Diagnosis of hypoglycemia in children and newborns: A review

Abstract :

Blood glucose is an important component of the internal environment of the body, which is obtained from foods rich in carbohydrates and whose concentration in the blood is kept at a relatively constant level. It is quite clear that the problem under discussion is closely related to the doctrine of the constancy of the internal environment of a living organism and its constancy as a guarantee of a person being healthy. The founder of the static doctrine of the internal environment of a living organism (homeostasis) is Claude Bernard (1813-1878). Its composition is widely known: "The constancy of the internal environment is a guarantee of a free and independent life," which is still relevant today. In the clearest and clearest form of the provisions of his teachings, he formulated them in 1871, shortly before his death. For more than 130 years now, many scientific schools have been developing problems first formulated by great physiologists. Here are some of them: 1. Bernard C. was the first to establish the origin of glucose in the blood. Prove that blood glucose comes from the liver. 2. It is found that glucose accumulates in the liver and turns into glycogen. If the blood sugar is insufficient, the glycogen in the liver is converted back into glucose. He was the first to express the idea of the enzymatic nature of breaking down carbohydrates, and the presence of an enzyme that quickly breaks down sugar in the blood into lactic acid, which is found in the muscles, in the liver, and especially in the fetus. texture. 4. Bernard K was the first to describe the development of hyperglycemia in a patient suffering from post-haemorrhagic shock.

Key words: hypoglycemia, newborns at risk, preeclampsia.

Overview:

Currently, hypoi / or hyperglycemia is considered as a marker of an acutely developed critical condition, often reflecting its severity and insulin resistance. Not the least role in its development is played by counterinsular hormones, which provide the regulation of homeostasis in health and safety conditions. At first, hypoglycemia was described in children born to mothers with diabetes mellitus, therefore, damage to the central nervous system (CNS) was associated not only with disorders of glucose metabolism, but also with other pathogenetic links of diabetic fetopathy **(1).**

(2)described 8 children born to mothers with preeclampsia, in whom clinical signs (apnea, cyanosis, coma, convulsions) were associated with a decrease in glucose concentration and were stopped by its intravenous infusion. In addition, subsequently, 2 children from this group developed severe neurological disorders, and 1 child died. These observations served as the impetus for numerous studies, the purpose of which was to identify the critical level of glucose and the frequency of hypoglycemia in newborns.

PATHOGENESIS

Features of glucose metabolism in newborns. In a fetus, glucose provides approximately 50% of the total energy requirement of the body. Another half is amino acids and lactate. Glucose transplacentally enters the fetus along a concentration gradient, therefore, the glucose level in the fetal blood plasma is normally about 60–80% of the plasma glucose concentration of the mother (pregnant woman).

Fetal glucose consumption is quite high, it is approximately 7 g per 1 kg of body weight per day, or 5 mg / kg / min. This value is approximately equal to endogenous glucose production after birth. It has been established that the enzymatic systems involved in gluconeogenesis and glycogenolysis are present in the fetal liver, at least in the third trimester of pregnancy **(3,4)**, but remain inactive during the embryonic period if additional factors, such as maternal starvation, do not act. Although fetal liver

contains 3 times more glycogen than adult liver, at birth, liver glycogen accounts for only about 1% of total energy stores. Thus, the fetus is almost entirely dependent on the level of glucose in the mother's blood, since he himself cannot actively form it. If the tissue needs of the fetus cannot be met due to maternal hypoglycemia or placental insufficiency, the fetus can use alternative energy sources, such as ketone bodies obtained from fatty acid oxidation **(5)**

With a long-term low glucose intake, fetal tissues begin to produce glucose, first by glycogenolysis, and then by gluconeogenesis. In addition, there are complex changes in glucose metabolism that affect the growth and development of the fetus and have unpredictable metabolic changes in the future. Insulin does not pass transplacentally, and therefore its level in the fetus does not depend on its level in the mother. The β-cells of the fetal pancreas become sensitive to glucose concentration only in the last trimester of pregnancy. It is at this moment that they noticeably increase in volume **(6,7)**

Another situation occurs when the glucose supply to the fetus is low. The sensitivity of tissues to insulin increases, and the flow of glucose into cells increases. Continuing glucose deficiency leads to dysfunction of the β-cells of the pancreas and a decrease in their production of insulin. In addition, against this background, the proximal insulin signal is blocked in the liver, leading to an increase in the activity of phosphoenolpyruvate carboxinase (an enzyme of gluconeogenesis) and an increase in glucose synthesis, and, accordingly, hyperglycemia **(8).**It should be borne in mind that long-term hyperglycemia, just as it happens in gestation-dependent diabetes mellitus in women, can cause both a decrease in insulin synthesis and a decrease in tissue sensitivity to it,The above partly explains the tendency of children with intrauterine growth retardation, both to hypo- and hyperglycemia **(9).**

Balance between gluconeogenesis and glycogenolysissupported by enzymes: glucogen synthetase and phosphorylase, respectively. Protein kinases, activating an increase in cAMP in the hepatocyte, stimulate the activity of hepatic phosphorylase and inactivate glycogen synthetase. Thus, an increase in the level of cAMP in the hepatocyte stimulates glycogenolysis, and a decrease in gluconeogenesis **(10).**

The change in the level of cAMP in hepatocytes depends on hormones that regulate glucose metabolism. These are insulin and the so-called counter-insular (counter-regulating) hormones (glucagon, somatostatin, catecholamines, cortisol). The main counterinsular hormones are glucagon and adrenaline. Epinephrine stimulates the release of lactate and alanine from cells by stimulating peripheral β-receptors. Other hormones act permissively, and cortisol has a very short-term effect on blood glucose levels **(11).**

In most tissues, including the brain, glucose enters along a concentration gradient, but muscle, fat cells, and hepatocytes are insulin-dependent. Intracellular glucose is phosphorylated. When fatty acids are oxidized in cells by cytoplasmic glucose-6-phosphatase, its concentrations increase, inhibiting hexokinase activity and decreasing the cell's ability to phosphorylate glucose. In general, fat oxidation in cells reduces the production of glucose in them and stimulates gluconeogenesis in the liver. Thus, the body maintains a balance between the production of glucose and its use. In the last 30 years, it has become possible, using glucose labeled with radioactive isotopes, to evaluate glucose production in newborns**(12).**

It has been proven **(13)** that glucose infusion in adults suppresses endogenous glucose production by increasing insulin synthesis. The same phenomenon has been proven in healthy newborns, while in patients the indicated effect is less pronounced, especially in deeply-born babies. These studies demonstrate the variability of the counter-regulatory response in sick and premature infants.

High consumption of exogenous glucose in the third trimester of pregnancy by a pregnant woman leads to the development of hypocalcemia. This effect is associated with glucose stimulation of the synthesis of enteroglucagon and gastrin, leading to high production of calcitonin, followed by a decrease in the concentration of calcium in the blood**(14).** According to the same observations, glucose intake does not affect the concentration of magnesium in the blood. On the other hand, it has been shown that women who have had transient hypoglycemia during pregnancy are more likely to develop preeclampsia**(15).**

At birth, a newborn should have a fairly abrupt switch to self-glucose production. The creation of normoglycemia depends on a sufficient amount of glycogen, the maturity of the mechanisms of gluconeogenesis and glycogenolysis, as well as the integrated endocrine response. Of great importance is catecholamines, which activate, together with glucagon, hepatic phosphorylase, which stimulates glycogenolysis. Catecholamines also stimulate lipolysis and enzymes involved in gluconeogenesis.

Increased cortisol secretion stimulates hepatic glucose-6-phosphatase and the release of glucose by hepatocytes **(16).**

In the postnatal period, the maintenance of glucose homeostasis depends on the balance between the synthesis of glucose by the liver and its consumption by its tissues. In term newborns, glucose is consumed at a rate of 4 to 6 mg / kg / min, in a fetus in the third trimester of pregnancy and premature infants, approximately 1-1.5 times more (8-9 mg / kg / min). Some pathological processes occurring in the neonatal period lead to an increase in the consumption of glucose by tissues. For example, during hypoxia due to ineffective anaerobic glycolysis or cold stress due to activation of the sympathetic nervous system and increased production of thyroid hormones **(17).** On the other hand, with full enteral nutrition, glucose is synthesized by gluconeogenesis from amino acids and glycerol, galactose, formed by hydrolysis of lactose in the intestine, increases the synthesis of hepatic glycogen. Enteral nutrition also promotes the formation of intestinal peptides (incretins) that stimulate insulin secretion. Insulin inhibits the formation of glucose by hepatocytes, promoting the formation of glycogen **(18).**

DIAGNOSTICS OF HYPOGLYCEMIA IN NEWBORNS

In our opinion, the contradictory opinions regarding the question of the level of normoglycemia are associated with the use of various methods for determining the safe level of glucose.

Basically, 4 methods used by different researchers are indicated: statistical, metabolic, neurophysiological and follow-up assessment of neuropsychic development.

Most researchers point out that the type of feeding, the time of latching to the breast, the gestational age, etc., significantly affects the level of glycemia.

At about the same time, some researchers suggested defining hypoglycemia based on metabolic parameters. They proceeded from the position that if glucose is considered as a primary metabolic substrate, then the level of hypoglycemia should be taken as such a glucose concentration at which the concentration of alternative energy sources (ketone bodies, lactate **(19).**

It should be remembered that a decrease in blood glucose concentration within one to two hours after birth is observed in all mammals and reflects the process of adaptation to the conditions of extrauterine life. Simultaneously with a decrease in glucose concentration, the content of ketone bodies, non-esterified fatty acids, increases. In our country, such conditions are traditionally called borderline **(20).**

The incidence of hypoglycemia, defined as a glucose level less than 2.6 mmol / l, in children with various pathologies is presented in Table.1.

When interpreting the data obtained, it is necessary to take into account some points that can distort the true blood glucose level: the method of determination, the place of blood sampling, concomitant conditions, etc.

For example, it has been shown **(21)**that if whole blood taken for analysis is stored at room temperature, then the glucose concentration decreases by 7% per hour, so erythrocytes should be separated from serum as quickly as possible (centrifugation).

It has been found that arterial blood has higher glucose concentrations than venous blood. If there are microcirculation disorders, the concentration of glucose in capillary blood can be significantly changed.

Table 1. Concentrations of glucose (mmol /l) in healthy term infants **(22).**

Clock life	M±m	Median	Range hesitation
3	3,0±1,05	2,8	1,4–8,3
6	2,95±0,75	2,8	1,6–5,4
24	2,89±0,79	2,9	1,3–7,6
72	3,0±0,79	2,8	1,4–7,1

Table 2. Frequency of hypoglycemia in newborns with various pathologies **(23).**

Group	n	Average glucose level (mmol / L)	Median (mmol / L)	Oscillation range	Number of children with glucose levels <2.6 mmol / L
1	76	3,07 (0,51)	2,90	1,7–4,4	9 (11,8%)
2	15	3,13 (0,47)	3,1	2,5–4,2	1 (6,6%)
3	4	2,82 (0,5)	2,85	2,3–3,9	0
4	2	3,0	3,0	2,9–3,1	0
5	15	2,88 (1,7–3,5)	2,8	1,7–3,5	3 (20%)

Note. Group 1 - children with asphyxia; group 2 - children with sepsis; group 3 - children with birth trauma; group 4 - children with polycythemic syndrome; group 5 - those born to mothers with diabetes mellitus.

It is known that the level of glucose in blood plasma is, on average, 18% higher than in whole blood; therefore, the hematocrit value significantly affects this indicator. This is especially true for newborns, given their tendency to polycythemia **(24).**

Glucose oxidase (colorimetric method) and glucose electrode method (using blood - gas analyzer) - 2 widely used methods for the analysis of blood glucose - are accurate and reliable. When testing, it is important to remember that the level in whole blood is 10-15% less than in the sample plasma. It should also be remembered that glucose levels drop from 14 to 18 mg / dL per hour,the value of glucose determination in arterial blood is higher than capillary values, and capillary values are higher than in venous blood. Continuous glucose monitoring is recommended for very low birth weight infants to avoid re-sampling **(25).**

CLINICAL PICTURE

The concentration of glucose in the blood of the umbilical cord vein in a newborn is 60 to 80% of the concentration in the venous blood of the mother. Immediately after birth, its concentration decreases, and 2–3 hours after birth, it begins to increase and stabilize**(26).** This increase is due to the "release" of glucose by the liver and is, as we have already indicated, 4-6 mg / kg / min. It has been proven that not only glycogenolysis, but also gluconeogenesis is activated in a newborn child. It is known that many pathological processes can disrupt the adaptation mechanisms of the newborn, and therefore, as with the development of other forms of pathology, it is customary to distinguish risk factors in neonatal hypoglycemia (Table.3). Accordingly, in children from these groups, it is necessary to monitor the concentration of blood glucose.

Unfortunately, there are no specific symptoms of hypoglycemia, and since its clinical manifestations can occur in other diseases of the neonatal period, such as asphyxia, sepsis, and other metabolic disorders, the so-called Whipple's triad is used to diagnose "neonatal hypoglycemia":

Table.3. Groups of high risk of newborns for the development of hypoglycemia**(27,28,29)**

Associated with altered maternal metabolism		Associated with disorders in the newborn		Others	
1	Glucose administration during labor	1	Adaptation disorders	7	A iatrogenic
2	Medications	2	Asphyxia of a newborn	8	Into congenital heart defects
	A terbutaline, ritodrin, propranolol	3	Hypothermia		Disorders of fetal development
	Oral antiglycemic drugs	4	Increased blood viscosity	9	Hyperinsulinism
3	Diabetes during pregnancy or	5	Polycethemic syndrome	10	Endocrine diseases

	impaired glucose tolerance				
4	Preeclampsia or increased blood pressure during pregnancy	6	Infectious process	11	Metabolic disorders
5	The birth of previous children with a large body weight				

Conclusion

Thus, the literature data allow us to conclude that the body of a newborn child with a lack of glucose can mobilize fatty acids, as well as form and utilize ketone bodies. It is possible that other mechanisms are involved in hypoglycemia. For example, in a number of works ,it was proved that neurons of the central nervous system of newborn puppies can oxidize amino acids and lactate. The protective mechanisms in hypoglycemia also include an increase in the volumetric velocity of cerebral blood flow. It increases especially significantly in premature infants at a glucose concentration of less than 1.7 mmol / L.

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