CLINICAL, NEUROPHYSIOLOGIC, AND NEUROPSYCHOLOGIC ASPECTS OF DEVELOPMENT OF NEUROLOGIC DISORDERS IN PRETERM INFANTS. PREMATURITY AND DISABILITY: NEUROLOGIC REHABILITATION ISSUES (LITERATURE REVIEW)

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Abstract

Pathogenesis of cell apoptosis with development of neurotoxic reactions on various levels of Central Nervous System in premature babies is presented here. Also, predictive characterization of various neurologic disorders in premature patients is described. Analysis of vegetative regulation allows selection of rehabilitation measures in born at gestational ages.

Keywords: prematurity, gestational age, severity of condition at birth, clinical, neurophysiologic, and neuropsychologic disorders.

In accordance with Declaration of United Nations (UN) about Children's Rights, governments are obliged to ensure protection of life and safety of children regardless of economic status of the society. Annual decline in infant death (about 5%) by the end of 80's stopped in 1990. Starting in 1991, increasing trend started being observed. In recent years, decrease in number of childbirth by 40-50% has been seen in Russia [2,5,6].

Based on the data of Ministry of Health and Medical Industry, in 1985 every 11th infant was born ill or became ill during neonatal period; this number became 8 in 1989, and 5 in 1992-1993. By 2003, healthy infants contributed to 15-20% of infant population in RF, while low level of childbirth was being retained [7]. Significant contribution to this figure is made by premature infants [8,10].

Survival directly correlates with birth weight. Among premature infants with birth weight of 15000 g or less, number of survived babies reaches 43-51%, out of which only up to 10-25% are healthy, while number of patients with severe psycho-neurologic disorders in this population may reach 12-19% [1,3,16,17]. Newborns with birth weight of 2001-750 g, perinatal death reaches 64-85%; number survived does not exceed 15-36%; severe disorders resulting in disability may be higher than 28%; and healthy newborns are no more than 8-15% [5,16,18]. Probability of lethal outcome in children with birth weight of less than 2500 g is

about 40-fold higher than the same value observed in babies with normal body mass. Problem of prematurity has obtained a medical and social significance [2,6,7].

Peri- and intracranial hemorrhages are one of the most frequently seen complications of hypoxic/ischemic brain damage in premature newborns causing disability. In newborns with low birth weight, hemorrhages in cerebral ventricles and germinal matrix are seen in 42-90% and most often (up to 50%) occur during first couple of days of life. Frequency of such type of hemorrhages in newborns with very low birth weight reaches 61% during first hours of life and 74% by the final hours of first day [3,4,8,11].

Gradual decrease of compensatory respiratory mechanisms is a unique feature of prematurely born babies. Expected lung hyperventilation in hypoxic conditions does not develop in all of them. Inhibition of respiratory center occurs in premature babies as a result of immaturity and hypoxia. Deterioration of neurologic status completes "vicious circle", triggering worsening of already existing lung hypoventilation and acidosis [3,8].

One of the selective factors affecting damage of brain structures is the peculiarity of NMDA-type glutamate receptors, density of which depends on gestational age and newborn maturity [16]. Premature development of nerve cells is characteristic for premature babies, which presents with inhibition of growth of paraplasm

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tic matter of hemispheres and termination of karyokinetic nuclear division in cerebellum. Disturbance of this process leads to rapid absorption of external embryonic layer in brain cortex and cerebellar vermis, causing decrease in number of nerve cells in these structures of brain in prematurely born babies [9,12].

Another specificity plays equally important role: very frequently, cerebral parenchyma, especially frontal section of it becomes involved in the pathologic process. In relatively low degree of intraparenchymal damage, only 29% of newborns die during early days of life and 14% present with major neurologic disorders. Upon extensive involvement of brain parenchyma in the process, mortality reaches 76% and disabling neurologic diseases occur in those who survive [1,4]. Risk of death within first year of life increases 5 times in infants with very low birth weight and these death cases account for 20% of all perinatal death cases [17,18].

Main causes of chronic brain disorders in premature newborns are as follows: diffuse cerebral gliosis, brain infarcts, porencephalic cysts, and necrotic changes in peri- and intraventricular sites [5,7]. Residual manifestations depend on degree of brain damage in acute period and may range from minimal inhibition of psycho-motor development to severe tetraplegic forms of cerebral palsy (CP), microcephaly, and resistant forms of epilepsy. Similar changes are observed in children who had a long-term coma.

Periventricular leukomalacia (PVL) is a process of damage of axons followed by involvement of oligodendrocytes, development of astrocytic gliosis, and demyelination [13,14]. Residual stage of development of PVL is accompanied by cyst-related brain degeneration, characterized by flabellate distribution of cysts towards peripheral sites of brain. Process of cyst formation may result in gliosis (in place of little cysts), as well as formation of cystic conglomerates. The latter is characterized with enlargement of ventricular structures, caused by atrophy of medullary substance [6,17]. Recovery is noted in 19.5% of premature newborns only and is considered relatively condi-

tional, as imperfections of fine motor functions and slight damage in motor/reflector sphere are retained.

On average, Cerebral Palsy develops in 80.5% of premature babies; spastic diplegia predominates in the structure of motor dysfunctions - 53.4%, dual hemiplegia is seen in 44.7% of cases, and convulsive syndrome occurs in 37.5% of cases, frequency of which among prematurely born babies exceeds populational parameters: neonatal convulsions are seen 20 times, febrile convulsions 1.5-2 times, and epilepsy 27 times more frequently compared to overall pediatric population [1,3,4]. Gender differences are very pronounced in addition to severity of nervous system damage in CP: all forms of the disease prevail among boys (1.3-1.9 times) [9].

Combination of several syndromes is frequently seen in premature babies. Based on data provided by various authors, clinical picture of spastic diplegia presents with two syndromes in 77% cases; spastic hemiparesis mainly presents with two (53.7% cases) or three (46.3% cases) syndromes. In 52.3% of cases bilateral hemiplegia clinically presents with three and in 47.7% of cases with four or more syndromes [13]. Combination of epilepsy and hydrocephaly is reported in 39% of premature babies, where symptomatic epilepsy is seen twice more in children with passive hydrocephaly [12,16].

Epilepsy syndrome has similar frequency in patients with spastic diplegia (21%) and bilateral hemiplegia (25%), with the frequency increasing twice in hemiparetic CP [1,17]. Overall, generalized convulsive attacks are prevailing: atypical absences (30-50%) and generalized tonic-clonic attacks (25-50%); partial attacks are more frequently reported in premature babies with hemiparetic form of CP (47%) [3,4,18]. In 85% of patients, epilepsy makes its debut within first 20 years of life, in 17% within first 2 years, and in 13% within preschooler and adolescence periods. Genetic predisposition for epilepsy accounts for 6-12% of cases; in monozygotic twins concordance of epilepsy reaches 55%, whereas in dizygotic ones this

number is 10% [18]. Risk factors for development of epilepsy in prematurely born babies are: presence of convulsions in neonatal period; retention of pseudo-cysts after 5 months of life; hypoplasia of corpus callosum [2,4,8]. Frequency of neonatal convulsions (NC) ranges from 0.7 to 14 per 1000 live-born babies and mortality due to NC varies between 16% to 40%. West Syndrome is one of the most severe forms of epilepsy in children with periventricular leukomalacia (25%).

Attention Deficit Hyperactivity Disorder (ADHD) is seen less frequently, in 23% of cases with boys dominating by 5:1 [9,10]. Clinical manifestation of ADHD is mainly seen in premature babies with spastic diplegia. Childhood cognitive and behavioral disturbances persist in about 70% of adolescents and more than 50% of adults and are characterized with echolalia/speech and visual memory disorders [5,15].

Functional activity of brain in premature babies has its own unique features [12]. During first ten days of life of premature babies bioelectric activity (BEA) of brain is suppressed and the so-called "explosive" or "volley" brain activity is registered in electroencephalography (EEG), which alternates with resting periods. With age, complete resting periods become shorter and a continuous BEA is established by two months of postnatal life [10]. EEG of premature babies born at 32nd-34th weeks of pregnancy is characterized with shortening of complete resting phase. Continuous BEA is identified in central parts of cortex in babies born at 35th-36th weeks of pregnancy; photostimulation provokes intensification of slow-wave activity [2,4]. EEG of premature babies during first 7 years of life is characterized with delays in cortical electrogenesis and almost complete absence of α -waves in 80% of cases; insufficiency of high-frequency θ -waves (50%); existence of signs of excessive irritation of caudal sections of brainstem (79%), which presents with domination of occipital high-amplitude irregular low-frequency waves of θ and Δ range [14].

X-ray imaging of cerebral damage is characterized with its diversity. More often several pathologic variations of neuro-imaging changes

are noted in the same patient. These include: changes in structure of hemispheres (sites of increased density, calcinates, hemispheric atrophy); changes in cerebrospinal fluid space (changes of lateral ventricles or 3rd and 4th ventricles, enlargement of subarachnoidal space, brain cisterns, and retrocerebellar space); congenital brain malformations (heterotopy, changes in white and grey matter ratio, hypo- or agenesis of corpus callosum, brain cysts, hypogiria, schizencephalia, hemispheric cerebellar vermis hypoplasia, Dandy-Walker and Arnold-Chiari malformations) [19]. Cortical congenital malformations are identified as one of the causes of CP and may serve as one of the more frequent sources of drug-resistant epilepsy [1,3,8]. In patients with mixed CP, they are identified more often (42.8%), compared to children with bilateral hemiplegia (23.9%), spastic diplegia (16%), atonic-astatic syndrome (13%), and hemiparetic CP (11.5%). In epilepsy patients focal dysplasia in brain cortex is identified in 46.5% cases, where 77-90% of patients with cortical malformations have epileptic attacks with clinical picture corresponding to localization of damage [16,19]. In premature babies, focal dysplasia is located in fronto-parietal lobes in 89% of cases [9,17].

Changes in cerebrospinal fluid space are next based on the frequency of X-ray imaging findings. It is observed in 49.2% of cases and prevails in children with atonic-astatic syndrome (73.9%) compared to children with paraplegia (50%), bilateral hemiplegia (47.8%), hemiparesis (44.2%), and mixed CP (42.8%) [2].

Analysis of vegetative regulation data allows identifying three types of CP in patients: high, insufficient, and functional stress of adaptational-compensatory systems. "Distorted" vegetative values are observed in 1 out of every 2 cases. Based on this information, three types are identified for course of adaptational-compensatory processes: exhaustion of ergotropic adaptation systems (prevails in patients with bilateral hemiplegia), periodic alternation of ergotropic and trophotropic effects of vegetative regulation (characteristic for patients with spastic diplegia), decrease in degree of severity of

deadaptation disorders during the course of the disease and child's development. The latter dominates in children with hemiparetic CP [2,7].

Suprasegmental and segmental levels of nervous system damage should be considered upon planning of rehabilitation of premature patients [5,11,17]. On one hand, immaturity at cortical level of integration causes delay in inhibitory effect of cortex on subcortical, stem, and segmental levels of regulation, which creates neurodynamic conditions for pathology in the system; on the other hand, prevalence of mechanisms of diffuse activation over local ones explains phenomenon of occurrence or intensification of convulsive attacks upon afferent stimulation of static/motor and psycho-vocal habits.

In addition, combination of central (suprasegmental) and peripheral (segmental) disorders may occur in late residual stage of CP, which explains presence of pronounced static deformations. Current changes are due to secondary degenerative dystrophic changes in peripheral nerve, caused by increasing muscle trophism disturbances and contractures. Existence of central

paralysis with secondary frontal corneous syndrome is possible upon long-lasting central deafference of segmental apparatus [2,5,7,10].

It is important to consider phenomenon of paratonia, i.e., increasing spasticity upon implementation of active movements in children of younger ages. It is explained by absence of reciprocity in involvement of tonic and phasic motor systems, as seen in healthy pediatric population. This data points to significant intra- and inter-systemic disintegration in limbic-reticular complex, which reduces adaptation capabilities and rehabilitation potential of CP patients [17]. As in majority of cases suprasegmental regulatory mechanisms in premature babies with cerebral palsy do not "mature" before 7-10 years, surgical intervention should be delayed before this age, using conservative orthopedic treatment techniques and kinesiotherapy [9,17]. Integration step for functional systems is necessary for establishment of above-mentioned adaptation-regulatory prerequisites: preventive immunomodulatory and vegetomodulatory therapy, afferent loads of average intensity during 10-12 days prior to main course of rehabilitation.

REFERENCES

1. Бадалова С.Т. Диагностика и лечение психо-моторного развития у детей с эпилепсией раннего возраста: Автореф. дис.... канд. мед. наук /С.Т. Бадалова /.-М., 2006. - 18с.
2. Белоусова Е.Д. Факторы риска, тактика лечения и прогноз судорожного синдрома и эпилепсии у детей с детским церебральным параличом: Автореф. дис.... докт. мед. наук /Е.Д. Белоусова/.- М., 2006. - 49с.
3. Бояринцева С.Е. Височно-долевая эпилепсия у детей школьного возраста (клиническая, нейропсихологическая и электроэнцефалографическая характеристика, лечебная тактика): Автореф. дис.... канд. мед. наук /С.Е. Бояринцева/.-Иркутск, 2007. - 24с.
4. Брин И.Л. Врожденные предпосылки лево- и правополушарных дисфункций мозга у детей /И.Л. Брин, М.Л. Дунайкин, С.Д. Вознякевич // Российский вестник перинатологии и педиатрии - 2007. - №4. - С.55-59
5. Бронников В.А. Неспецифические системы мозга и реабилитация детей с церебральными параличами / В.А. Бронников, Ю.И. Кравцов // Журнал неврологии и психиатрии им. С.С. Корсакова. - 2005. - №6. - С.45-50
6. Воронкова К.В. Эволюция эпилепсии и трансформация эпилептических приступов: Автореф. дис.... докт. мед. наук /К.В. Воронкова /.-М., 2007. - 51с.
7. Гончарова О.В. Современные биохимические критерии диагностики перинатальных гипоксических поражений ЦНС у новорожденных детей / О.В. Гончарова, М.И. Баканов, А.Г. Мулатов [и др.] // Российский педиатрический журнал. - 2007. - №4. - С.13-18
8. Долгих Г.Б. Состояние мозгового кровотока у детей в ранний восстановительный период перинатальных энцефалопатий / Г.Б. Долгих // Российский вестник перинатологии и педиатрии - 2008. - №1. - С.28-30
9. Екушева Е.В. Вклад правого и левого полушария головного мозга в полиморфизм и гетерогенность пирамидного синдрома /Е.В. Екушева, М.И. Вендрова, А.Б. Данилов [и др.] // Журнал неврологии и психиатрии им. С.С. Корсакова. - 2004. - №3. - С.8-12
10. Зенков Л.Р. Психические и поведенческие расстройства при идиопатических эпилептиформных фокальных разрядах / Л.Р. Зенков, П.А. Константинов, И.Ю. Ширяева [и др.] // Журнал неврологии и психиатрии им. С.С. Корсакова. - 2007. - №6. - С. 39-49.
11. Зенков Л.Р. Эпилептический синдром нарушения развития правого полушария / Л.Р. Зенков // Неврологический журнал. - 2007. - №1. - С.29-33.

12. Клаучек С.В. Особенности биоэлектрической активности головного мозга детей с различными формами последствий перинатальных поражений центральной нервной системы / С.В. Клаучек, Г.В. Клиточенко // Журнал неврологии и психиатрии им. С.С. Корсакова. - 2006. - №4. - С.43-45
13. Липатова Л.В. Механизмы нейроиммунных нарушений при эпилепсии и обоснование их коррекции /Л.В. Липатова, С.А. Громов // Неврологический вестник им. В.М. Бехтерева. - 2007. - Том XXXIX. - вып.3. - С. 108-112.
14. Bouillot E.E. Distinct multi-joint control strategies in spastic diplegia associated with prematurity or Angelman syndrome / E.E. Bouillot, E. Bengoetxea, S.G. Boyd // Clin. Neurophysiol. 2005. № 9. P.1618 1625
15. Chung M.Y. Risk factors for hemodynamically-unrelated cystic periventricular leukomalacia in very low birth weight premature infants / M.Y. Chung, P.C. Fang, C.H. Chung // J. Formos. Med. Assoc.-2005.- № 8.-P.571-577
16. Downie A.L. The impact of periventricular brain injury on reading and spelling abilities in the late elementary and adolescent years / A.L. Downie, V. Frisk, L.S. Jakobson // Neuropsychol. Dev. Cogn. C. Child. Neuropsychol. -2005. -№ 6. - P.479 - 495
17. Garcia Arias M.B. Risk factors for mortality in very low birth weight infants with respiratory distress syndrome / M.B. Garcia Arias, P. Zuluaga Arias, M.C. Arrabal Teran // An Pediatr.-2005. - № 2.-P.109-115
18. Glukhovets B.I. Pathogenetic features of respiratory distress syndrome in newborns with extremely low body weight / B.I. Glukhovets, I.V. Gaivoronskii, N.A. Belousova // Arkh. Patol.-2005. - № 1.-P.3-5
19. Rvachew S. Vocal development of infants with very low birth weight / S. Rvachew, D. Creighton, N. Feldman // Clin. Linguist Phon.-2005.- № 4.- P.275

РЕЗЮМЕ

КЛИНИКО-НЕЙРОФИЗИОЛОГИЧЕСКИЕ И НЕЙРОПСИХОФИЗИОЛОГИЧЕСКИЕ АСПЕКТЫ ФОРМИРОВАНИЯ НЕВРОЛОГИЧЕСКИХ НАРУШЕНИЙ У НЕДОНОШЕННЫХ ДЕТЕЙ. НЕДОНОШЕННОСТЬ И ИНВАЛИДНОСТЬ: ПРОБЛЕМЫ НЕЙРОРЕАБИЛИТАЦИИ (ОБЗОР ЛИТЕРАТУРЫ)

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В статье представлен патогенез формирования апоптоза клетки с развитием нейротоксических реакций на различных уровнях центральной нервной системы у недоношенных пациентов. Описана прогностическая характеристика вариантов неврологических нарушений у недоношенных пациентов. Анализ вегетативной регуляции позволяет выработать тактику реабилитационных мероприятий у пациентов с разными сроками гестации.

Ключевые слова: недоношенность, срок гестации, тяжесть состояния при рождении, клиничко-нейрофизиологические и нейропсихофизиологические нарушения.

XÜLASƏ

VAXTINDAN ƏVVƏL DOĞULMUŞ UŞAQLARDA NEVROLOJİ POZULMALARIN FORMALAŞMASININ KLİNİK-NEYROFİZİOLOJİ VƏ NEYROPSİXOFİZİOLOJİ ASPEKTLƏRİ. VAXTINDAN ƏVVƏL DOĞULMA VƏ ƏLİLLİK: NEYROREABİLİTASIYANIN PROBLEMLƏRİ (ƏDƏBİYYAT İCMALI)

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Məqalədə vaxtından əvvəl doğulmuş pasiyentlərdə mərkəzi sinir sisteminin müxtəlif səviyyələrində neyrotoksik reaksiyaların inkişafı ilə hüceyrənin apoptozunun formalaşmasının patogenezi təqdim edilmişdir. Vaxtından əvvəl doğulmuş pasiyentlərdə nevroloji pozulmaların variantlarının proqnostik xarakteristikası təsvir edilmişdir. Vegetativ requlyasiyanın analizi hestasiyanın müxtəlif mərhələlərində pasiyentlərə reabilitasiya tədbirlərinin taktikasının işlənilib hazırlanmasına imkan verir.

Açar sözlər: vaxtından əvvəl doğulma, hestasiya mərhələsi, doğulanda vəziyyətin ağırlığı, klinik-neyrofizioloji və neyropsixofizioloji pozulmalar.

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