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A. G. Malov
Perm, Russia

PATHOGENESIS OF MENTAL UNDERDEVELOPMENT IN HEREDITARY DISEASES ACCOMPANIED BY BRAIN LESIONS

Abstract. On the basis of clinical experience and materials of special literature, it is traditionally suggested to single out three groups of pathogenetic factors of mental underdevelopment in hereditary diseases. These factors may include structural lesions of the brain, metabolic disorders or epileptic processes. In structural disorders of brain development of hereditary genesis, the pathological change of brain formation, complicating its normal functioning, is the main pathogenetic factor of mental underdevelopment. In metabolic genetic diseases (hereditary metabolic disorders) brain lesion is associated with toxic effect of some neurometabolic drugs and deficiency of others. In monogenic idiopathic epilepsies, epileptic seizures and/or prolonged epileptiform (between seizures) activity emerging on the electroencephalogram of the developing brain may lead to the formation of "epileptic developmental encephalopathy". Pathogenetic variants of mental underdevelopment should be taken into account while planning medical and rehabilitation activities. In hereditary diseases, a combination of these three factors in different variants is often observed, for example, in phakomatoses, and specifically in cases of tuberous sclerosis, the existing structural brain lesion is, as a rule, accompanied by symptomatic "structural" focal epilepsy, aggravating mental development. To prescribe adequate treatment, make plausible prediction and prevent birth of sick siblings in the family, it is extremely important to determine the right nosological form of the hereditary disease, to confirm it with laboratory tests, and not simply state the presence of "genetically determined syndrome" in the child.

Keywords: hereditary diseases; nervous system; mental underdevelopment; pathogenetic factor; metabolic genetic diseases; monogenic idiopathic epilepsies.

About the author: Malov Aleksandr Germanovich, Doctor of Medicine, Associate Professor.

Place of employment: Professor of Department of General and Clinical Psychology, Perm State National Research University; Associate Professor of Department of Neurology named after V.P. Pervushin, E.A.Vagner Perm State Medical University.

E-mail: malovag1959@mail.ru.

As is known, hereditary diseases [6, p. 936] are one of the main causes of the psychological underdevelopment syndrome, or inherited intellectual disability (oligophrenia).

It should be stressed at once that the popular conception of hereditary diseases as "those passed down from the parents" is not exact enough. It would be more correct to say that hereditary diseases are disorders caused by mutation ("breakdown") of the genetic material of gametes (sex cells) and inherited from the parents. "Breakdown" of the genetic material takes place in the chromosomes, nuclear DNA genes, or mitochondrial DNA. But the parents and other relatives of the patient may be healthy, and may not carry the mutant gene in the case if the "breakdown" takes place directly in the sperm cell or ovum of the child's parents – the so-called sporadic mutation *de novo* (new random mutation). For example, about 80% of the cases of Rett syndrome (RTT), coming second (after Down syndrome) among hereditary cases of intellectual disability in girls, are brought about by mutation *de novo of the* MeCP2 gene situated in X-chromosome [11].

Moreover, many forms of hereditary intellectual disability are passed by a complex non-Mendelian inheritance method, when it is next to impossible to trace genetic predisposition across generations. Thus, Fragile X syndrome (FXS), coming second (after Down syndrome) among hereditary cases of intellectual disability in boys, refers to the "trinucleotide repeat expansion" diseases [12]. Expansion (from Latin *expansio* – increase in size, number, etc.), i.e. increase of the number of nucleotide repeats in generations after meiosis, leads to the phenomenon of anticipation (Latin *anticipatio* – premature assumption) when increase of the number of trinucleotide repeats predetermines more severe manifestations of the disease in children and grandchildren in comparison to the older generation.

A number of well-known cases of Angelman syndrome (AS) and Prader-Willi syndrome (PWS) accompanied by psychological underdevelopment are not caused by gene

mutation directly but by epigenetic factors, specifically by the "uniparental disomy" phenomenon when a diploid offspring reveals homologous chromosomes of singular (maternal or paternal) origin [4, pp. 9-14].

We believe that pathogenesis of psychological underdevelopment in hereditary diseases may be associated with three groups of pathogenetic factors: structural lesions of the brain, metabolic brain disorders and epileptic processes. Detailed clinical and paraclinical examination with obligatory inclusion of neurovisualization (preferably magnetic resonance imaging of the brain) and electroencephalography (preferably not only in wakefulness but also during daytime and nighttime sleep) should be carried out to distinguish these groups.

In structural defects, i.e. congenital disorders of brain development of hereditary genesis, the pathological change of brain formation, complicating its normal functioning, is the main pathogenetic factor of psychological underdevelopment. This may be illustrated by the cases of neuronal migration disorders, such as heterotopias (from Greek *heteros* — "other" and *topos* — "place") of the grey matter, when the major part of neurons stays in the periventricular (around the ventricle) brain region (without reaching the cortex), and lissencephaly (which means "smooth brain" in Greek), when the brain remains "smooth" due to the absence of normal convolutions [1, pp. 183-232].

In metabolic genetic diseases (hereditary metabolic disorders) brain lesion is associated with toxic effect of some neurometabolic drugs and deficit of others. This situation can be illustrated by well-known phenylketonuria, previously known as "phenylpyruvic oligophrenia" [10]. In phenylketonuria, the child's organism accumulates phenylalanine and its products, specifically ketoacids (phenylpyruvic acid, phenylacetic acid, and phenyllactic acid) producing toxic effect upon the brain and preventing transformation of tryptophan into serotonin. The deficit of tyrosine, from which thyroxine and catecholamines, specifically the dopamine neuromediator are synthesized in normal development, is none the least important.

Early diagnostics of metabolic hereditary diseases and their pathogenetic treatment, in the cases when it has been worked out, and diet therapy give a chance to normalize the psychological status. Thus, prescription of biotin in biotinidase deficiency [3, pp. 71-74] in all cases under examination has lead to full recovery from "metabolic encephalopathy".

In monogenic idiopathic epilepsies, epileptic seizures and/or prolonged epileptiform (between seizures) activity emerging on the

electroencephalogram of the developing brain may lead to the formation of “epileptic developmental encephalopathy” [7; 13]. We can illustrate it by Dravet syndrome [9] and other “epileptic encephalopathies of infancy”, which, in spite of the absence of significant structural and metabolic brain defects, are accompanied by arrested psychological development, and sometimes even by loss of habits acquired before. In this case, it is only the selection of effective anticonvulsant therapy, sometimes in combination with immunotherapy with the help of glucocorticoids and special ketogenic diet that gives a possibility to avoid formation of the psychological underdevelopment syndrome.

In hereditary diseases, a combination of these three pathogenetic factors in different variants is often observed, for example, in phakomatoses, and specifically in cases of tuberous sclerosis [2, pp. 27-31], the existing structural brain lesion is, as a rule, accompanied by symptomatic “structural” focal epilepsy, aggravating psychological development. In hereditary metabolic diseases, the primary metabolic defect may lead both to secondary, mostly atrophic changes in the brain and to symptomatic “metabolic” focal epilepsy [5, pp. 31-34].

In conclusion, it should be noted that to prescribe adequate treatment, make plausible prediction and prevent birth of sick siblings in the family, it is extremely desirable to determine the right nosological form of the hereditary disease, to confirm it with laboratory tests, and not simply state the presence of “genetically determined syndrome” in the child.

Thus, various factors (structural, metabolic and epileptiform) or their combination may play a certain role in the pathogenesis of disorders of psychological development, which should be taken into account while planning therapeutic and rehabilitation activities.

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