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Neurodevelopmental Disorders in Children with Hereditary Diseases (Review of Literature, Clinical Case Report)

Introduction. Recently a number of rare diseases have been suspected and diagnosed in pediatric practice, the core of which is mental health disorders manifested by impaired neurodevelopment, autistic spectrum disorders, delayed psycholinguistic development, anxiety and hyperactivity. Most of the research focuses on psychiatric or psychological-pedagogical problems, but the genetic component of these diseases also plays an important role, in the presence of which is important to accomplish genetic studies for its verification and determination the "target organs" inherent in the respective hereditary disease [9].

The analysis of current realities shows that neurodevelopmental disorders are among the most common forms of hereditary pathologies, covering 1.0-3.0 % of general population. They include diverse phenomena from a clinical viewpoint and most often lead to disability in early childhood. All these phenomena unite the disorders of adaptive behavior, detected at an early age (during the formation of the psyche), associated with insufficient development of cognitive abilities, underdevelopment of the emotional-volitional sphere, language, motor skills and personality in general. These disorders significantly affect the quality of life of sick individuals, their families and society as a whole. On the one hand, young children with impaired development need a special environment and conditions, while on the other hand, they need communication with peers with normative development. The adaptation of such children in society depends on the harmonious balance of these conditions [2].

Disorders of psychological development are among the key areas of child development - speech and communication, imagination, attention, understanding of spoken language, social interaction, self-control, intelligence - all these signs are mostly manifested at an early age. The most common disorders of mental development are autistic spectrum disorders (ASD), attention deficit hyperactivity disorder (ADHD), tic disorder, language development disorder, delayed psychological development, which is understood as a syndrome of temporary delay in the development of the psyche as a whole or individual functions (sensory, motor, speech, emotional and volitional), disorder of intellectual development, anxiety.

The aim of the study. To analyze current literature dedicated to the problem of impaired neurodevelopment in children with hereditary diseases, and make a presentation of clinical case report on Rett syndrome - a rare genetic anomaly accompanied by impaired neurodevelopment in a child.

Materials and methods. The method of systematic and comparative analysis, the biblio-semantic method of studying the results of current research directed towards the investigation of the influence of hereditary diseases in the neurodevelopment disorder in children was used. As much as 22 publications were analyzed. A clinical case report on Rett syndrome in a child was accomplished, including the analysis of clinical symptoms and used laboratory-instrumental examinations, the main of which is the next generation sequencing (NGS) molecular genetic method.

Results and discussion. Review of literature. Based on the analysis of recent publications it was estimated that clinical cases of rare A. Rett syndrome in children occur with a frequency of 1:10.000-1:15.000. This syndrome is caused by a mutation in the MECP2 gene associated with X-linked A. Rett syndrome/atypical Rett syndrome (UID MedGen: 48441) or X-linked MECP2 duplication syndrome (MedGen: 337496).

The spectrum of MECP2-associated phenotypes in females ranges from classic Rett syndrome to variant Rett syndrome with a broader clinical phenotype (either milder or more severe than classic Rett syndrome) to mild scholastic impairment. The spectrum in males ranges from severe neonatal encephalopathy, pyramidal symptoms, parkinsonism, and macroorchidism syndrome to severe syndromic/nonsyndromic intellectual disability.

Classic Rett syndrome, a neurodevelopmental disorder with increasing severity, affecting mainly girls, is characterized by apparently normal psychomotor development during the first 6-18 months of life, followed by a short period of developmental stagnation, followed by a rapid regression of language and motor skills, and then long-term stability. During the rapid regression phase, repetitive, stereotyped hand movements replace purposeful hand use. Additional findings include bouts of screaming and inconsolable crying, signs of autism, panic attacks, bruxism, episodic apnea and/or hyperpnea, ataxia and apraxia of gait, tremors, seizures, and acquired microcephaly. Males: severe neonatal encephalopathy, the most common phenotype in affected males, is characterized by a continuous clinical course, which is accompanied by a metabolic-degenerative type, abnormal tone, involuntary movements, severe convulsions and respiratory disorders [MedGen: 337496] [22].

Red flags that may indicate warning signals of impaired neurodevelopment of the child:

- Does not respond to his/her name by 12 months.
- Does not point to objects (such as an airplane in the sky) to show interest until 14 months.
- Does not pretend during play (for example, as if feeding a doll) until 18 months.
- Avoids eye contact and prefers to be alone.
- Has difficulty expressing his/her feelings and does not understand other people's feelings.
- Does not speak at the age of 2.
- Repeats words or phrases.
- Gets upset over minor changes.
- Has obsessive interests.
- Spins, swings arms, sways.
- Unusually reacts to sounds, smells, tastes, etc.

In fact, one or more of these symptoms can also be seen in children without ASD, that is why complex observation is required to confirm the diagnosis. Numerous screening tools have been created to assess the development and preliminary diagnosis of ASD [11].

The first screening test to determine the risk (low, medium, high) of ASD is a questionnaire – the screening test for autism (Checklist for Autism in Toddlers - CHAT). This survey, designed to monitor the behavior of a child at the age of 18 months, takes about 15 minutes. The CHAT-questionnaire reveals existing deviations in the child's psychophysical development and makes it possible to identify children who form a risk group and are predicted to have autism. "Modified Checklist for Autism in Toddlers - M-CHAT" was created to conduct a screening examination for autism spectrum disorders in children aged 16-30 months [4, 8].

The second stage of the examination under the conditions of the child's entry into the risk group is the "Diagnostic Interview" (The Autism Diagnostic Interview-Revised - ADI-R). This is an interview with the parents of children older than 18 months, who were included into the risk group according to M-CHAT. The ADI-R includes questions to assess the quality of a child's social interactions with other people, communication and speech, behavioral patterns, and unusual sensory preferences. The duration of the interview is up to two hours [4, 7, 10].

"The Childhood Autism Rating Scale" (CARS) contains 15 items: relationships with people, imitation, emotional reactions, motor dexterity, use of objects, adaptive changes, visual reaction, taste and smell reactions, tactile reaction, anxiety reactions, fears, verbal communication, non-verbal communication, indicators of the child's activity and intellectual development [4, 7, 10].

The "gold standard" is the observation scale for the diagnosis of autism (The Autism Diagnostic Observation Schedule - ADOS), which makes it possible to observe social and communicative behavior caused by the diagnosis, general developmental disorders. Contains four modules that are selected depending on his speech level and age. The first module is designed for children with speech difficulties or non-verbal children; the second is for children who have minor speech problems; the third module is designated for children who speak fluently; the fourth module is for teenagers and adults who speak fluently [3].

The ADOS autism observation scale is a differential diagnosis of developmental abnormalities that determines the type and category of impairment [6, 18].

Autism is a variety (spectrum) of manifestations of the same complexity - complexity in social interaction and communication. But, as it turns out, autism spectrum disorders are not only a psychiatric or psychological-pedagogical problem, the genetic component takes an important place here. Chromosomal and genetic syndromes, brain abnormalities, and metabolic disorders are found in children with impaired development. Such a disease can be accompanied by symptoms of damage to other organs and systems (digestive, skin, organ of vision, connective and bone tissue, urinary and hepatobiliary systems), which are often overlooked by clinicians. Therefore, every case of impaired development (ID) in a child requires a comprehensive examination with the involvement of a multidisciplinary team of experts. For a long time, the association of autism with other clinical symptoms was not payed much attention; however, the frequency of cases when autism was associated with other symptoms or a multisystem lesion of the body made scientists and practitioners think. This is how the term ″syndromal autism″ was born. This term explains that autism or autism spectrum disorder as a symptom of another hereditary disease [5, 15, 18].

Five leading American organizations (e.g. American College of Medical Genetics and Genomics, American Academy of Neurology, Child Neurology Society) consider deoxyribonucleic acid (DNA) testing appropriate for autism [1, 7]. All recommended genetic testing has four sequential steps: karyotyping, chromosomal microarray analysis, single gene sequencing, and whole-exome sequencing. Genetic, chromosomal and genomic mutations are subdivided in hereditary pathogenesis. Chromosomal mutations change the structure of chromosomes, genomic mutations change the genome of the

organism as a whole, due to what is added or subtracted from the total set of chromosomes. Gene mutations change the sequence of nucleotides in genes [19].

The first step - karyotyping - is a cytogenetic method that detects the total count of chromosomes, analyze their size and shape. It is the numerical and structural stability of chromosomes that is the most important condition for the formation of a phenotypically normal organism during the development of the proband. That is, during a cytogenetic study, a cytogeneticist can detect genomic abnormalities in the number of chromosomes, which are accompanied by a change in phenotype, damage to the central nervous system (CNS), mental retardation, and polysystemic damage. An example can be the following - J. L. Down syndrome (trisomy 21), D. Edwards syndrome (trisomy 18). Syndromes caused by a change in the number of sex chromosomes - H. Klinefelter syndrome (47 XXY), which can be accompanied by reduced intelligence; N. Shereshevsky - H. Turner (45X0). Chromosomal mutations are violations of the structure of chromosomes due to translocations (interchromosomal rearrangements), deletion (loss of a chromosome section), duplication (repetition of a chromosome section) [17].

Only large structural rearrangements of chromosomes can be detected by karyotype study. If we are talking about microdeletions and microduplications, then, unfortunately, they are invisible under a microscope. That is, if obtained a normal karyotype in a child with a developmental disorder, is recommended to use the second step of genetic research - the method of fluorescence hybridization (Fluorescence in situ hybridization - FISH), or an even more sensitive method - chromosomal micromatrix test. The FISH method allows to detect small chromosomal rearrangements that the cytogeneticist cannot see with a standard karyotype study. This method has one major drawback: the probes are specific to each individual region of the chromosome and, accordingly, a separate probe is required for each microdeletion syndrome. In practice, it looks like this: the geneticist sees the proband's phenotype and accompanying malformations and directs detection of the corresponding deletion using the FISH method. For example, the proband has facial dysmorphism that gives the impression of an "elf's face", echocardiography (Echo-CG) diagnosed supravalvular aortic stenosis, ophthalmologist diagnosed hypermetropia, assessment of the musculoskeletal system - kyphosis, as well as delayed psychomotor development. All the abovelisted signs are characteristic of microdeletion 7q11.2, or J. C. P. Williams syndrome. With the FISH method, which is suitable for the region 7q11.23, the diagnosis should be confirmed or rejected. Therefore, prior to using FISH method, a phenotypic and clinical signs should be identified in order to look for a microdeletion in certain chromosome. Chromosomal microarray analysis makes it possible to figure out or diagnose simultaneously all microdeletion and microduplication syndromes. This molecular cytogenetic method is based on detecting variations in the number of DNA copies compared to a control sample [2, 12].

This diagnostic method examines all clinically significant parts of the genome, allowings to identify chromosomal abnormality in the examined person with maximum accuracy. The literature describes some syndromes that are characteristic of ASD, while others are characterized by intellectual impairment. Below are listed some microdeletions associated syndromes, accompanied by a violation of psychological development:

A. M. Di Georgi syndrome - deletion of 22q11. Characteristic problems with learning, congenital heart defects, immunological deficiency [14].

1p36 deletion syndrome is characterized by malformations of the skull, intellectual disability, convulsions, brain and heart defects.

H. Angelman syndrome - deletion of 15q11. Clinical signs: delayed mental development, impaired speech skills, convulsions.

A. Prader - H. Willi syndrome - deletion of 15q11. Clinical signs: hypotonia, obesity, delayed motor and language skills, delayed mental development, hypogonadism [12].

Cri-du-chat (Fr. "cat's cry") syndrome – a delay in mental development and speech, a child's cry resembles cat's cry.

U. Wolf - K. Hirschhorn syndrome - mental retardation, heart and brain abnormalities, growth retardation, hypotonia, craniofacial features.

P. Jacobsen syndrome - deletion of 11q23. Characteristic disorders of blood supply (H. Paris - A. Trousseau syndrome), heart defects, characteristic facial features (e.g. macrocephaly, trigonocephaly, small lower jaw and small low ears), learning difficulties, delayed development of motor skills, cognitive impairment, impaired communication skills.

L. Langer - A. Giedion syndrome - 8q24 deletion. Clinical signs: short stature, thin upper lip, wide nose, small and abnormal number of teeth, thinning scalp hair, deformed bones and joints, intellectual disability, osteochondromas (benign tumors).

A. Smith - R. Magenis syndrome - 17p11.2 deletion. Clinical features: language delay, speech delay, intellectual disability, sleep disturbance, behavioral problems, scoliosis, dental abnormalities, facial features, vision problems, reduced sensitivity to pain/temperature, ear abnormalities [13].

The basis of any genetic disease is DNA mutation. To date, more than 10,000 genes have been mapped, the mutations of which lead to a hereditary disease. In the 70s and 80s of the XX century. a molecular-genetic method was created that makes it possible to isolate individual genes and their segments, to determine their nucleotide sequence.

A large group of monogenic diseases that can cause disorders of psychological development, from retardation of mental development to impaired intelligence, are hereditary metabolic defects, in particular, enzymopathies. More than 100 enzymopathies are known, which are inherited by autosomal recessive or X-linked recessive types. Timely diagnosis of hereditary metabolic diseases

can dramatically affect the course and prognosis of the disease. The most common metabolic disease is phenylketonuria. The basis of the hereditary disorder is the absence of the normal process of hydroxylation of phenylalanine into tyrosine. Screening for phenylketonuria allows early suspicion of the disease, and molecular genetic research - to verify the diagnosis. A diet low in phenylalanine prevents neurological and psychological disorders. In the absence of timely diagnosis and treatment of this disease, it leads to disability and severe intellectual impairment of the child [1].

It is worth mentioning another genetic hereditary disease accompanied by psychological disorders, namely autism spectrum disorder and intellectual disability: D.-M. Bourneville - J. J. Pringle disease (tuberous sclerosis) is an autosomal dominant genetic disease with incomplete gene penetrance and a high frequency of spontaneous mutations. Mutations occur in TSC1 and TSC2 genes, which are located in chromosomes 9 and 16, which leads to the formation of benign tumors in "target organs" - these are the heart, kidneys, eyes, brain, lungs [21].

Primary (major) signs of tuberous sclerosis include: renal angiomyolipomas (AML); lymphangioleiomyomatosis; facial angiofibromas and fibrotic plaques on the forehead; non-traumatic periungual fibromas; hypopigmented spots (three or more); areas of "brown skin"; multiple retinal hamartomas; cork tubers; subependymal nodes; giant cell astrocytoma; rhabdomyoma of the heart (single or multiple). Secondary (minor) signs include the following: multiple kidney cysts; hamartomatous rectal polyps; hamartomas of internal organs; damage to the white matter of the brain-radial migratory tracts; achromatic area of the retina; bone cysts; fibromas of the gums; "confetti" spots on the skin; numerous depressions in tooth enamel. To establish a definite diagnosis of tuberous sclerosis (Definite tuberous sclerosis complex - DTSC), the presence of two primary (major) signs or one primary (major) sign + two secondary (minor) signs is required. The diagnosis of probable tuberous sclerosis (Probable tuberous sclerosis complex - PTSC) is established in the presence of one primary (major) sign + one secondary (minor) sign.

Characteristic for tuberous sclerosis is the occurrence of epilepsy (various forms and types of seizures), cognitive impairment and autistic spectrum disorders, which occur in 25.0-60.0 % of patients [16, 21].

Therefore, each case of impaired development in a child requires a multifaceted comprehensive examination involving a multidisciplinary team of experts. To rule out or diagnose a hereditary disease and choose the right diagnostic route, one needs to do the following:

• Conduct genealogical and clinical examinations in children with impaired neuropsychological development.

• Assess psychological features and cognitive functions in young children with impaired neuropsychological development.

• Conduct a laboratory examination of the hepatobiliary, urinary and endocrine systems in children with neuropsychological developmental disorders.

• Conduct an instrumental ultrasound examination (USS) of internal organs, thyroid gland and echocardiography in these children.

• Conduct genetic research to verify hereditary disease in children with impaired neuropsychological development.

• To improve the algorithm for early diagnosis of PND caused by genetic diseases.

Description of a clinical case. A 15-year-old child was referred by a neurologist for impaired neurodevelopment. Complaints: school skills are difficult to learn, lack of independence, inability to learn the rules of behavior, school maladjustment, muscle weakness in the legs and difficulty climbing stairs. D. Wechsler test: the total intelligence quotient (intelligence quotient - IQ) is 56, which indicates mild cognitive impairment. Electroencephalogram (EEG): focal disturbances of a sharp-discharge nature in the frontal areas, the changes increase during exercise tests in all areas of the brain with preservation of focality. Objectively at 15 years old: height 173.0 cm; body weight 55.0 kg. Scoliosis posture; X-shaped deformity of the lower limbs. Skin lesions: two oval-shaped hypopigmented spots on the lateral surface of the chest and abdomen. Neurological status: consciousness is clear; M. H. Romberg position is stable; deep and superficial sensitivity is not disturbed on both sides.

Preliminary diagnosis: tuberous sclerosis?

The following examination route is proposed: karyotype; 3-hour EEG monitoring; ultrasound of internal organs; electroneuromyography (EMG); consultation of an ophthalmologist; magnetic resonance imaging (MRI) of the brain; genetic testing: Invitae epilepsy panel (306 genes).

- Brain MRI: no signs of organic brain damage were found.
- Karyotype: 46 xx, fra(17)(p12) - a variant of the norm according to the international nomenclature.
- ENMG: fibular nerve on the left - signs of weakening of function (20.0 of the nerve on the right); weakening of root function at the lumbosacral level on the left.
- Ultrasound of internal organs: multiple cysts of both kidneys.
- 3-hour EEG monitoring: no changes.
- Ophthalmologist: age norm.
- 2 variants were found in the MECP2 gene: 4 copies of MECP2 instead of 2 - pathogenic variant, amplification, complete coding sequence c.1127C > G(pPro376Arg) in the heterozygous state of uncertain clinical significance.

The mother turned out to be a heterozygous carrier of the variant of unknown clinical significance c.1127C>G(pPro376Arg) found in the proband.

Genetic testing of the proband's father and sister: no variants of the proband were detected MECP2 gene is associated with X-linked Rett syndrome / atypical A. Rett syndrome (UID MedGen: 48441) or with X-linked duplication MECP2 syndrome (MedGen: 337496).

In the proband, four copies of the MECP2 gene were found instead of two - a pathogenic variant with amplifica-

tion of the gene dose by two additional complete coding sequences.

Given the lack of additional copies of the MECP2 gene in the proband`s parents, the mutation arose de novo.

Final diagnosis: X-linked / atypical A. Rett syndrome.

Conclusions. For a long time, the connection of impaired neurodevelopment with other clinical symptoms was not given much importance, but the frequency of cases when other symptoms or polysystemic damage of the body were diagnosed with impaired development of the child made scientists and practitioners think. This is how the term "syndromal autism" was born. This term explains that developmental delay in children or autism spectrum disorder is a symptom of another hereditary disease. Recently, a number of rare diseases have been suspected and diagnosed in pediatric practice, the core of which are disorders of the autistic spectrum, retardation of psycholinguistic development, hyperactivity disorders. Therefore, it is necessary to improve the existing algorithm of early diagnosis of the hereditary origin of a child's impaired development, conduct an examination of the hepatobiliary, urinary and endocrine systems, evaluate the psychological characteristics and cognitive functions of each child with impaired development. The main goal of these actions: providing individual care for each child, creating space for the development of modern medical care for the children of Ukraine. The formation of analytical and strategic planning processes for medical care for children, as well as further study of existing challenges and needs, is extremely relevant. This will make it possible to change the negative dynamics of morbidity, disability and mortality indicators of the child population and to implement measures aimed at creating conditions for the safe and prosperous growth of every child.

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Conflict of interest
The authors declare no conflicts of interest.

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Introduction. The majority of studies on disturbed neurodevelopment in children focus on psychiatric or psychological-pedagogical issues, but the genetic component of pathology also occupies an important place, in which is important to conduct genetic investigation to verify hereditary pathology, and to identify target organs inherent in particular hereditary disease.

The aim of the study. To conduct a review of current literature dedicated to the problem of impaired neurodevelopment in children with hereditary diseases, to describe a clinical case of A. Rett genetic syndrome, accompanied by impaired neurodevelopment in a child.

Materials and methods. The method of systematic and comparative analysis, as well as the biblio-semantic method of studying modern views on the influence of hereditary diseases in the disruption of neurodevelopment in children were used. A clinical case of A. Rett syndrome in a child is described, where the analysis of clinical symptoms and laboratory-instrumental examinations were used, the main of which is the molecular genetic method of next generation sequencing (NGS).

Results. Based on the literature analysis it was estimated that clinical cases of rare A. Rett syndrome in children occur with a frequency of 1:10.000-1:15.000. This syndrome is caused by a mutation in the MECP2 gene associated with X-linked A. Rett syndrome/atypical A. Rett syndrome (UID MedGen: 48441) or X-linked MECP2 duplication syndrome (MedGen: 337496).

Conclusions. For a long time, the connection of impaired neurodevelopment with other clinical symptoms was not payed much attention, but the enhanced frequency of cases when a child with impaired neurodevelopment was diagnosed with other symptoms or a multisystem lesion stimulated research in this area. This is the story how the term "syndromal autism" was born. This term means developmental delay or autism spectrum disorder in children with symptoms of another hereditary disease.

Keywords: mental health, autism spectrum disorders, psycholinguistic delay, anxiety, genes, mutations.

Порушення нейророзвитку у дітей зі спадковими недугами (огляд літератури, опис клінічного випадку)

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Вступ. У педіятричній практиці щораз частіше запідозрюють і діягностують низку рідкісних хвороб, ядром яких є порушення психічного здоров'я, що виявляються розладами аутичного спектра, затримкою психомовного та нейророзвитку, тривожністю і гіперактивністю. Більшість досліджень порушень нейророзвитку у дітей зосереджені на психіятричній чи психолого-педагогічній проблематиці. Важливе місце посідає і генетичний складник цієї патології, який вимагає генетичних досліджень для верифікації спадкової патології, визначення органів-мішеней, властивих тій чи іншій спадковій хворобі. Аналіз інформації з літератури свідчить, що розлади нейророзвитку у дітей – одна з найпоширеніших форм спадкової недуги (1,0–3,0 % населення), що охоплює різні з клінічного погляду зору явища і найчастіше призводить до інвалідизації у ранньому дитячому віці.

Мета. Здійснити огляд сучасної літератури, присвяченої проблемі порушення нейророзвитку у дітей зі спадковими недугами, описати клінічний випадок генетичного синдрому А. Ретта, що супроводжувався розладами нейророзвитку у дитини.

Матеріяли й методи. Використовували метод системного й порівняльного аналізу, бібліосемантичний метод вивчення результатів актуальних наукових досліджень щодо сучасного погляду на вплив спадкових недуг у порушенні нейророзвитку у дітей. Описали клінічний випадок синдрому А. Ретта у дитини, застосували аналіз клінічних симптомів і лабораторно-інструментальні обстеження, зокрема, молекулярно-генетичний метод секвенування нового покоління (next generation sequencing – NGS).

Результати. З'ясували, що клінічні випадки рідкісного синдрому А. Ретта у дитини трапляються з частотою 1:10000–1:15000. Цей синдром спричинюється мутацією гена MECP2, що асоціюється з Х-зчепленим синдромом А. Ретта / атиповим синдромом А. Ретта (UID MedGen: 48441) або з Х-зчепленою дуплікацією MECP2 синдром (MedGen: 337496).

Висновки. Довший час зв'язку порушення нейророзвитку дитини з іншими клінічними симптомами не надавали важливого значення. Проте частота випадків, коли через порушення розвитку дитини діягностували інші симптоми або полісистемне ураження організму, привернула увагу науковців і практиків. Так виник термін «синдромальний аутизм», який пояснює, що аутизм, чи розлад аутичного спектра – це симптом іншої спадкової недуги. У практиці запідозрено й діягностовано низку рідкісних хвороб, ядром яких є розлади аутичного спектра, затримка психомовного розвитку та гіперактивність. Отже, потрібно вдосконалити алгоритм ранньої діягностики спадкового походження порушення розвитку дитини, здійснити обстеження гепатобіліярної, сечовидільної та ендокринної систем, оцінити психологічні особливости й когнітивні функції дітей із порушенням розвитку, щоб забезпечити індивідуальну допомогу, створити простір для вдосконалення медичної допомоги дітям. Актуальним є формування аналітично-стратегічного планування медичної допомоги дітям, а також подальше вивчення викликів і потреб. Це уможливить змінити негативну динаміку показників захворюваности, інвалідности і смертности серед дітей, впровадити заходи, спрямовані на створення умов для безпечного і щасливого зростання кожної дитини.

Ключові слова: психічне здоров'я, розлади аутичного спектра, затримка психомовного розвитку, тривожність, гени, мутації.

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