

Characteristics of energy metabolism in full-term newborns with neonatal hyperbilirubinemia

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ABSTRACT

Aim: To study the peculiarities of energy metabolism in full-term newborns with neonatal hyperbilirubinemia.

Materials and Methods: It was conducted the comprehensive examination of 30 full-term newborns with signs of neonatal jaundice (main group) and 30 healthy infants (control group).

It was determined the level of lactate, pyruvate and lactate/pyruvate ratio in the blood serum; in the bloods lymphocytes – level of Glycerol-3-phosphate Dehydrogenase (GPDH), Succinate Dehydrogenase (SDH), and Nicotinamide Adenine Dinucleotide Dehydrogenase (NADH-D), Aerobic Respiration Rate (AR) and Electronic Transport Chain coefficient (ETC).

Statistical analysis of the results was conducted using STATISTICA (Version 10) software, MedCalc Software (Version 16.1).

Results: Newborns of main group – in comparison to control group was defined: statistically significant lower lactate and pyruvate levels with statistically higher lactate/pyruvate ratio (53.62 ± 6.49 and 29.02 ± 9.87 , $p < 0.0001$ respectively); statistically significant lower GPDH, SDH and NADH-D activities; statistically significant lower ETC coefficient (14.58 ± 3.56 and 21.13 ± 1.51 a.u., $p < 0.0001$ respectively) with statistically significant higher AR coefficient (13.22 ± 9.13 and 8.42 ± 3.29 a.u., $p = 0.0102$ respectively).

Conclusions: Full-term newborns with signs of pathological hyperbilirubinemia have significant disruptions in the relationship between aerobic and anaerobic energy processes in comparison to healthy infants. The higher discriminatory ability level was defined in diagnostic model using ETC coefficient (cut-off level ≤ 19.48 , AUC 0.918; 95 % CI 0.841; 0.966, $p < 0.0001$, sensitivity 92.45 %, specificity 91.67 %).

KEY WORDS: newborn, neonatal hyperbilirubinemia, bilirubin, mitochondrial respiration

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INTRODUCTION

Neonatal jaundice and neonatal hyperbilirubinemia (NH) is a clinical condition that is characterized by yellowing of the skin, sclera, and mucous membranes in newborns due to accumulation of bilirubin in tissues [1]. Physiological jaundice has majority (60 – 80 %) of full-term infants and usually it is a transient condition. But excessive accumulation of unconjugated bilirubin (UB), especially with NH (for example as a result of hemolysis, infections, metabolic disorders) may lead to its penetration through blood-brain barrier and to developing of acute bilirubin encephalopathy or its chronic consequences – kernicterus [2, 3]. And at the same time physiological increase in bilirubin may have an impact as a transient antioxidant after birth till maturation of the antioxidant system [4].

Newborns adaption to the life after womb is accompanied by the huge changes in the energy metabolism

aimed on to maintaining of homeostasis, thermoregulation and supplying of the energy for growing and development [5]. The key role in these processes have mitochondria, where the oxidative phosphorylation occurs which is the main way of ATP synthesis [6, 7]. Therefore, the body compensates by switching to a less effective anaerobic way of glucose breakdown which is the key metabolic adaptation to the hypoxia intrauterine. Lactic acid (lactate) is the end product of an anaerobic glycolysis. Its excessive accumulation in blood and tissues leads to the metabolic acidosis (reducing of bloods pH level), known as lactic acidosis. The lactate level is a key marker of severity of hypoxic-ischemic injury in the newborns [8, 9]. Under these conditions, the body's ability to detoxification is significantly reduced, which leads to accumulation of interim products of the exchange, that may have a

negative impact on to bilirubin's metabolism in infants with jaundice accompanied with perinatal pathology.

There are theoretical premises to believe that NH may have an impact on to condition of energy exchange of newborn. Firstly, UB itself in high concentrations is considered as a potential toxin capable to disrupt the cell functions, including mitochondrial respiration [3, 10]. Secondly, one of the mechanisms of bilirubin toxicity is an oxidative stress (OS) induction, which, in turn, is a known factor of mitochondrial injury and energy production disruption [4, 11, 12]. Toxical bilirubin levels, similar to hypoxia, provokes the formation of free radicals and exhausts antioxidant systems – glutathione. On the other hand, bilirubin in physical concentrations can act as endogenous antioxidant [13-15]. Finally, the processes of bilirubin's conjugation and excretion and also cell responsiveness to its potential toxicity may need additional energy consumption. So, perinatal pathology, especially conditions associated with hypoxia significantly affect intracellular energy metabolism in newborns, that leads to a series of metabolic disorders which can be evaluated by certain biochemical indicators. But, in spite of prevalence of the NH and fundamental importance of energy metabolism, the relationship between these conditions in newborns has not been sufficiently studied, especially at the clinical level.

AIM

To study the features of energy metabolism in full-term newborns with neonatal hyperbilirubinemia

MATERIALS AND METHODS

To achieve this goal, a comprehensive clinical and laboratory examination of 30 newborns with gestational age more than 37 weeks (main group) was conducted. Comparison group (control group) consists of 30 conditionally healthy newborns. Inclusion criteria in research: gestational age at birth ≥ 37 weeks, clinical signs of neonatal jaundice. Exclusion criteria: gestational age at birth ≤ 37 weeks, birth defects, neonatal sepsis. Diagnoses were determined according to International classification of diseases X revision. In addition to generally accepted standard methods of clinical and laboratory examination the condition of intracellular energy exchange was determined [12]. List of indicators: blood serum – level of Glycerol-3-phosphate Dehydrogenase (GPDH), Succinate Dehydrogenase (SDH), and Nicotinamide Adenine Dinucleotide Dehydrogenase (NADH-D), Aerobic Respiration Rate (AR) and Electronic Transport Chain coefficient (ETC) were calculated. Lab-

oratory studies were conducted using micromethods using the peripheral and cord blood 1.0 ml in volume.

The scientific researches were conducted in compliance with "Rules of ethical principles of scientific researches conducting involving human subjects" that was adopted by Declaration of Helsinki (1964 – 2013), ICH GCP (1996), Council Directive № 609 (from 24.11.1986), Decree of Ministry of Health of Ukraine № 690 from 23.09.2009. Protocol of the scientific research of the Commission of biomedical ethics of BSMU from 12.09.2015. Before the start of research, informed written consent was obtained from parents with an explanation of the purpose, objectives, and methods of the laboratory study.

Statistical analysis of the results was conducted using STATSTICA (Version 10) software, MedCalc Software (Version 16.1). Comparison of quantitative indicators with normal distribution was carried out using Student's t-test ($p < 0.05$). Analysis of Receiver Operating Characteristic Curve, ROC was conducted using MedCalc Software (Statistical Software Package for Biomedical Research, 2023, Version 16.1).

RESULTS

The results of the study showed that based on sex, gestational age, information about physical development at birth examination groups did not differ statistically significantly. The average indicators of body mass index at birth for infants of main group – 3320.71 ± 440.84 g, infants of comparison group – 3332.67 ± 433.5 g ($p > 0.05$), body height – 53.1 ± 2.38 and 53.11 ± 2.67 cm ($p > 0.05$) recursively. The ratio by sex according to the survey groups was as follows: 18 (60.0 %) and 16 (53.3 %) males ($p > 0.05$); 12 (40.0 %) and 14 (46.7 %) females ($p > 0.05$).

Average Apgar score at birth at the end of 1-st minute of life for infants of main group is 7.4 ± 0.79 points, control group – 7.6 ± 0.74 points ($p > 0.05$), at 5-th minute of life – 8.6 ± 0.97 and 8.2 ± 0.76 points ($p > 0.05$) recursively.

The study of somatic pathology of mothers, features of pregnancy and childbirth showed no statistically significant difference between the study groups. Thus, somatic pathology of mothers is presented in form of anemia (36.7 and 33.3 %, $p > 0.05$), pathology of the thyroid gland (20.0 and 26.7 %, $p > 0.05$), vegeto-vascular dystonia (20.0 and 23.3 %, $p > 0.05$), chronic cholecystitis (16.7 and 13.3 %, $p > 0.05$) and chronic pyelonephritis (13.3 and 20.0 %, $p > 0.05$). The list of gynecological diseases includes previous colpitis (16.7 and 13.3 %, $p > 0.05$) and chronic adnexitis (10.0 and 6.7 %, $p > 0.05$). Medical complications of gestational period are related to placental insufficiency (30.0 and 36.7 %, $p > 0.05$),

Table 1. Level of lactate, pyruvate and lactate/pyruvate ration in blood serum of infants of survey groups on 1 – 3 days of life ($M \pm m$)

Indicator	Main group (n = 30)	Control group (n = 30)	p
Lactate, mmol /l	6.48 $\pm$ 1.17	8.78 $\pm$ 2.09	< 0.0001
Pyruvate, mmol /l	0.22 $\pm$ 0.14	0.42 $\pm$ 0.19	< 0.0001
Lactate/Pyruvate	53.2 $\pm$ 6.49	29.02 $\pm$ 9.87	< 0.0001

Source: compiled by the authors of this study

Table 2. ROC-curve Analysis of lactate, pyruvate levels and lactate/pyruvate ration in blood serum of infants of survey group on 1 – 3 days of life

Indicator	AUC	Standard deviation	P	95% CI	Youden's index	Sensitivity %	Specificity %
Lactate, mmol/l	0.642	0.0693	= 0.0410	0.533 – 0.740	0.5257	88.68	63.89
Pyruvate, mmol/l	0.519	0.0635	= 0.7631	0.411 – 0.626	0.2940	37.74	91.67
Lactate/Pyruvate	0.671	0.0597	= 0.0047	0.563 – 0.767	0.5136	73.58	77.78

Source: compiled by the authors of this study

Table 3. Activity of enzyme's mitochondrial oxidation in blood serum of infants of survey groups on 1 – 3 days of life ($M \pm m$)

Indicator	Main group (n = 30)	Control group (n = 30)	P
GPDH, μm^2	1.75 $\pm$ 0.63	3.45 $\pm$ 1.22	< 0.0001
SDH, μm^2	6.22 $\pm$ 1.64	9.74 $\pm$ 0.94	< 0.0001
NADH-D, μm^2	10.39 $\pm$ 2.19	14.84 $\pm$ 0.96	< 0.0001
AR coeff., a.u.	13.22 $\pm$ 9.13	8.42 $\pm$ 3.29	= 0.0102
ETC coeff., a.u.	14.58 $\pm$ 3.56	21.3 $\pm$ 1.51	< 0.0001

Source: compiled by the authors of this study

Table 4. Data of ROC-curve analysis of AR and ETC in blood serum of infants of survey groups in 1 – 3 days of life

Indicator	AUC	Standard deviation	P	95% CI	Youden's index	Sensitivity %
AR coefficient	0.513	0.0641	0.8379	0.405 – 0.621	0.2794	41.51
ETC coefficient	0.918	0.0327	< 0.0001	0.841 – 0.966	0.8412	92.45

Source: compiled by the authors of this study

threat of termination of pregnancy (30.0 and 33.3 %, $p > 0.05$), preeclampsia (16.7 and 13.3 %, $p > 0.05$) and eclampsia (10.0 and 6.7 %, $p > 0.05$). Overall, a difficult obstetric history had a woman of main group in 46.7 %, control group – 53.3 % of cases, $p > 0.05$.

The main group of the survey included 30 newborns with an average gestational age of 38.9 ± 0.66 weeks. 23 infants (76.7 %) were born by vaginal birth, 7 infants (23.3 %) – Caesarean section. Urgent Caesarean section was performed for 3 women (10 %), including 2 (6.7 %) – due to fetal distress. The main pathology observed among the infants of this group is represented by a neonatal encephalopathy in 30.4 % of cases, hemolytic disease of infants – 21.7 % of cases, meconium aspiration syndrome and, as a result, severe respiratory disorders – 2.2 % of cases, moderate respiratory disorders – 2.2 % of cases. One infant (2.2 %) had a birth trauma of cervical spine on C6 – C6 level, low body weight – 2 infants (4.4 %). Majority of infants of main group – 26

(86.7 %) were exclusively on breastfeeding, 4 infants (13.3 %) – mixed feeding.

Control group includes 30 healthy full-term infants with gestational period 38.95 ± 0.87 weeks. Twenty-four infants (80.0 %) were born by natural childbirth, 6 infants (20.0 %) – Caesarean section, out of which 3 cases (10.0 %) – urgent. General condition of newborns of current group was satisfactory during all the stay in maternity hospital, infants stayed in joint stay chambers with mothers and in 96.6 % of cases (29 infants) – exclusively breastfeeding, 1 infant – mixed feeding. It should be noted that 22 of infants (73.3 %) were in risk group about hemolytic disease of newborns, but in no case has the pathological jaundice developed.

All the infants of main group have signs of pathological neonatal jaundice during early neonatal period, which required to conduct advanced diagnostic and medical measures, including control bilirubin level and conducting of phototherapy. Average value of cord

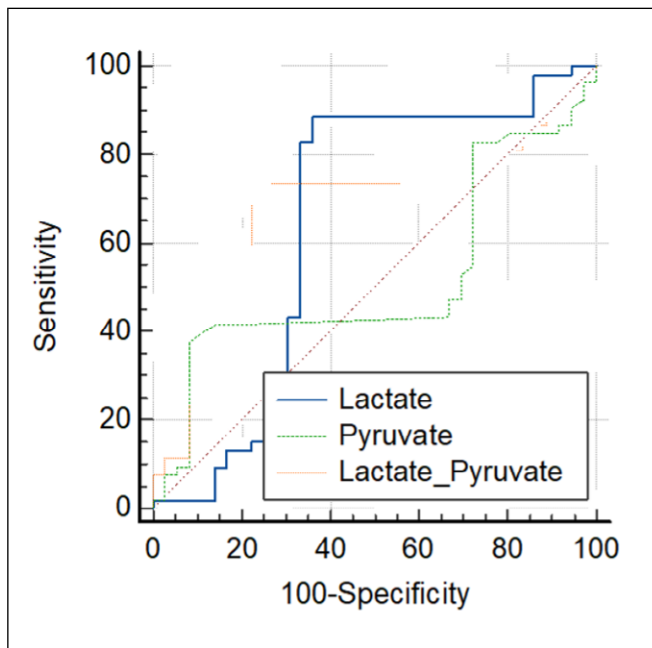


Fig. 1. ROC-curve analysis of lactate, pyruvate levels and lactate/pyruvate ratio in blood serum of infants of survey group on 1 – 3 days of life
Picture taken by the authors

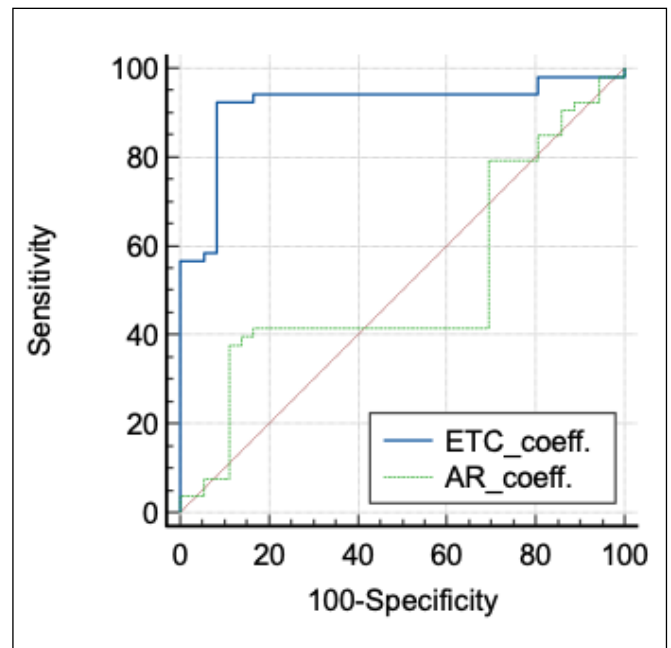


Fig. 2. ROC-curve analysis of AR and ETC in blood serum of infants of survey groups in 1 – 3 days of life
Picture taken by the authors

blood bilirubin level statistically significant did not differ between surveys group and was $38.46 \pm 1.49 \mu\text{mol/l}$ for infants of main group and $32.3 \pm 0.59 \mu\text{mol/l}$ – infants of control group. General bilirubin level of blood serum on 1 – 3 days of life was significant higher in group of infants with signs of pathological neonatal jaundice in comparison to healthy newborns (237.19 ± 18.34 and $164.01 \pm 8,2 \mu\text{mol/l}$, $p < 0.05$ respectively).

The specifics of energy exchange in blood serum of infants of surveys group on 1 – 3 days of life was studied during the research (Table 1).

It is necessary to note the laboratory signs of imbalance between the aerobic and anaerobic processes of energy formation in newborns under the conditions of development of pathological hyperbilirubinaemia. Thus, for infants of main group in comparison to control group it was defined statistically significant lower lactate level (6.48 ± 1.17 and $8.78 \pm 2.09 \text{ mmol/l}$, $p < 0.0001$ respectively) and pyruvate (0.22 ± 0.14 and $0.42 \pm 0.19 \text{ mmol/l}$, $p < 0.0001$ respectively) with simultaneously statistically higher lactate/pyruvate ratio (53.62 ± 6.49 and 29.02 ± 9.87 , $p < 0.0001$ respectively). Ratio lactate/pyruvate himself is marker that objectively characterizes relations between aerobic and anaerobic components of cell metabolism. Its increasing may be a sign aerobic processes activation or pyruvates disposal disruption in mitochondria [9].

We conducted Receiver Operating Characteristic Curve, ROC Analysis for defining of diagnostic and prognostic values of represented laboratory indicators (Table 2 and Fig.1).

Results of statistical analysis showed significant associative lactate level at $\leq 8.51 \text{ mmol/l}$ (AUC 0.642; 95 % CI 0.533; 0,74, $p = 0.041$) and lactate/pyruvate ration at ≥ 29.02 (AUC 0,671; 95% CI 0.563; 0.767, $p = 0.0047$). These indicators values, based on our data, have average discriminatory ability. The absence of statistically significant AUC level at pyruvate level $> 0.47 \text{ mmol/l}$ (AUC 0.519, 95% CI 0.411; 0.626, $p > 0.05$) confirmed insufficient informative value of this indicator for disruption diagnostics of energy metabolism in newborns with signs of neonatal jaundice.

The Table 3 presents the results of the study of some blood serum enzymes activities in infants of survey groups, that may indirectly indicate about peculiarities of intracellular mitochondrial oxidation and explain its disorders mechanisms.

The generalized results of the study showed the depression of activity of these enzymes in blood serum of infants in main survey group with present signs of pathological jaundice in comparison to healthy full-term infants. GPDH activity in infants of main group is $1.75 \pm 0.63 \mu\text{m}^2$, infants of control group – $3.45 \pm 1.22 \mu\text{m}^2$ ($p < 0.0001$), SDH activity – 6.22 ± 1.64 and $9.74 \pm 0.94 \mu\text{m}^2$ ($p < 0.0001$) respectively, NADH-D – 10.39 ± 2.19 and $14.84 \pm 0.96 \mu\text{m}^2$ ($p < 0.0001$) respectively. This may indirectly indicate on disorders of intracellular mechanisms of energy processes regulation in newborns against the backdrop of high bilirubin level and therapeutic activities conducting.

In comparison to healthy full-term infants, infants with signs of pathological hyperbilirubinaemia has

statistically significant higher aerobic respiration coefficient (AR), which is calculated based on formula $(SDH - GPDH + NADH-D) / GPDH$. This indicator level in infants of main group was 13.22 ± 9.13 a.u., control group – 8.42 ± 3.29 a.u., $p = 0.0102$. Opposite results were noticed on electronic transport chain coefficient (ETC) that is calculated based on formula $SDH - GPDH + NADH-D$. Its level was statistically significant in the main group in comparison to control group (14.58 ± 3.56 to 21.13 ± 1.51 a.u., $p < 0.0001$ respectively). Detected changes on our opinion confirm the thought about mitochondria disruption in newborns together with significant increase of total bilirubin level.

Table 4 and Fig. 2 shows ROC-curve analysis results of AR and ETC coefficients in blood serum of infants of survey groups in 1 – 3 days of life.

AR coefficient > 8.11 shows absence of diagnostic significance of sufficient level to identify the possible difference between groups of full-term newborns with presence of clinical manifestation of pathological jaundice (AUC 0.513; 95 % CI 0.405; 0.621, $p > 0.05$). For ETC coefficient of ≤ 19.48 was spotted the highest level of discriminatory ability among all the laboratory indicators that were studied in this research. This was evidenced by the differ level of AUC (0.918; 95 % CI 0.841; 0.966, $p < 0.0001$) and high indicators of sensitivity (92.45 %) and specificity (91.67 %), and also Yonden's index (0.8412) that confirm the sufficient balance of sensitivity and specificity among the presented indicators.

DISCUSSION

In vitro research on isolated mitochondria or cell cultures (mainly neuronal) showed that high concentration of UB can inhibit activity of main enzyme complex of respiratory chain (especially complex I and IV) and Krebs cycle enzymes [3, 14]. This leads to a decrease in oxygen consumption by mitochondria, reducing the ATP synthesis and potential switching on anaerobic way of metabolism. It was show also that bilirubin may cause mitochondrial swelling and release of cytochrome C, which and apoptosis inductor [14-16]. These effects usually present at toxic bilirubin concentration and may depend on the bilirubin/albumin ratio and on presence of free bilirubin [17].

It should be noted that there are practically no direct studies on determining of the ATP level or mitochondria's enzymes activity in newborns tissues with NH due to ethical considerations, and most scientific data relate to indirect indicators. Thus, increase of lactate level in blood may indicate on tissue hypoxia or mitochondrial dysfunction with activation of anaerobic glycolysis.

Some research discovered increasing of lactate level in newborns together with significant NH, especially for those who needed a blood transfusion, which may indicate on dysfunction of aerobic metabolism [18]. However, other studies have not found a clear correlation between bilirubin level and lactate [19].

The data on interaction of glucose as an energy source and bilirubin is contradictionary. Theoretically, a malfunctioning of oxidative phosphorylation could lead to increased glycolysis level and potential hypoglycemia with existed glycogen reserves. On the other hand, a stress reaction may cause a hypoglycemia. Some studies indicate no significant changes of glycemia when having NH, while others report about hypoglycemia cases in infants with severe jaundice, especially against the backdrop of hemolysis [20].

Numerous studies confirm that significant NH is associated with increased OS markers level (for example, lipid peroxidation products such as malondialdehyde) and decreased activity of antioxidant enzymes (superoxide dismutase, glutathione peroxidase) in newborns [12]. OS can directly damage mitochondrial membranes and components of respiratory chain, leading to a decreasing in the efficiency of ATP synthesis and increasing of the production of active oxygen species, closing the vicious circle [21]. Some authors indicate that OS is the key mechanism of bilirubin-induced neurotoxicity [3, 22, 23].

Scientific interest is the study of the impact of phototherapy, which is the main method of NH treating, on cellular metabolism. Although its effectiveness in lowering of bilirubin levels is proven, its metabolic effects are less well studied. Phototherapy can potentially affect energy balance through increased unconscious water losses and possible effects on thermoregulation [24, 25]. There are also consumptions that phototherapy may increase OS [26], which could theoretically further affect mitochondrial function [27]. However, there is currently no clinical evidence about significant negative impact of standard phototherapy on energy metabolism.

So, NH is a powerful factor that may cause cascade of metabolic disorders related to mitochondrial dysfunctions which is reflected in changes of the relevant laboratory indicators. However, it is always necessary to take into account the presence of comorbidities (hypoxia, acidosis, infections, premature birth) which may increase the negative impact of NH on to these indicators and also individual genetically determined sensitivity of newborns to level and duration of hyperbilirubinemia.

CONCLUSIONS

1. The results of the survey showed that full-term newborns with signs of pathological hyperbiliru-

binaemia in comparison to healthy infants show significant relations disorders of aerobic and anaerobic processes. This is confirmed by the established statistically significantly lower levels of lactate and pyruvate with higher lactate/pyruvate ration and also statistically significantly less activity of GPDH, SDH, NADH-D in blood serum on 1 – 3 days of life.

2. Integral markers of mitochondrial dysfunction confirm significantly higher informativeness than separate substrate or intermediate products of metabolism. The highest level of discriminatory ability has a diagnostic model using ETC coefficient (cut-off level ≤ 19.48 , AUC 0.918; 95 % CI 0.841; 0.966,

$p < 0.0001$, sensitivity 92.45 %, specificity 91.67 %, Yuden's index 0.8412).

PROSPECTS FOR FURTHER RESEARCH

Prospects for further research are aimed at studying of the diagnostic value of modern markers of mitochondrial function (analysis of mitochondrial DNA, specific biomarkers in blood or urine) and conducting of prospective studies for defining of correlation between indicator of energy metabolism and oxidative stress to bilirubin level, clinical severity of NH and its long-term consequences.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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