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Neonatal Hypoglycemia as the Factor in the Development of Neurologic Impairments in Infants.

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Key words: hypoglycemia, newborns, neurodevelopment.

Damaging effect of hypoglycemia on the brain is caused by formation of substances adversely influencing on cerebral tissue metabolism in the oxidation process.) Hypoglycemia syndrome can be of various clinical presentation, and in certain cases of asymptomatic course. In the presence of clinical semiology more often mild and moderately severe hypoglycemia is shown in the form of hyperexcitability syndrome, and profound one – distress syndrome.

Ключевые слова: гипогликемия, новорожденные, неврологическое развитие.

Выявлено, что гипогликемический синдром может иметь различную клиническую картину, а в некоторых случаях имеет бессимптомное течение. При наличии клинической симптоматики чаще всего легкая и среднетяжелая гипогликемия проявляется в виде синдрома гипервозбудимости, а тяжелая – синдрома угнетения.

The nervous system affection in cases of glucose homeostasis in an organism has been studied thoroughly for the last years [12, 14, 15, 16, 19].

Glucose is the basic, and typically the unique substratum of power exchange in brain. If it stops supplying the brain, endogenetic resources can provide its normal metabolism only within 10-15 minutes [5, 8].

Damaging effect of hypoglycemia on the brain is caused by formation of substances adversely influencing on cerebral tissue metabolism in the oxidation process. Besides, glucose,

as glucolise substratum, is necessary for functioning potassium-sodium pump, for maintenance neuroplectrum processes as well [4].

In hypoglycemia oxygen consumption of the brain is decreased, therefore, prolonged and often repeating episodes of hypoglycemia result in irreversible changes in nervous cells. Cerebral cortex functions are affected firstly, followed by midbrain (cerebral hypoglycemia). Oxidizing processes slow down in the brain structure and all kinds of metabolism are impaired abruptly in the brain. Blood inflow to the brain increases, vessel walls lose usual elasticity and tone, causing the enlargement of microcirculatory vessels, increasing their permeability, blood flow speed slow down and clots are formed. In prolonged carbohydrate starvation not only functional, but also morphological changes are noted, up to hypostasis and cerebral necrosis [6, 9].

R.N. Auer [10, 11] states that in some brain parts the cellular destruction after hypoglycemia appears to be of greater intensity. First of all, they refer to cerebral cortex cells, hyppocamp and a striped body. Considering that neurons hyppocamp play an important role in the process of studying and storing, hypoglycemia causes the deterioration of cerebral tissue function and inhibition process of memory formation.

S.W. Suh [18] identified that the active forms of oxygen were formed after glucose concentration restored in blood as a result of previous hypoglycemia. During this period nitrotirosine is formed as well as activation of weed (ADF-riboza) of polymerases (PARP-1), enzyme in DNA [17]. Hence, pathogenesis of neuron damage in hypoglycemia is alike to the restoration of blood flow after ischemia, the tissue damaging causing oxidant stress [13].

On the other hand, cerebral functions are affected not only by blood glucose content, but also its quantity passing into the brain. The symptom complex of hypoglycemia can develop at a normal level of glycemia (if small quantity of glucose passes into the brain), and not to be noted at a lower level of glycemia (if necessary quantity of glucose is received). In this connection, it is necessary to take into account variants of absence of the complete dependence between blood glucose level and hypoglycemic syndrome presentation among various patients and even at the same patient within one day [9]. However, the structural affection of nervous system is noted even at asymptomatic course of hypoglycemia (by Kojvisto M, etc., 1972) which can cause the nearest and remote psychoneurological manifestations, thus, the later hypoglycemia is identified, the higher rate of it can be expressed [7].

All above-stated data point out the importance of carrying out the researches concerning the study of the neurologic status features in newborns having hypoglycemia.

Goal: to study the neurodevelopment of newborns having hypoglycemia.

Materials and methods.

Within the research a complex clinical, psychoneurological and laboratorial examination of 151 newborns was performed including the subsequent supervision during 4 – 6 years.

The children examined (n = 151) were divided into two groups: experimental (n = 114) and control (n = 37).

The experimental group included 114 children who had hypoglycemia with various degrees of manifestation. The control group consisted of 37 children who did not have hypoglycemia in the neonatal period. All children (experimental and control groups) were born at more than 37^{th} weeks of gestation in satisfactory state, with 7/8 points on Apgar's scale (not less), without signs of somatic and neurologic pathology, from mothers with satisfactory course of pregnancy and delivery.

According to severity of the hypoglycemia course the experimental group was divided into three subgroups:

Children with mild hypoglycemia	Children with moderately hypoglycemia	Children with profound hypoglycemia
n = 37	n = 40	n = 37

Criteria of hypoglycemia severity:

The severe hypoglycemia was determined as the steady course lasting more than 3 days and tending to recurrence and reduced glucose in blood below 1,3 mmol/l. In 40 % of cases with severe course of hypoglycemia it was necessary make to parenteral injection of glucose rating 10 – 15 mg/kg/minutes.

The degree was considered to be mild hypoglycemia with reduced blood sugar above 1,67 mmol/l.

All children underwent the somatic and neurological examination generally accepted in neonatologic practice, laboratory tests (full blood count; biochemical blood count with definition of total proteins, total bilirubin; definition of glucose in blood by glucose-oxidized method), neurosonography, ultrasonic investigation of inner organs.

The analysis of neurologic status was carried out by means of "Distress Profile – excitation"[3]. For differential diagnostics of neurologic manifestations caused by hypoglycemia Whipple's triad was used [1] with pathological semiology caused by affection of CNS of another etiology, it consisting of:

1) Symptoms incident in hypoglycemia;
2) Low concentration of blood glucose;
3) Symptoms disappearance at glucose correction after its injecting to a patient.

The technique of carrying out the neurologic examination on studying motor system and cranial-cerebral innervation at postneonatal age was borrowed from the general scheme of the clinical neurologic examination of children based on L.O.Badaljan [2].

Procedures of the statistical analysis were carried out by means of statistical packages SAS 9.2, STATISTICA 8 and SPSS-17. When checking zero hypotheses a critical level of the statistical importance amounted for 0,05. If statistical criterion of this value exceeded the reached level, the zero hypothesis was accepted.

Results and discussion

The research showed that prevalence of hypoglycemia (at a lower rate of blood glucose of 2,6 mmol/l) was 17,5 % from 2500 children of free sample for 2001-2004.

Indices concerning the physical development at birth corresponded to their gestational age. The majority of children had weight from 3500 to 4500g and height from 52 to 55 sm.

The basic group of newborns with hypoglycemia consisted of boys – 59%.

Hypoglycemia in newborns often had no clinical semiology or had monosymptomatic and atypical clinic.

In the experimental group the asymptomatic flow of hypoglycemia was identified in 62.2% of all children. Clinical manifestations of hypoglycemia were frequently observed in the moderately severe course.

Table 1

Data on hypoglycemia symptoms presence according to the disease course severity

	asymptomatic hypoglycemia course % (abs)	symptomatic hypoglycemia course % (abs)
mild hypoglycemia	59,5% (22)	40,5% (15)
moderately severe hypoglycemia	70% (28)*	30% (12)
profound hypoglycemia	56,8% (21)	43,2% (16)

*at value rate $p < 0,05$

As the data show (Table 1), even severe hypoglycemia, proceeding with decrease of blood glucose below 1,3 mmol/l, can be of an asymptomatic course.

The basic manifestation of a symptomatic hypoglycemia at newborns were:

1) hyperexcitability, tremor, irritability, twitchings, the raised reflex of Moro often combined with the increase of a muscular tone.

2) slackness, unemotional shout, decrease in muscular tone, sucking weakness.

3) posseting, anorexia, instability of body temperature.

The following results were obtained after carrying out the research «Distress Profile – excitation»:

Table 2

The research «Distress Profile – excitation» data

	«distress Profile – excitation» indices					
	- 1	- 0,5	- 0,2 + 0,2	+0,5	+1	+1,5
Mild hypoglycemia (n = 37)	2,7 % (1)	-	59,5 % (22)	16,2 % (6)	21,6 % (8)	-
Moderately severe hypoglycemia (n = 40)	5 % (2)	2,5 % (1)	70 % (28)	7,5 % (3)	10 % (4)	2,5 % (1)
Profound hypoglycemia (n = 37)	10,8 % (4)	5,4 % (2)	56,8 % (21)	5,4 % (2)	21,6 % (8)	-

When analyzing the data presented above, we revealed that the symptomatic hypoglycemia proceeded mostly in the form of a hyperexcitability syndrome.

Notably, the quantity of children with distress syndrome hypoglycemia ($p < 0,05$) increases at severe degree of hypoglycemia.

During the data analysis of neurologic inspection of these children aged 4 - 6 we found out that more than 87 % of them in the experimental group had the complaints to mood swings expressed in fast mood change: anger, low mood, behavior disorder combined with aggression, etc. Moreover, in experimental group children with disseminated focal signs in the form of muscular dystonia, mild pyramidal insufficiency with increase of muscular and periosteal reflexes, mild tongue deviation, signs of cerebellar insufficiency (staggering in Romberg's pose, uncertainty in doing finger-nose test) were registered more often than in the control group. Evidence and number of these symptoms varied, but prevailed in the group with sever and moderately severe neonatal hypoglycemia course.

Additionally, in the experimental group more than 50 % of children had signs of vegetative disturbance – acrocyanosis, mottled skin integuments, red proof dermographism. These signs were registered in a certain degree of intensity being disregulation of vegetative nervous system.

The detailed characteristics of neurologic disorders are summarized in the Table 3.

Table 3.

Neurological characteristics of patients

	Experimental group (n=114) % (abs)	Control group (n=37) % (abs)	P
Neurological status in norm	25,4% (29)	73% (27)	< 0,005
Bruxism	5,3% (6)	2,7% (1)	<
Enuresis	7,9% (9)	8,1% (3)	
Stutter	3,5% (4)	2,7% (1)	

Tics	1,8% (2)	-	0,005
Febrile convulsions	1,8% (2)	-	
Nightmares	6,1% (7)	2,7% (1)	
Residual encephalopathy	23,7% (27)	8,1% (3)	< 0,005
Attention deficit hyperactivity disorder	21,1% (24)	2,7% (1)	
Epilepsy	1,75 % (2)	-	< 0,005
ICP	0,9 (1)	-	

As appears from table 3, in control group healthy children prevail making 73%, whereas in the experimental one only 25,4 % of children had no neurologic pathology. Enuresis and stutter in both groups were determined approximately with identical frequency. Bruxism, tics, febrile convulsions and nightmares were registered more often in the experimental group is. High rates, i.e. 21,1 %, on attention deficit hyperactivity disorder were indicated in the experimental group. In the control group attention deficit hyperactivity disorder was found in one child that made 2,7 %. Residual encephalopathy was observed in 23,4 % of children of the experimental group, that is much higher compared with the control group (8,1%). The significant consideration should given to the presence of children with profound neurological disorders, such as epilepsy (1,75%) and ICP (0,9%) in the experimental group. In the control group the profound neurological pathology was not defined. Contingency between severity of neurological manifestation and presence of changes in neurosonogram during the neonatal period was not found (p = 0,1; Cramers V = 0,34).

The interrelation between severity of neurological pathology and presence of neonatal hypoglycemia semiology was identified (Table 4).

Table 4.

Indicators of neurological pathology contingency in children with neonatal hypoglycemia semiology

Presence of hypoglycemia clinical manifestations		Severity of neurological impairments			Total %
		mild	moderately severe	profound	
No	%	20,4%	32,7%	14,3%	67,35%
	Cell Chi-Square	1,21	0,8	0,15	
Yes	%	22,5%	6,1%	4%	32,65%
	Cell Chi-Square	2,5	1,65	0,29	

P = 0,03; Cramers V = 0,37

As shown in Table 4 newborns with symptomatic hypoglycemia had mild neurological manifestations whereas moderate severe and profound neurological pathologies are more often identified at hypoglycemia asymptomatic course in catamnesis.

Therefore, awareness about the features of glucose exchange, cause of disorders development, diagnostics and treatment methods makes possible to avoid the development of many pathological conditions, so to improve the quality of medical aid, to elevate the survival rate, and to decrease the degree of children's disability.

Conclusions:

1) The planned monitoring of glycemia is an important condition for prevention of development of neonatal neurological disorders.

2) Hypoglycemia syndrome can be of various clinical presentation, and in certain cases of asymptomatic course. In the presence of clinical semiology more often mild and moderately severe hypoglycemia is shown in the form of hyperexcitability syndrome, and profound one – distress syndrome.

3) Frequency and evidence of neurological impairments in infants correlates with severity of hypoglycemia in the neonatal period.

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