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CURRENT STATE OF THE DIAGNOSTICS PROBLEM OF PRE- AND PERINATAL CENTRAL NERVOUS SYSTEM DAMAGE IN CHILDREN WHO SUFFERED CRITICAL CONDITION IN THE NEONATAL PERIOD

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The basic achievements of diagnostics of pre-and perinatal central nervous system damage in newborns that were in critical condition, using modern techniques of neuroimaging, have been analyzed.
Keywords: pre-and perinatal central nervous system damage, newborn, neonatal period.

Pre- and perinatal central nervous system (CNS) damage in infants and young children is one of the most urgent health and social problems of modern pediatrics and neurology. Topicality of the problem is conditioned by a high mortality of newborns and young children with pre-and perinatal CNS damage, as well as a large proportion of this pathology in the structure of childhood disability [3,5,10,11].

Severe pathological conditions, regardless of whether they are caused by some disease or is a consequence of different environmental factors, are almost always accompanied by hypoxia, the depth of which often determines the severity and consequences of the critical state, which leads to irreversible changes in the nervous system [7,51].

The critical state must be understood as a state of a patient with the disorders of physiological functions and systems that cannot be corrected by means of self-regulation and require a partial or complete correction or replacement 6].

Improvement of neonatal intensive care for the newborns that were in the critical condition because of a severe perinatal disorder development and use of modern perinatal care technologies of preterm infants contributed to a significant reduction of neonatal mortality. However, the level of morbidity and disability in these children doesn't decline, especially among babies with an extremely low birth weight (ELBW) at birth.

Progress in perinatology, which led to a significant reduction in mortality among children with the gestational age (GA) <30 weeks, has not resulted in a similar morbidity decrease among children in this group. And despite the fact that the individual authors [14,31] provide the examples of successful nursing and satisfactory development of the children weighing even less than 500 grams, the overall level of infant morbidity and disability among preterm infants remains quite high; the quality of life of premature infants is inversely proportional to the body weight of the baby at birth and its GA.

With the adoption in Ukraine of international criteria, live-birth infants, nursing of children with ELBW is one of the most challenging aspects of domestic medicine. The data presented by foreign authors show that among infants with GA of 22 weeks only 6% survive. The overall mortality rate among children with GA 22–28 weeks is 28%. Thus in 84% of deaths the treatment or life support of a newborn are terminated because of the pathology development which will cause severe disability in the future 29,50].

According to foreign authors, neurological disorders in children during the first years of life at present constitute 27–60%. During the dynamic observation of children who underwent resuscitation and/or intensive care in the neonatal age, the Russian scientists found that 35% of these children had severe developmental delay, significant disorders of physical activity, and only about 20% were not diagnosed neurological disorders 1,3].

Cerebral disorders caused by asphyxia, occupy the leading position in the structure of morbidity of

newborns and infants. Pre-and perinatal hypoxia and ischemic brain damage are observed in 15–30% of full-term newborns and 40% of preterm infants [8,9].

It is the hypoxia, which is one of the main links in the pathogenesis of brain edema that causes increased intensity of lipid peroxidation (LP). In its turn, the excess of chemically-active LP products damages cell membranes, inhibits the antioxidant system of the organism, and thereby deepens hypoxia. In addition, there is an inverse effect of various brain structures on the development of somatic pathological changes that enhances the degree of the organism destruction and its systems [4].

Most infants with ELBW, discharged from the hospital, have significant health problems in future, and these children need constant medical supervision and rehabilitation. In general, neurological disorders in premature babies, born with weight less than 1000 g, constitute on the average 25–35%. But these data are contradictory. Thus, during the examination of psychomotor development of such infants at the age of 1 using the Bayley scale, only 30% of children were found to develop according to their age, and about 70% of children had neurological problems [40,42,46].

National Norwegian studies show that infantile cerebral paralysis (ICP) in children with ELBW occurs 78 times more often than in full-term newborns. Overall, 20% of children with GA of 24 weeks are diagnosed with ICP [16,34,35].

Despite of the obvious major clinical neurological syndromes in newborns, it is difficult to determine the type of CNS damage only on the basis of clinical data. This is due to difficulties in defining the boundaries between physiological adaptation states and CNS damage that may have the same clinical effects (e.g., irritability, tremors, or, conversely, inhibition).

In addition, clinical signs of perinatal CNS damage do not have a certain nosological specificity, causing great difficulty in determining the type of CNS damage, even with a thorough examination of clinical and anamnestic data [2,8].

Thus, neonatal seizures in 35–65% of children result from hypoxic and ischemic damage, in 12–26% — intraventricular hemorrhage (IVH) in 5–20% — neuroinfections, in 5–10% — congenital abnormalities of the brain, in 5–19% — metabolic disorders. In the premature infants they are observed 6 times more often than in full-term newborns [5,24,45].

Detecting of structural changes in the brain makes it possible to effectively predict the development of not only the disease, but even some of its forms. These diagnostic capabilities provide more effective treatment choices based on diagnosed disorders and working out of preventive measures.

Today there are three main methods of neuroimaging in neonatal children and children of early childhood: neyrosonography (NSG), computed tomography (CT) and magnetic resonance imaging (MRI).

NSG received a wide practical application, especially in patients of the first year of life, since this method has several advantages: informative, portability, relatively low material costs. Using this method, one can assess the macrostructure and echogenicity of the medulla, the size and shape of the cerebrospinal fluid space. NSG data at different stages of the pathological process help to estimate changes in dynamics. NSG today is the main method of imaging in the intensive care unit of newborns due to its portability and safety for the patient in the critical condition. This method is most often used in the examination of premature infants to detect IVH, monitoring of the damage development of alba and ventricular dilatation [3,33].

NSG is characterized by high sensitivity in identifying of IVH of III–IV stages and cystic periventricular leukomalacia forms, specific for premature infants, and the basic reason for the future development of severe neurological consequences, such as ICP, post-hemorrhagic hydrocephaly, mental retardation. Taking this into consideration, the American Academy of Neurology has included in its recommendations the need for NSG of all the newborns with GA≤30 weeks, between 7th and 14th day of life and re-examination between 36 and 40 weeks of post-conceptional age [15,16,30,49].

However, the use of NSG to predict the development of neurological disorders in children born with ELBW is sharply criticized by Abbot R. Laptook et al. [11]. In the retrospective study among 1473 children, born weighing less than 1000 g and without pathological changes in the NSG in the neonatal period, about 30% had ICP or rough mental retardation at the age of 2 years of the corrected age. The ability to visualize on NSG such changes as small petechial hemorrhages diffuse changes in alba was significantly weaker as compared with MRI. In addition, this method cannot assess the degree of myelination of alba, which also reduces its prognostic value in preterm infants [11,16,33].

In full-term infants NSG use may be limited due to the structural features of the skull bones, reduced size of the crown, and due to the nature of the struc-

tural localization of damage. The deep nuclei of cinerea and cortical neurons on convexital cerebral surfaces are difficult to visualize using NSG [13,27].

According to many foreign authors, NSG is an ineffective and non-specific method of diagnosis of hypoxic and ischemic brain damage in full-term infants, because of the impossibility of imaging of focal ischemic damage on the background of the primary edema of the brain substance. Robertson N.J. and Wyatt J.S. believe that NSG has a very limited ability to determine the location and size of the ischemic areas of the brain after hypoxic damage. In addition, Francis G. Blankenberg and co-authors, when examining 47 newborns with hypoxic and ischemic encephalopathy (HIE) by NSG, CT and MRI showed that the diagnosis of cortical and stem damage of the brain of the hypoxic and ischemic character using latest NSG sets is almost 2 times less effective than MRI [30,44].

Ischemic stroke in newborns is a fairly common disease and occurs with a frequency of 1 per 2300–5000 births, who do not always have typical signs of asphyxia. Manifest symptoms of arterial stroke are seizures occurring during the first hours/days of life. Ischemic stroke usually occurs in full-term newborns. 50–75% of children, who had the neonatal stroke, suffer from cerebral seizures or psychomotor retardation, and about 80% suffer from hemiplegic form of ICP. Taking into consideration the urgency of the pathology, Meredith R. Golomb et al. conducted a study to assess the NSG effectiveness in the diagnosis of this pathology. Among 37 full-term newborns, which were diagnosed ischemic stroke by means of CT and MRI, only 30.5% appeared to be on the primary NSG [28,37].

Scientists, who have been working in the perinatal neurology, believe that MRI has several advantages over other methods: the absence of any radiation exposure, no need for the use of contrast agents, the possibility of reflection in any plane and simultaneously in multiple projections, a clear differentiation of anatomical structures and the sensitivity of the device. All these factors provide a high diagnostic value of the method. This method is optimal for obtaining of information about structural changes in convexital parts of brain and structures of the posterior cranial fossa in infants and young children [13,19].

Images are obtained in T1 and T2 modes, with the help of which it is possible to get the differentiated image of alba and cinerea, to determine the location, extent of the pathological focus and structural changes in the brain, the severity of the atrophic process and other brain damage on the early stages in the newborn, which is of great importance for providing doctors and parents with accurate information for determining of the rehabilitation measures. MRI became very important abroad for the full-term newborns to diagnose hypoxic and ischemic damage, as well as for the objective assessment of brain structures and to predict its consequences 17,25,36,41 .

According to research by foreign authors, brain damage is mainly correlated with the type of hypoxia-ischemia. The main patterns of damage were: damage of basal ganglia and thalamus, which in 95% of children is due to the acute severe asphyxia and dominated in full-term newborns; damage of the alba, that in 82% of cases is caused by the development of acute and chronic fetal hypoxia. Overall, 50–94% of infants with the basal ganglia damage have ICP, mental retardation and seizures at the age of 1–2 years in future [20,43].

For the chronic moderate hypoxia according to MRI the characteristic symptoms are as follows: the damage of alba of intravascular boundary areas, as well as a more severe damage, increasing of the intensity of MR signal of the cortex and alba subcortex, especially in the frontal and temporo-occipital parts. The study by Boichot S. et al. indicated that the MR-signal of cortex in neonates with the hypoxic-ischemic damage, especially of frontal, frontotemporal and parietotemporal areas, in 70% is correlated with gross neurological damage at the age of 1. Alba damage is found almost in a quarter of newborns with the signs of HIE. Cysts may occur during repeated examinations, but atrophy, glious cortex and subcortex alba changes are diagnosed most frequently [17,20,25,26,47].

The development of MRI technology in highly developed countries has led to the active research of diagnostic and prognostic value of other MRI methods. Diffusion-weighted MRI (DW-MRI) allows to estimate the diffusion of water molecules along the myelin sheath of axons of neuronal brain cells and thus obtain information on the integration of the structures of alba and their connection. RS-MRI use in neonates after severe asphyxia during the first day enables early diagnostication of HIE by means of detection on tomograms the reduction of diffusion indices in the thalamus, basal nuclei and posterior limb of the internal capsule, that allows to begin pathogenic treatment on the earliest stages. Magnetic resonance spectroscopy (MRS) is a method

that allows determining the changes in the brain tissue on the metabolic level. Changes of water diffusion in the tissues and metabolic disorders occur before structural changes, that is why the use of these techniques in perinatal neurology significantly improves the quality of diagnostics of pre-and perinatal damage, as well as metabolic disorders of CNS. In general, RS-MRI and MRS are the most sensitive methods of imaging of hypoxic-ischemic damage of CNS in the acute phase [21,25,26,28].

According to the recommendations of the American Academy of Neurology, MRI should be performed to all full-term children with severe and moderate degree of HIE at the age of 2–8 days of life to determine the prognostic data on neurological effects. If there is an opportunity to have RS-MRI or MRS examination, they should be done during the first 8 days of life [26].

Today fetal MRI in women with high risk of having children with pre-and perinatal CNS pathology is widely used. The objects of research are the determination of congenital malformations, hypoxic or metabolic damage of the central nervous system of the fetus. NSG is quite effective for determination of gross malformations of the brain, particularly involving ventricular system or cerebrospinal fluid space. However, the information value of ultrasonography (USG) in the diagnosis of lissencephalia, Arnold-Chiari malformation II, agenesia and dysgenesis of corpus callosum, vascular malformations is extremely low. In national studies pregnant women of high risk were fully examined. Fetal USG revealed isolated CNS malformations in 33.3% of women. They subsequently had fetal MRI for the diagnosis specification. According to the latest, structural abnormalities of the brain of the fetus were detected only in 16.4% of pregnant women. 7.5% of these cases were diagnosed with defects incompatible with the normal development of a child [5,34].

Due to the structural and functional features of the brain of premature babies hypoxic and ischemic CNS damage is characteristic for them. Therefore, timely and adequate diagnosis of the latter is extremely important to determine the tactics and treatment of these children. Severe hypoxic and ischemic damage in preterm infants is characterized by the damage of the deep structures of cinerea, brain stem and cerebellum. Conducting MRI it is possible during second-third day of life to detect the changes in the thalamus and basal nuclei in the form of increased signal intensity on the images in T2 mode. Approximately 12–30% of preterm infants with GA less than 30 weeks have hemorrhages of varying degrees of severity on MRI. In this case, 50% of children with IVH of III–IV degree develop hemorrhagic hydrocephalus. Hemorrhages into the substance of the cerebellum in preterm infants on MRI is determined in 68% of babies and in 31% combined cerebellar and supratentorial hemorrhages are observed [22,23,26,45 .

MRI of the brain of infants born to gestational age less than 28 weeks, allows to effectively assess the corpus callosum state and periventricular alba. Carried out studies indicate that the most common disorders is the reduction in the volume of alba without glious changes (36.0%) and in 16.0% of children periventricular leukomalacia (PVL) was observed, in 18.0% — thinning of the corpus callosum 39 .

Due to modern advances in nursing of small premature infants, the focal periventricular damage are less frequent, about 5% of cases. The diffuse form of PVL is a common disorder in premature newborns and is one of the major causes of mental disorders of children in this group. Recent studies, using MRI, have shown a high prevalence of diffuse forms of PVL in premature infants with the corrected age of 40 weeks, which in some studies reached 70%. MRI in T2 mode is able to detect mild forms of destruction of the alba. Children with such changes belong to a high risk of cognitive function inhibition and behavioral disorders in future. Lianne J. Woodward et al. found that only 28% of children had no alba damage on MRI, 21% of children had moderate and severe alba damage, 51% of the observed babies had slight changes in the alba structure. The phenomenon of diffuse high signal intensity («Diffuse excessive high signal intensity» (DEHSI)), detected by MRI in T2 mode is caused by the disorders of fluid circulation along the fibers of alba. These changes in the structure of the brain cause adverse neurological effects [13,32,39].

Using MRI it is possible to detect «glial scars» left after small cysts resorption, as well as smaller local subcortical white matter lesions observed in 75% of preterm infants, and thalamic lesions [18].

A number of foreign works the diagnostic and prognostic value of both methods of neuroimaging are compared. Mirmiran M., et al. [38] when determining the predictive value of the NSG results compared with MRI data, done before the discharge of preterm infants with GA <30 weeks, found that the sensitivity of these methods for the development of ICP

is under 71% for MRI versus 39% for NSG. Moreover, according to Laptook A.R. et al. [11] 30% of newborns with normal NSG at discharge (GA <28 weeks) at the age of 18 and 22 months had ICP or mental retardation.

It should be noted that although the MRI method has some drawbacks (long-term research, the need for the patient sedation, limited use in the ICU and during the examination of non-transportable patients), but it is more common in Western countries for the objective assessment of brain structures.

The rapid development of perinatology has led to the reduction in perinatal loss and neonatal mortality. But doctors and scientists faced new problems: care of newborns, which are in a critical condition, diagnosis and pathogenetically grounded treatment of post intensive cure states, as well as taking care of premature infants. Underestimation and insufficient examination of newborns with severe neurological symptoms, as well as lack of the follow-up observation of children who have suffered a critical condition in the neonatal period, is one of the main causes of numerous groups of children with disabilities.

The main pathology that defines further prognostication of quality of life is CNS disorders. Therefore, the search for new diagnostic and therapeutic possibilities in perinatal neurology points to the need for comprehensive use of modern imaging methods for objective and differential diagnosis of various forms of cerebral damage.

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