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FREE BILIRUBIN AS A PREDICTOR OF NEUROTOXICITY IN INFANTS

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Abstract: The purpose of the study: to study the degree of neurotoxicity in newborns with unconjugated bilirubinemia. Materials and methods of research: 100 newborns with unconjugated hyperbilirubinemia were examined. The gestational age of newborns varied from 38 to 41 weeks, body weight at birth, depending on the gestational age, ranged from 2930-4200g, body length - from 47 to 55 cm group 1 - 58 infants with prolonged unconjugated hyperbilirubinemia with a gestational age of 38.8±0.08 weeks, birth weight - 3427.1±28.1 g, body length - 55.6±2.7 cm; group 2 - 40 children with physiological jaundice with a gestational age of 38.5 ± 0.09 weeks, with a birth weight of 3216.0 ± 15.7 g, body length -54.3 ± 1.0 cm. The study revealed a statistically significant increase in the level of NSE in children of all groups, but in the group of children with prolonged hyperbilirubinemia, a high content of NSE was noted, which was significantly higher than in the compared group ($p<0.05$). Thus, the determination of the level of total and unconjugated bilirubin, as well as the activity of neurospecific enolase in newborns, can reduce the severe consequences of hyperbilirubinemia and prevent the risk of developing irreversible neurological disorders caused by kernicterus.

Key words: unconjugated hyperbilirubinemia, newborn, neurospecific enolase, bilirubin encephalopathy.

Assessment of the degree of hyperbilirubinemia, identification of its cause, as well as timely hospitalization and adequate therapy of such patients is an important task for pediatricians and neonatologists due to the risk of developing such a severe complication as bilirubin encephalopathy with an excessively high level of bilirubin. Neurotoxicity is the main consequence of neonatal hyperbilirubinemia. Indirect non-conjugated bilirubin is toxic to the central nervous system, is able to penetrate the blood-brain barrier, easily dissolves in lipids of cell membranes, disrupts the processes of oxidative phosphorylation in mitochondria, protein synthesis, and thus negatively affects the state of the central nervous system, which is manifested by bilirubin encephalopathy. Acute encephalopathy can be accompanied by a number of neurological pathologies, including cerebral palsy and sensory-motor, cognitive impairment. Kernicterus is the most severe form of neurotoxicity caused by the deposition of unconjugated bilirubin in the basal ganglia and brainstem nuclei due to acute or chronic hyperbilirubinemia. Normally, bilirubin binds to serum albumin, remaining in the intravascular space. However, bilirubin can cross the blood-brain barrier and cause kernicterus when the serum bilirubin concentration is significantly elevated and exceeds more than 300 mmol/L.

The aim of our work was to study the degree of neurotoxicity in newborns with unconjugated bilirubinemia.

Materials and methods of research. We examined 100 newborns with unconjugated hyperbilirubinemia. The gestational age of newborns varied from 37 to 41 weeks, body weight at birth, depending on gestational age, was in the range from 2800-4200g, body length was from 47 to 55 cm. Based on gestational age and body weight at birth, children with critical conditions divided into 2 groups:

group 1 - 58 infants with prolonged unconjugated hyperbilirubinemia with a gestational age of 38.8±0.08 weeks, birth weight - 3427.1±28.1 g, body length - 55.6±2.7 cm;

group 2 - 40 with physiological jaundice, gestational age 38.5 ± 0.09 weeks, body weight at birth - 3216.0 ± 15.7 g, body length -54.3 ± 1.0 cm;

The control group consisted of 20 practically healthy full-term newborns without jaundice, with a gestational age of 38.9±4.6 weeks, with a birth weight of 3120.0±156.6 g, and a body length of 52.4±4.2 cm. , whose average age was 15.4±1.8 days

Criteria for exclusion from the study:

- newborns and infants with a gestational age of less than 37 weeks
- children with congenital malformations

-children with other specified variants of hyperbilirubinemia (mechanical, parenchymal, hemolytic jaundice)

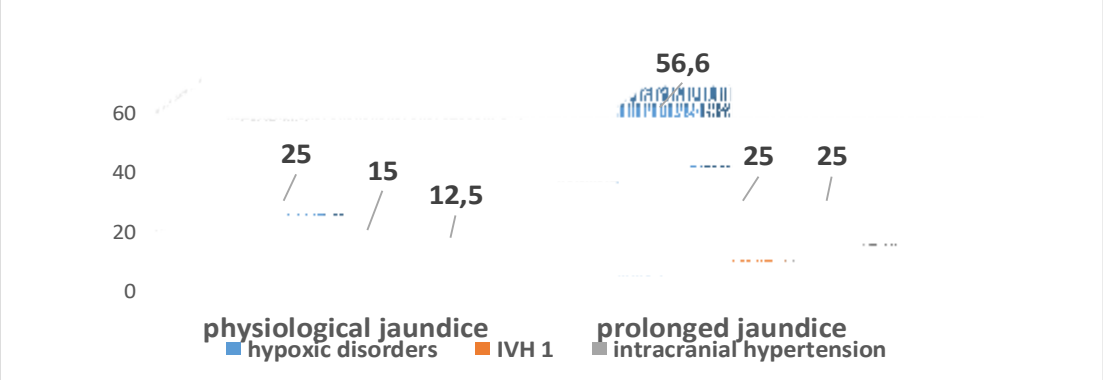
- newborns with an increase in the direct fraction of bilirubin. In addition to clinical, laboratory and instrumental diagnostics (NSG), special biochemical research methods were carried out, which consisted in determining the level of NSE in the blood serum using the Fujirebio kit (Sweden).

Static processing of the obtained results was carried out using software programs for mathematical and statistical analysis BIOSTAT.

Research results. According to the results of clinical and neurological examinations, almost all children of groups 1 and 2 showed signs of perinatal damage to the central nervous system.

In the examined group of infants with prolonged non-conjugative jaundice, such signs as the syndrome of movement disorders (20%), depression of the central nervous system (18%), arousal syndrome (10%) prevailed. The syndrome of depression manifested itself in the form of reduced spontaneous induced motor activity, muscle hypotension, hyporeflexia, and reduced response to examination. During the first day of hospitalization, the neurological status of children with hyperbilirubinemia was characterized by adynamia (16.6%), severe diffuse hypotension (10%) or atony (5%), hypo- (13%) or areflexia (10%). Spinal automatism reflexes were reduced in 6 (10%) infants. In the analysis of clinical manifestations in children of both groups, both isolated syndromes and a combination of two or more syndromes were observed.

The results of neurosonographic studies of children with physiological jaundice and children with prolonged jaundice revealed such signs as posthypoxic changes in the brain in 25% and 56.6% of cases, IVH of the 1st degree in 15% and 25%, and signs of intracranial hypertension in 12.5% and 25% of cases respectively.



Rice.1 Signs of neurosonographic disorders in the examined children (%)

Infants with prolonged jaundice are often born in asphyxia during childbirth, resulting in hypoxic damage to the hepatobiliary and central nervous system. At the same time, there is a delay in the formation of the glucuronyl transferase system, dissociation of the bilirubin-albumin complex, the permeability of the blood-brain barrier increases, which contributes to the formation of protracted non-conjugated hyperbilirubinemia. The identified risk factors and these pathological conditions, alone or in associations, contribute to the development of protracted non-conjugated hyperbilirubinemia in infants.

The study of the dynamics of the level of total bilirubin and its fraction showed an increase in these indicators in all patients. The icteric syndrome was formed due to an increase in indirect bilirubin.

Upon admission of newborns with physiological jaundice, the content of total bilirubin was 199.9±12.4 mmol/l, and the level of indirect bilirubin fraction was 164.5±9.2 mmol/l. These indicators in children with prolonged jaundice were 245.8±13.7 mmol/l and 209.3±12.4 mmol/l, respectively.

To assess the degree of damage to the CNS, along with standard clinical and instrumental methods of examination, we determined the level of NSE in the blood serum of newborns. An important advantage of the immunochemical determination of the level of NSE in a biological fluid in comparison with other diagnostic methods is its high sensitivity, accuracy, and a small amount of the test material.

NSE is an intracellular CNS enzyme, the only common marker of all differentiated neurons. By its level, one can judge about violations of the overall integrity of the blood-brain barrier, which characterizes the degree of bilirubin damage to the brain. The blood-brain barrier (BBB) plays a role in maintaining a balance between the neurotoxic and protective effects of bilirubin. In newborns, the permeability of the BBB is increased and the brain is most susceptible to the negative effects of hyperbilirubinemia. One of the confirming factors for the increase in BBB permeability is an increase in the content of neurospecific enolase (NSE) in the blood of newborns. With an increase in the permeability of the blood-brain barrier with cerebrospinal fluid, NSE enters the venous blood.

Table 1.
The content of neurospecific enolase in the examined newborns (ng/ml)

Groups	Indicator in the dynamics of observation				
	1 day	14 day	1 month	1,5 month	P
Children with physiological jaundice	18,3±2,8*	35,2±7,3*	20,6±6,4*	8,9±6,4*	<0,001
Children with persistent jaundice	24,8±2,4**	57,3±9,0**	38,4±5,3	30,5±6,1**	<0,05
Control group	6,1±0,9	8,8 ±1,9	6,2±1,	5.4±2,9	<0,05

Note: * the reliability of the difference in the performance of children with the control group,** - the reliability of the difference in the performance of children in the compared groups.

The study revealed a statistically significant increase in the level of NSE in children of all groups, especially in infants with prolonged hyperbilirubinemia (table 1.). A comparative study of indicators in the blood serum according to the content of NSE revealed the presence of significant differences between groups of newborns, depending on the severity and degree of bilirubin damage to the central nervous system

Higher NSE rates were registered in children of the main group who had a high level of indirect fraction of bilirubin in the blood. In the study group of children with prolonged hyperbilirubinemia, a high content of NSE was noted, which was significantly higher than in the compared group ($p<0.05$). In 48 (80%) infants with prolonged jaundice, a decrease in ES values by 1 month of life by 1.7 times was recorded compared with the indicator on the 14th day of life. This may indicate a decrease in the destructive processes of neurons and an improvement in clinical manifestations at the age of one month. In 18 (30%) infants, the ES indicators tended to decrease, but remained elevated compared to the indicators of children with physiological jaundice, and significantly exceeded the similar data of the control group ($p<0.001$).

Analyzing fluctuations in the concentration of NSE, depending on the severity of hyperbilirubinemia, it becomes possible to judge the structural disorders of the brain. Of undoubted interest is the study of the relationship between the NSE indicator, the severity of neonatal hyperbilirubinemia and the severity of CNS damage.

The conducted correlation analysis showed that the content of NSE is in direct correlation with the amount of indirect bilirubin in the blood ($r=0.59$; $p<0.05$). There was a regular direct dependence of the level of NSE in the blood serum on the severity of hyperbilirubinemia. The revealed data confirm the increased permeability of the BBB and the increased sensitivity of brain structures to the neurotoxic effect of bilirubin.

This feature confirms the susceptibility of the blood-brain barrier to the action of various damaging factors - hypoxia, infection, including the toxic effect of indirect bilirubin. An increase in vascular permeability under the influence of these factors leads to greater damage to the brain by toxic substrates (for example, indirect bilirubin). It was found that a statistically significant high concentration of serum NSE confirms a more severe neurological pathology.

Thus, the determination of the level of total and unconjugated bilirubin and the activity of neurospecific enolase in newborns can reduce the severe consequences of hyperbilirubinemia and prevent the risk of developing irreversible neurological disorders caused by kernicterus.

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