neurology. 2015; 84 (4): 382–90. https://doi.org/10.1212/wnl.0000000000001182.
9. Veroniki A.A., Rios P., Cogo E., et al. Comparative safety of antiepileptic drugs for neurological development in children exposed during pregnancy and breast feeding: a systematic review and network meta-analysis. BMJ Open. 2017; 7 (7): e017248. https://doi.org/10.1136/bmjopen-2017-017248.
10. Koch S., Tritze K., Zimmermann R.B., et al. Long-term neuropsychological consequences of maternal epilepsy and anticonvulsant treatment during pregnancy for school-age children and adolescents. Epilepsia. 1999; 40(9): 1237–43. https://doi.org/10.1111/j.1528-1157.1999.tb0832x.x.
11. AlSheikh M.H. Prevalence of epilepsy in Saudi pregnant women and possible effects of anti-epileptic drugs on pregnancy outcomes. Neurosciences (Riyadh). 2020; 25 (1): 32–7. https://doi.org/10.17112/nsj.2020.1.20190077.

About the authors:
Nadezhda F. Mikhailova – PhD (Psych.), Associate Professor, Chair of Developmental Psychology and Differential Psychology, Faculty of Psychology, Saint Petersburg State University (Saint Petersburg, Russia). ORCID ID: https://orcid.org/0000-0002-4183-8171; RSCI SPIN-code: 6203-6013. E-mail: mail.mikhailova@gmail.com.

Anastasia S. Krasco – 2-nd-year Postgraduate, Chair of Developmental Psychology and Differential Psychology, Faculty of Psychology, Saint Petersburg State University (Saint Petersburg, Russia). ORCID ID: https://orcid.org/0000-0002-3985-5060; RSCI SPIN-code: 1501-0092.
Galina V. Odintsova – MD, PhD, Head of Epilepsy Department, Russian Polenov Neurosurgical Institute – branch of Almazov National Medical Research Center (Saint Petersburg, Russia). ORCID ID: https://orcid.org/0000-0002-7186-0054; WoS ResearcherID: G-8940-2012; Scopus Author ID: 55510371000; RSCI SPIN-code: 1303-4651.

Irina V. Larina – Neurologist, City Epileptology Center, City Psychiatric Hospital No. 6 (hospital with dispensary) (Saint Petersburg, Russia).

Vladimir A. Mikhailov – Dr. Med. Sc., Head of Neuropsychiatry Department, Scientific Supervisor of Department of Integrative Therapy of Neuropsychiatric Patients and Department of Exogenous Organic Disorders and Epilepsy, Bekhterev National Medical Research Center for Psychiatry and Neurology (Saint Petersburg, Russia); ORCID ID: https://orcid.org/0000-0002-7700-2704; WoS ResearcherID: B-3272-2017; RSCI SPIN-code: 5563-1009.

Сведения об авторах

Михайлова Надежда Федоровна – к.психол.н., доцент кафедры психологии развития и дифференциальной психологии факультета психологии ФГБОУ ВО «Санкт-Петербургский государственный университет» (Санкт-Петербург, Россия). ORCID ID: https://orcid.org/0000-0002-4183-8171; РИНЦ SPIN-код: 6203-6013. E-mail: mail.mikhailova@gmail.com.

Краско Анастасия Сергеевна – аспирант 2-го года обучения кафедры психологии развития и дифференциальной психологии факультета психологии ФГБОУ ВО «Санкт-Петербургский государственный университет» (Санкт-Петербург, Россия). ORCID ID: https://orcid.org/0000-0002-3985-5060; РИНЦ SPIN-код: 1501-0092.

Одинцова Галина Вячеславовна – к.м.н., руководитель отдела эпилепсии Российского научно-исследовательского нейрохирургического института им. проф. А.Л. Поленова – филиала ФГБУ «Национальный медицинский исследовательский центр им. В.А. Алмазова» Минздрава России (Санкт-Петербург, Россия). ORCID ID: https://orcid.org/0000-0002-7186-0054; WoS ResearcherID: G-8940-2012; Scopus Author ID: 55510371000; РИНЦ SPIN-код: 1303-4651.

Парина Ирина Владимировна – врач-невролог Городского эпилептологического центра СПб ГКУЗ «Городская психиатрическая больница № 6 (станционар с диспансером)» (Санкт-Петербург, Россия).

Михайлов Владимир Алексеевич – д.м.н., начальник отдела нейropsychиатрии, научный руководитель отделения интегративной терапии больных нейропсихиатрического профиля и отделения экзогенно-органических расстройств и эпилепсии ФГБУ «Национальный медицинский исследовательский центр психиатрии и неврологии им. В.М. Бехтерева» Минздрава России (Санкт-Петербург, Россия); ORCID ID: https://orcid.org/0000-0002-7700-2704; WoS ResearcherID: B-3272-2017; РИНЦ SPIN-код: 5563-1009.