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Research Article

TRANSIENT HYPERAMMONEMIA IN NEWBORNS: CLINICAL AND LABORATORY PARAMETERS AND NEUROLOGICAL OUTCOMES IN PATIENTS IN THE FIRST YEAR OF LIFE

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BACKGROUND: Transient hyperammonemia in newborns (THAN) is a dangerous condition of the neonatal period that does not have a specific clinical picture, which often makes timely diagnosis difficult. Insufficient coverage of the problem of THAN in the literature, as well as the need to assess the neuropsychiatric development (NPD) of patients in the follow-up, served as the basis for this study.

AIM: To evaluate clinical and laboratory manifestations of THAN and its influence on the neuropsychological development during the first year of life.

MATERIALS AND METHODS: During the study, 22 preterm newborn patients were divided into 2 groups depending on the presence or absence of THAN: study group (n = 11) and comparison group (n = 11). All patients were assessed for risk factors, features of clinical manifestation of THAN, and neurological outcomes using the CAT/CLAMS scale at 3, 6, 9, and 12 months of age.

RESULTS: Analysis of the obtained data showed that the depression syndrome was the leading one in the clinical picture of THAN (81.8%). Laboratory changes are characterized by the respiratory failure (p = 0.039), anemia (p = 0.023), hypoproteinemia (p = 0.049), hypoalbuminemia (p = 0.048), lower blood sodium levels (p = 0.019). In the constructed prognostic model for determining the probability of having THAN, the critical cutoff p level was 20% (p = 0.012). Assessment of the neuropsychiatric development showed that 41.6% of children who had THAN maintained a moderate neuropsychiatric development delay in the first year of life with predominant impairment of motor skill formation.

CONCLUSIONS: Allocation of a risk group for THAN formation, timely prescription of a low-protein diet, correction of syndromic therapy, and monitoring of patients in the first year of life will help to avoid severe neurological disorders and reduce the need for rehabilitative measures.

Keywords: hyperammonemia; newborns; metabolic crisis; inborn errors of metabolism; low-protein diet; transient hyperammonemia; outcomes; neurological delay.

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ТРАНЗИТОРНАЯ ГИПЕРАММОНИЕМИЯ НОВОРОЖДЕННЫХ: КЛИНИЧЕСКИЕ ПРОЯВЛЕНИЯ И ВЛИЯНИЕ НА НЕРВНО-ПСИХИЧЕСКОЕ РАЗВИТИЕ ДЕТЕЙ НА ПЕРВОМ ГОДУ ЖИЗНИ

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Актуальность. Транзиторная гипераммониемия новорожденных (ТГАН) — опасное состояние неонатального периода, не имеющее специфической клинической картины, что часто затрудняет своевременную диагностику. Недостаточная освещенность в литературе проблемы ТГАН, а также необходимость оценки нервно-психического развития (НПР) пациентов в катамнезе послужили основой для проведения данного исследования.

Цель работы — оценить клинико-лабораторные проявления ТГАН и ее влияние на нервно-психическое развитие в течение первого года жизни ребенка.

Материалы и методы. В ходе исследования 22 доношенных новорожденных были разделены на 2 группы в зависимости от наличия или отсутствия ТГАН: основную группу (n = 11) и группу сравнения (n = 11). Всем пациентам была проведена оценка факторов риска, особенностей клинической манифестации ТГАН и неврологических исходов с использованием шкалы КАТ/КЛАМС (речевые функции КАТ, интеллектуальный уровень КЛАМС, моторика) в возрасте 3, 6, 9 и 12 мес.

Результаты. Анализ полученных данных показал, что синдром угнетения — ведущий порок в клинической картине ТГАН (81,8 %). Лабораторные изменения характеризуются развитием дыхательной недостаточности (p = 0,039), анемией (p = 0,023), гипопротеинемией (p = 0,049), гипоальбуминемией (p = 0,048), более низкими уровнями натрия в крови (p = 0,019). В построенной прогностической модели определения вероятности наличия ТГАН критический уровень отсечения p составил 20 % (p = 0,012). Оценка нервно-психического развития показала, что 41,6 % детей, имевших ТГАН, сохраняют умеренную задержку развития на первом году жизни с преимущественным нарушением формирования моторных навыков.

Заключение. Выделение группы риска по формированию ТГАН, своевременное назначение низкобелковой диеты, коррекция посиндромной терапии и контроль за пациентами на первом году жизни позволит избежать тяжелых неврологических нарушений и сократить необходимость в реабилитационных мероприятиях.

Ключевые слова: гипераммониемия; новорожденные; метаболический криз; наследственные болезни обмена веществ; низкобелковая диета; транзиторная гипераммониемия; исходы; неврологический дефицит.

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BACKGROUND

Hyperammonemia (HA) syndrome is characterized by an increase in plasma ammonia levels above 100 μmol/L in newborns and 50 μmol/L in older patients. High ammonia levels generally cause severe damage to the central nervous system (CNS) [1] due to the penetration of ammonia through the blood–brain barrier, which is manifested by nonspecific syndromes such as convulsive syndrome, suppression syndrome of varying severities, and vomiting syndrome [7, 10]. Currently, the prevalence of HA syndrome is described only for inborn errors of metabolism (IEM) and affects approximately 1:30,000 newborns (depending on the individual nosology) [6].

IEM-associated HA syndrome is primarily caused by disorders of the urea formation cycle, organic aciduria, disorders of fatty acid b-oxidation, and several mitochondrial diseases [3, 6, 7]. These diseases are described sufficiently in recent studies and have clear algorithms for treatment and diagnostics [1, 5, 6, 10, 11]. Neurological outcomes are also covered, and their severity generally depends on various factors, such as adherence to a low-protein diet (LPD) and its necessity; number, incidence, and severity of metabolic crises; and HA levels throughout life [9, 13].

In HA syndrome not associated with IEM, neurological outcomes primarily depend on the causes of HA syndrome. Thus, in the case of HA syndrome accompanying genetically determined epileptic encephalopathies, newly diagnosed convulsive syndrome, or severe perinatal hypoxic lesions of the CNS, outcomes are determined by both the underlying disease severity and the consequence of CNS damage with high ammonia levels [12].

The outcomes of children with transient HA of the newborn (THAN) are the least studied. THAN occurs in the neonatal period and is characterized by ammonia levels of >100 μmol/L in the blood plasma of newborns. According to literature data, THAN is caused by the functional immaturity of liver enzymatic systems, hypoxia during childbirth, tendency of newborns to hypercatabolism, and physiological deficiency of carnitine in the first days of life [1–3]. In THAN, ammonia can reach high levels, comparable to HA syndrome in IEM, which is a risk factor of CNS damage and development of neurological deficit in the follow-up period [12]. Timely detection and correction of THAN can prevent irreversible changes in the CNS.

The insufficient number of publications and conflicting data on the course and outcomes of THAN necessitated this study [9].

The study aimed to evaluate the clinical and laboratory manifestations of THAN and its effect on neuropsychic development during the first year of a child's life.

MATERIALS AND METHODS

The study was conducted in accordance with the Declaration of Helsinki (2013) and was approved by the Ethics Committee of the Volga Research Medical University (Protocol No. 4 dated March 18, 2020). Informed consent was obtained from the parents of the patients in accordance with Federal Law No. 323 on November 21, 2011.

The study was performed at the Children's City Clinical Hospital No. 1 of Nizhny Novgorod between 2017 and 2022. Patients with THAN syndrome were monitored in the resuscitation and intensive care units, department of pathology of newborns and premature babies, neurological department, and department of young children.

HA was assessed by plasma ammonia levels. For newborns, the upper limit of normal is 100 μmol/L [6, 8]. The severity of HA syndrome was assessed in accordance with federal clinical guidelines [6] (mild, 100–150 μmol/L; moderate, 150–250 μmol/L; severe, >250 μmol/L).

Study design. The study was conducted following a prospective cohort, single-center, quasi-randomized controlled case–control design.

Inclusion criteria. Presence of HA syndrome (ammonia level > 100 μmol/L), absence of changes according to tandem mass spectrometry and urine tests for organic acids, newborns, gestational age at birth of >37 weeks, and parental informed consent for participation in the study.

Exclusion criteria. prematurity; confirmed diagnosis of IEM (using molecular genetic research methods); generalized bacterial and viral infections, infectious, and non-infectious hepatitis, malformations, oncological diseases, terminal stage of chronic disease, hepatic cirrhosis, acute respiratory viral infection, and exacerbations of chronic diseases during the study; and absence of informed consent of the parents for the patient's participation in the study.

The patient enrollment algorithm is presented in Fig. 1. The reason for the initial examination for HA syndrome was CNS depression of varying severity, convulsions, regurgitation, and vomiting syndrome without apparent cause. To confirm or exclude the diagnosis of IEM, patients with identified HA syndrome underwent tandem mass spectrometry and urine analysis for organic acids. Subsequently, in the presence of deviations, a molecular genetic

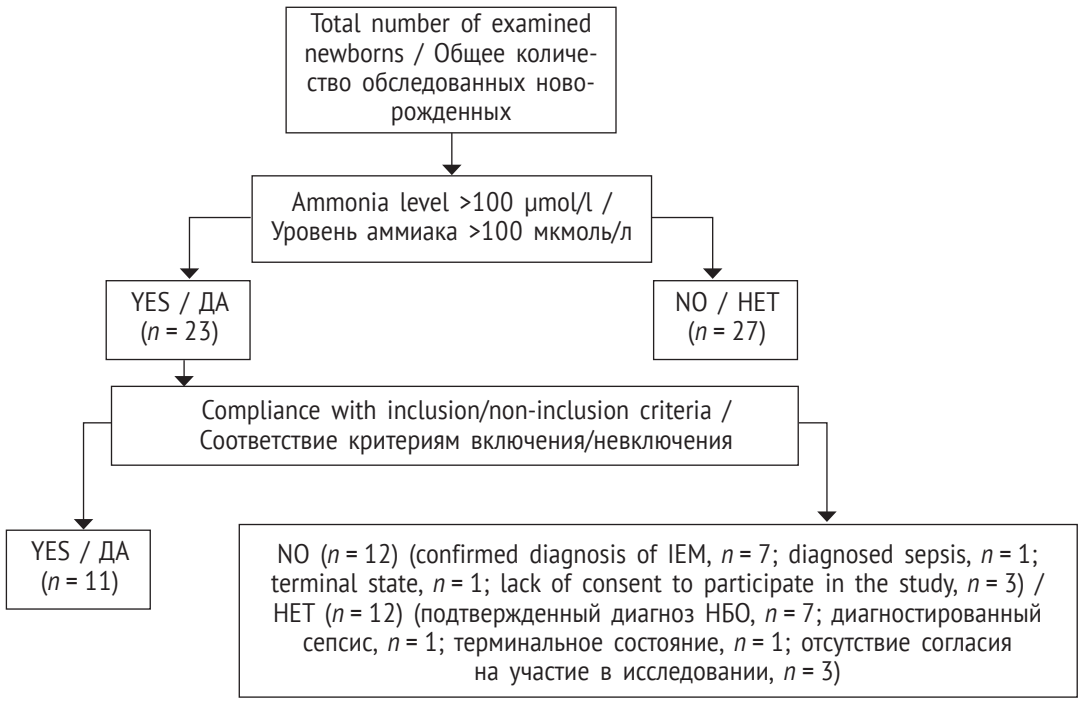

Fig. 1. Algorithm for selecting patients for participation in the study. IEM — inborn errors of metabolism
Рис. 1. Алгоритм отбора пациентов для участия в исследовании. НБО — наследственная болезнь обмена

study was performed (whole-genome sequencing or clinical-exome sequencing by next-generation sequencing).

The main group consisted of 11 newborns with THAN who met the inclusion criteria. A comparison group was formed to compare clinical and laboratory parameters and neurological outcomes. The comparison group was enrolled by copy-pair method ($n = 11$), with comparable clinical symptoms, anamnesis, and course of the perinatal period, and differed from the main group in one sign (absence of HA syndrome). The main group and comparison group underwent hereditary history assessment, assessment of the course of the perinatal and neonatal periods, assessment of the child's condition before the clinical manifestation of symptoms, and clinical, and laboratory characteristics during the disease course.

Diagnostics of HA syndrome. The ammonia level was determined on a portable ammoniameter PocketChem BA, with indicator strips Ammonia Test Kit II. To clarify the level >283 mmol/L (analyzer limit), venous blood was examined using a biochemical analyzer from the Konelab 2400 Randox Laboratories Ltd., according to the manufacturer's protocol.

Neurological outcomes of the main group and comparison group were assessed using the clinical adaptive test/clinical linguistic and auditory milestone scale (CAT/CLAMS) at the age of 3, 6, 9, and 12 months. Speech functions (CLAMS), intellectual level (problem solving, CAT), and motor skills in a point equivalent were taken into account. The results were evaluated in relation to the development coefficient (DC): DC > 75 corresponds to normal development, ≤75 corresponds to retardation, and the differences in CAT/CLAMS and motor skill indicators suggest developmental dissociation [4].

Methods of statistical analysis and determination of the sample size. Statistical data processing was performed using SPSS Statistics. The required number of study patients was determined using Lehr's formula for mean values (with 90% study power) and the equation for calculating the sample size when comparing two means (Bland's method). The validity of the sample size, given their small number, was confirmed retrospectively. The minimum sample size was calculated, which was nine patients for each group.

The Shapiro–Wilk test was used to determine the type of distribution. Owing to the non-normal type or distribution, descriptive statistics are presented as Me and interquartile interval [Q_1–Q_3], and data were processed using nonparametric methods. The statistical significance of the differences between the two independent samples was determined by the nonparametric Mann–Whitney *U*-test.

To assess the influence of factors on the resulting variable, correlation analysis was used (Spearman's correlation coefficient, ρ), and the correlation strength was assessed using the Chaddock scale.

The predictive model for the probability of developing THAN was constructed using the binary logistic regression method. For the "before–after" studies, the Friedman test was used to assess the neuropsychic development in patients. Differences were considered statistically significant at $p < 0.005$.

STUDY RESULTS

Characteristics of the perinatal period

No statistically significant differences in the incidence of factors aggravating the course of the perinatal period were found in the compared groups. The factors analyzed are presented in Table 1.

The hereditary factor did not have any particular influence in 100% of the cases. However, acute fetal hypoxia was registered in both groups, and the development of respiratory failure (RF) followed by the use of artificial lung ventilation, not associated with neonatal respiratory distress syndrome, was statistically significantly more common in the THAN group ($p = 0.039$). No correlation was detected between the degree of RF and the ammonia level.

Clinical and laboratory characteristics of patients with THAN

The median age at THAN onset in the main group was 12 [8.0; 14.5] days. Depression was the most common clinical presentation, and it was diagnosed in 81.8% of the cases ($n = 9/11$). Convulsive syndrome was observed in 45.5% of cases

Table 1 / Таблица 1

Characteristics of risk factors in the perinatal period in patients of the compared groups
Факторы, отягощающие течение перинатального периода у пациентов сравниваемых групп

Characteristic / Характеристика	Main group / Основная группа ($n = 11$)	Comparison group / Группа сравнения ($n = 11$)	p
Mother's age, years, *Me* [Q_1–Q_3] / Возраст матери, лет, *Me* [Q_1–Q_3]	30.0 [26.0–33.0]	29.0 [27.0–32.5]	0.799
Pregnancy, *Me* [Q_1–Q_3] / Беременность, *Me* [Q_1–Q_3]	3.0 [2.0–4.0]	1.0 [1.0–3.0]	0.104
Childbirth, *Me* [Q_1–Q_3] / Роды, *Me* [Q_1–Q_3]	2.0 [2.0–3.0]	1.0 [1.0–2.0]	0.118
Complications of pregnancy, childbirth and extragenital pathology of mothers / Осложнения беременности, родов и экстрагенитальная патология матерей			
Anemia / Анемия	4 (33.3%)	3 (25%)	0.438
Maternal hypothyroidism / Гипотиреоз матери	1 (8.3%)	1 (8.3%)	0.738
Vegetative dystonia / Вегетососудистая дистония	1 (8.3%)	4 (33.3%)	0.185
Acute respiratory viral infection / Острая респираторно-вирусная инфекция	3 (25%)	1 (8.3%)	0.256
Gestational diabetes mellitus / Гестационный сахарный диабет	0	3 (25%)	0.124
Violation of the utero-placental-fetal blood flow / Нарушение маточно-плацентарно-плодового кровотока	2 (16.6%)	2 (16.6%)	0.669
Meconium amniotic fluid / Мекониальные околоплодные воды	2 (16.6%)	1 (8.3%)	0.462
Preeclampsia / Преэклампсия	0	1 (8.3%)	0.524
C-section / Кесарево сечение	3 (25%)	2 (16.6%)	0.450
The state of the newborn in the early neonatal period / Состояние новорожденного в раннем неонатальном периоде			
APGAR1 minute, *Me* [Q_1–Q_3] / АПГАР 1-я минута, *Me* [Q_1–Q_3]	7.0 [6.0–8.0]	8.0 [7.0–8.0]	0.349
APGAR5 minutes, *Me* [Q_1–Q_3] / АПГАР 5-я минута, *Me* [Q_1–Q_3]	8.0 [8.0–9.0]	8.0 [8.0–9.0]	0.557
Acute fetal hypoxia / Острая гипоксия плода	4 (33.3%)	4 (33.3%)	0.608
Respiratory failure III grade / Дыхательная недостаточность III степени	3 (25%)	0	0.039*
Dysmorphias / Малые аномалии развития	5 (41.6%)	2 (16.6%)	0.175

* Values are statistically significant. *Note*. APGAR — Newborn Birth Hall Score Scale for 1 and 5 minutes; *Me* — median; [Q_1–Q_3] — interquartile interval. * Значение статистически значимое. *Примечание.* АПГАР — шкала оценки новорожденного в родовом зале на 1-й и 5-й минутах; *Me* — медиана; [Q_1–Q_3] — межквартильный интервал.

(n = 5/11), and regurgitation, and vomiting syndrome was registered in 9.1% (n = 1/11).

In the evaluation of individual physiological parameters and laboratory parameters, newborns with THAN tend to develop anemia (p = 0.023), hypoproteinemia (0.049), and hypoalbuminemia (0.048). Electrolyte disorders were represented by statistically significant differences in the levels of sodium, which were lower in the main group (p = 0.019) (Table 2).

An inverse, statistically significant correlation was revealed between the levels of ammonia and hemoglobin (ρ = –0.409; p = 0.049), total protein (ρ = –0.380; p = 0.035), and albumin (ρ = –0.510; p = 0.026). No statistically significant correlations were found between sodium levels and ammonia levels in the main group (p = 0.288).

Based on the data obtained using the binary logistic regression method, a predictive model was constructed to determine the probability of THAN development:

$$p = 1/(1 + e^{-z}) \cdot 100\%,$$
$$z = 113.089 - 0.001 \cdot X_1 - 0.834 \cdot X_2 - 0.003 \cdot X_3 + 21.98 \cdot X_4,$$

where p is the probability of THAN development, %, X_1 is the hemoglobin level, g/l; X_2 is the sodium level, mmol/l; X_3 is the level of total protein, g/l; and X_4 indicates the presence of RF requiring artificial lung ventilation (0, was not used; 1, was used).

Based on the regression coefficients obtained, the probability of THAN development increased with a decrease in the levels of hemoglobin, total protein, sodium, and albumin, and development of RF requiring artificial lung ventilation. The separating value of the logistic function (critical cutoff level) p was 20%. At p > 20%, a high probability of THAN development was predicted, whereas with p < 20%, its development had a low probability.

The levels of hemoglobin, total protein, and its fractions may decrease because of hypercatabolism in the neonatal period, which also causes HA syndrome. Lower blood levels of sodium in patients with THAN may be associated with hypoxia and consequently the development of the syndrome of inappropriate antidiuretic hormone secretion, hepatic dysfunction associated with immaturity, or hypoxic liver damage [9].

The resulting model was statistically significant (p = 0.012). In accordance with Nigelkirk's coefficient of determination R^2, the resulting prognostic model took into account 68.1% of the factors that influence the probability of THAN development. The sensitivity, specificity, and Youden's index of the model were 77.8%, 77.8%, and 0.56, respectively.

Table 2 / Таблица 2

Characteristics of selected physiological parameters and laboratory parameters in patients of the compared groups, *Me* [Q_1–Q_3]
Характеристики отдельных физиологических параметров и лабораторных показателей у пациентов сравниваемых групп, *Me* [Q_1–Q_3]

Characteristic / Характеристика	Main group / Основная группа (n = 11)	Comparison group / Группа сравнения (n = 11)	p
Birth weight, g / Масса тела при рождении, г	3020 [2715–3230]	3400 [3025–3490]	0.512
Weight loss, % / Убыль массы тела, %	7.0 [5.0–8.1]	7.0 [4.7–7.1]	0.590
Hemoglobin, g/l / Гемоглобин, г/л	185.5 [144.0–192.0]	192.0 [180.0–196.0]	0.023*
Platelets, 10^9/l / Тромбоциты, 10^9/л	297.0 [253.0–306.0]	236.0 [211.5–311.0]	0.151
pH	7.39 [7.34–7.5]	7.40 [7.37–7.42]	0.436
Anion gap / Дефицит оснований	–2.25 [–5.9… –0.7)]	–3.0 [–4.7… –2.4)	0.079
Lactate, mmol/l / Лактат, ммоль/л	2.1 [1.1–5.1]	2.5 [2.0–3.2]	0.503
Glucose, mmol/l / Глюкоза, ммоль/л	3.6 [2.9–4.2]	4.2 [3.6–4.6]	0.566
Sodium, mmol/l / Натрий, ммоль/л	135.5 [133.0–136.0]	137.0 [136.5–140.5]	0.019*
Potassium, mmol/l / Калий, ммоль/л	3.9 [3.7–4.3]	3.7 [3.3–4.6]	0.423
Calcium, mmol/l / Кальций, ммоль/л	0.56 [0.53–0.94]	0.54 [0.47–0.67]	0.382
Chlorine, mmol/l / Хлор, ммоль/л	110.5 [101.5–113.0]	105.0 [102.5–109.5]	0.730
Total protein, g/l / Общий белок, г/л	48.2 [43.0–49.0]	55.0 [52.1–56.0]	0.049*
Albumin, g/l / Альбумин, г/л	31.7 [25.8–34.2]	36.5 [35.4–38.2]	0.048*
Creatinine, mmol/l / Креатинин, ммоль/л	48.0 [40.1–58.0]	59.0 [45.0–77.0]	0.180
Urea, mmol/l / Мочевина, ммоль/л	4.4 [2.0–4.7]	3.3 [2.7–4.5]	0.381

* Values are statistically significant. / * Значения статистически значимые.

LPD in patients with THAN of varying severity

The approach of managing patients with THAN primarily included syndromic therapy depending on the condition severity and prevailing syndromes and the use of LPD as the main method to reduce ammonemia [3]. Patients with mild THAN received only syndromic symptomatic therapy, which consisted of infusion therapy, adequate respiratory support if necessary, treatment of convulsive syndrome, and adequate enteral, and parenteral nutrition corresponding to physiological needs. LPD has been used in patients with moderate-to-severe THAN. In LPD, the level of consumed protein decreased to 0.5–0.8 g/(kg · day) until the normalization of the ammonia levels in the blood, followed by a gradual increase under the control of ammonemia level.

In patients with mild THAN ($n = 7$; median ammonia level of 107.85 [104.2–111.5] μmol/L), a decrease in ammonemia level was noted during symptomatic therapy by day 2.5 [2.0–3.0]; therefore, LPD was not necessary for these patients. Ammonia levels reached normal values by day 10.5 [7–14] (89.4 [75.4–103.7] μmol/L; $p = 0.018$).

Moderate ($n = 2$) and severe ($n = 2$) THAN (212.8 [175.3–247.9] μmol/L) required LPD. Against the decrease in protein in the diet of newborns, the ammonia level decreased by approximately two times by day 6.0 [5.0–8.5] over time and normalized by day 11.0 [12.5–14.5] (89.2 [77.1–103.9] μmol/L, $p = 0.049$).

Assessment of the neuropsychic development in patients with THAN

When assessing the parameters of the neuropsychic development of patients with THAN, statistically significant disorders are more often recorded in the first 3 months of the child's life. Patients with THAN had low scores on the CAT/CLAMS scale (speech function for CLAMS, $p = 0.028$; intellectual level for CAT, $p = 0.039$; motor development, $p = 0.045$). Moreover, a trend toward lower rates of neuropsychic development in children was noted during the first year of life, mainly due to a delay in motor skill development (Table 3).

When evaluating the neuropsychic development in patients with THAN, depending on the severity of the HA syndrome, no statistically significant differences were found; however, the tendency toward lower values for all three indicators of the scale for the neuropsychic development in patients with severe HA syndrome is noteworthy. Moreover, 41.6% of pediatric patients with moderate or severe HA syndrome maintained a moderate delay

Table 3 / Таблица 3

Indicators of neuropsychiatric development in patients of the main group and the comparison group at the age of 3, 6, 9 and 12 months of life according to the CAT/CLAMS scale, *Me* [Q_1–Q_3]

Показатели нервно-психического развития пациентов основной группы и группы сравнения в возрасте 3, 6, 9 и 12 мес. жизни по данным шкалы КАТ/КЛАМС, *Me* [Q_1–Q_3]

Characteristic / Характеристика	Main group / Основная группа	Comparison group / Группа сравнения	*p*
3 months / 3 месяца			
CLAMS / КЛАМС	66.0 [33.0–83.0]	100.0 [66.0–100.0]	0.028*
CAT / КАТ	65.5 [33.0–91.5]	100.0 [74.5–100.0]	0.039*
Motor skills / Моторика	58.0 [24.5–74.5]	66.0 [66.0–100.0]	0.045*
6 months / 6 месяцев			
CLAMS / КЛАМС	76.0 [41.5–95.5]	83.0 [71.5–83.0]	0.443
CAT / КАТ	70.5 [33.0–87.0]	83.0 [74.5–87.0]	0.242
Motor skills / Моторика	70.5 [33.0–91.5]	71.5 [66.0–83.0]	0.443
9 months / 9 месяцев			
CLAMS / КЛАМС	88.0 [44.0–94.0]	85.5 [77.0–91.0]	0.755
CAT / КАТ	82.5 [35.5–88.0]	88.0 [77.0–91.0]	0.347
Motor skills / Моторика	71.5 [33.0–94.0]	77.0 [66.0–82.5]	0.590
12 months / 12 месяцев			
CLAMS / КЛАМС	75.0 [45.5–89.0]	83.0 [83.0–91.0]	0.143
CAT / КАТ	79.0 [37.0–91.0]	83.0 [83.0–91.0]	0.443
Motor skills / Моторика	75.0 [33.0–89.0]	83.0 [70.5–87.0]	0.671

* Values are statistically significant / * Значения статистически значимые.

Table 4 / Таблица 4

Indicators of the neuropsychiatric development of patients with transient hyperammonemia in newborns, depending on the severity of the hyperammonemia syndrome, *Me* [Q_1–Q_3]

Показатели нервно-психического развития пациентов с транзиторной гипераммониемией новорожденных в зависимости от степени тяжести синдрома гипераммониемии, *Me* [Q_1–Q_3]

Scale characteristics / Характеристики шкалы	The severity of hyperammonemia syndrome / Степени тяжести синдрома гипераммониемии			*p*
	mild severity / легкая степень тяжести (*n* = 7)	moderate severity / средняя степень тяжести (*n* = 2)	severe severity / тяжелая степень тяжести (*n* = 2)	
CLAMS / КЛАМС				
3 months / 3 месяца	74.5 [50.0–100.0]	66.5 [33.0–83.0]	33.0 [10.0–66.0]	0.498
6 months / 6 месяцев	87.0 [50.0–100.0]	71.5 [49.5–88.5]	37.5 [10.5–75.0]	0.454
9 months / 9 месяцев	91.0 [55.0–100.0]	82.5 [55.0–88.0]	47.0 [10.5–94.0]	0.623
12 months / 12 месяцев	89.0 [77.0–100.0]	75.0 [45.5–75.0]	43.5 [10.0–87.0]	0.297
p	0.708	0.091	0.392	–
CAT / КАТ				
3 months / 3 месяца	74.5 [50.0–100.0]	66.5 [33.0–91.5]	32.5 [10.0–65.0]	0.477
6 months / 6 месяцев	87.0 [50.0–100.0]	66.0 [41.0–74.5]	37.5 [10.0–75.0]	0.394
9 months / 9 месяцев	88.0 [55.0–100.0]	71.5 [41.0–82.5]	44.0 [10.0–88.0]	0.556
12 months / 12 месяцев	91.0 [83.0–100.0]	70.5 [37.0–75.0]	45.5 [10.0–91.0]	0.228
p	0.599	0.337	0.392	–
Motor skills / Моторика				
3 months / 3 месяца	74.5 [50.0–100.0]	41.5 [24.5–58.0]	33.0 [10.0–66.0]	0.342
6 months / 6 месяцев	91.5 [66.0–100.0]	58.0 [33.0–71.5]	37.5 [10.0–75.0]	0.324
9 months / 9 месяцев	91.0 [75.0–100.0]	60.5 [35.5–71.5]	37.5 [10.0–75.0]	0.528
12 months / 12 месяцев	89.0 [77.0–100.0]	66.5 [33.0–75.0]	43.5 [10.0–87.0]	0.268
p	0.904	0.419	0.392	–

in neuropsychic development in the first year of life with a predominant impairment in motor skill development (Table 4).

By the age of 1 year, patients with mild THAN compensated for the neuropsychic development disorders, and the CAT/CLAMS score exceeded 75 points. In patients with moderate and severe THAN, developmental retardation persisted during the first year of life, which required continuous rehabilitation measures after the first year of life.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

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