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A CLINICAL CASE OF A CHILD WITH TYPE I DIABETES MELLITUS WITH THE SUBSEQUENT DEVELOPMENT OF ENCEPHALOPATHY

© Nina V. Evdokimova, Aleksey A. Timofeev, Anna N. Zav`yalova, Milena N. Yakovleva, Kristina V. Skobeleva

Saint Petersburg State Pediatric Medical University. 2 Lithuania, Saint Petersburg 194100 Russian Federation

Contact information:
Nina V. Evdokimova — Candidate of Medical Sciences, Assistant at the Department of Propaedeutics of Childhood Diseases with a course in General Child Care. E-mail: posohova.nina2014@yandex.ru ORCID: https://orcid.org/0000-0001-9812-6899 SPIN: 6552–7359

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Abstract. The aim of the work was to review a clinical case of a child with type 1 diabetes mellitus (DM1) with severe cognitive impairment due to the development of diabetic encephalopathy. The analysis of the preceding factors of the manifestation of DM1 in a child is carried out, as a result of which, against the background of prolonged hyperglycemia and insulin deficiency, there was an increase in metabolic acidosis with a subsequent complication in the form of diabetic encephalopathy (DE). Subsequent metabolic and hypoxic changes in the child's body led to a decrease in cognitive functions.DE is a characteristic complication of DM1 in children, since its development is mainly due to ineffective metabolic control, as well as incorrectly selected therapy. An assessment of anthropometric data, as well as laboratory parameters, was carried out before and after adjusting the treatment of DM1.

Keywords*: type 1 diabetes mellitus (DM1), diabetic encephalopathy (DE), diabetic coma, metabolic acidosis treatment of DM1, children*

КЛИНИЧЕСКИЙ СЛУЧАЙ РЕБЕНКА С САХАРНЫМ ДИАБЕТОМ 1-го ТИПА С ПОСЛЕДУЮЩИМ РАЗВИТИЕМ ЭНЦЕФАЛОПАТИИ

© Нина Викторовна Евдокимова, Алексей Алексеевич Тимофеев, Анна Никитична Завьялова, Милена Николаевна Яковлева, Кристина Владимировна Скобелева

Санкт-Петербургский государственный педиатрический медицинский университет. 194100, г. Санкт-Петербург, ул. Литовская, 2

Контактная информация:
Нина Викторовна Евдокимова — к.м.н., ассистент кафедры пропедевтики детских болезней с курсом общего ухода за детьми. E-mail: posohova.nina2014@yandex.ru ORCID: https://orcid.org/0000-0001-9812-6899 SPIN: 6552-7359

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Резюме. Цель работы — обзор клинического случая ребенка с сахарным диабетом 1-го типа (СД1) с выраженным нарушением когнитивных способностей из-за развития диабетической энцефалопатии. Проведен анализ предшествующих факторов манифестации СД1 у ребенка, вследствие которых на фоне длительно протекавшей гипергликемии и дефицита инсулина случился метаболический ацидоз с последующим осложнением в виде диабетической энцефалопатии (ДЭ). Дальнейшие метаболические и гипоксические изменения в организме ребенка привели к снижению когнитивных функций. ДЭ является характерным осложнением СД1 у детей, поскольку ее развитие обусловлено преимущественно неэффективным метаболическим контролем, а также некорректно подобранной терапией. Была проведена оценка антропометрических данных и лабораторных показателей до и после корректировки лечения СД1.

Ключевые слова: *сахарный диабет 1-го типа, диабетическая энцефалопатия (ДЭ), диабетическая кома, метаболический ацидоз, дети*

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INTRODUCTION

In recent years, the morbidity of diabetes mellitus has increased significantly in developed countries with high economic growth. In a number of countries, there is a disproportionately high increase in the incidence of type 1 diabetes mellitus (DM1) in children under 5 years of age. According to the International Diabetes Federation (IDF) for 2021, the total number of children and adolescents (under 19 years) with DM1 in the world is more than 1,2 million people, of which more than half (54%) are children under 15 years of age. The morbidity of DM1 is increasing every year. Annually, more than 108 thousand children aged 0 — 14 years and more than 41 thousand adolescents aged 15 — 19 years fall ill [3, 4, 12].

In most countries, the onset of DM1 develops in up to 90% of cases, most often in childhood, while among older age groups the prevalence of DM1 is from 5 to 10% [3, 4, 6]. The peak incidence occurs during the period of early puberty and is detected in girls 1–2 years earlier than in boys. By the end of puberty, the morbidity decreases for children of both sexes [8, 17].

DM1 is accompanied by complications of the kidneys, retina, peripheral nervous system and blood vessels. Recently, diabetic complications of the central nervous system (CNS) have been studied more closely. There is no generally accepted definition of diabetic encephalopathy (DE), but it does not include cerebral edema that develops during ketoacidosis or hypoglycemia.

Clinically, DE manifests itself as neurosis-like disorders and psychotic-like experiences, organic, neurological and autonomic clinical presentation [8]. It includes characteristic biochemical, electrophysiological and morphological changes that can lead to cognitive impairment and significantly reduce the quality of life of both the patient and his relatives [3, 10, 16].

DE in its pure form occurs only in patients with DM1 (in 80% of cases) since its development is mainly due to ineffective metabolic control [3, 4].

According to epidemiological data, the onset of diabetes mellitus at an early age has a major negative impact on the developing brain. The application of single-photon emission computed tomography has shown a reduction in cerebral blood flow in the frontal lobe areas and in the basal ganglia. Chronic hyperglycemia is associated with a decrease in neurophysiological test results and structural changes [4, 5].

ENCEPHALOPATHY IN TYPE I DIABETES MELLITUS

Recently, there has been increasing evidence of adverse effects of DM1 on the CNS and cognitive functions. Studies of children with DM1 have shown impairments in attention, processing speed, executive functions, intelligence and memory [5, 7, 14].

The mechanism underlying DE in DM1 is multifactorial and is still far from being fully understood (Fig. 1). It is assumed that insulin deficiency and its impact on other neurotrophic factors play an important role in mediating the effects of neurotransmitters and ensuring interneuronal interactions. Concomitant oxidative stress and activation of apoptosis may be associated with hyperglycemia, but perhaps to a greater extent with impaired insulin signaling, which can be corrected by C-peptide and intranasal administration of insulin [1, 4]. All disorders over time lead to neuronal cell loss and disintegration of neuronal networks that are the basis of cognitive function.

White matter atrophy associated with hyperactivation of receptors for advanced glycation end products is revealed [8, 10, 13].

The mechanism of cells and tissue damage by endogenous and exogenous AGEs (advanced glycation end products) is as follows:

1) activation of receptor-mediated signaling pathways leading to oxidative stress, inflammation and gene expression modulation;
2) changes in the structure and function of stable long-lived proteins, in particular connective tissue proteins due to irreversible cross-linking with AGEs;
3) glycation of intracellular proteins and lipids leads to disruption of cellular function [2, 9, 11].

White matter changes relate to decreased expression of myelin protein, oligodendrocyte loss, and are associated with increased astrogliosis, which is accompanied by increased expression of receptors for advanced glycation end products, tumor necrosis factor-alpha and interleukin-6 in the white matter [2].

Absolute insulin deficiency leads to decreased utilization of glucose by insulin-dependent tissues. Hyperglycemia develops in the blood, and severe energy "starvation" occurs in the tissues. This contributes to a sharp increase in the level of all insulin-counteracting hormones in the blood (glucagon, catecholamines, cortisol, adrenocorti-

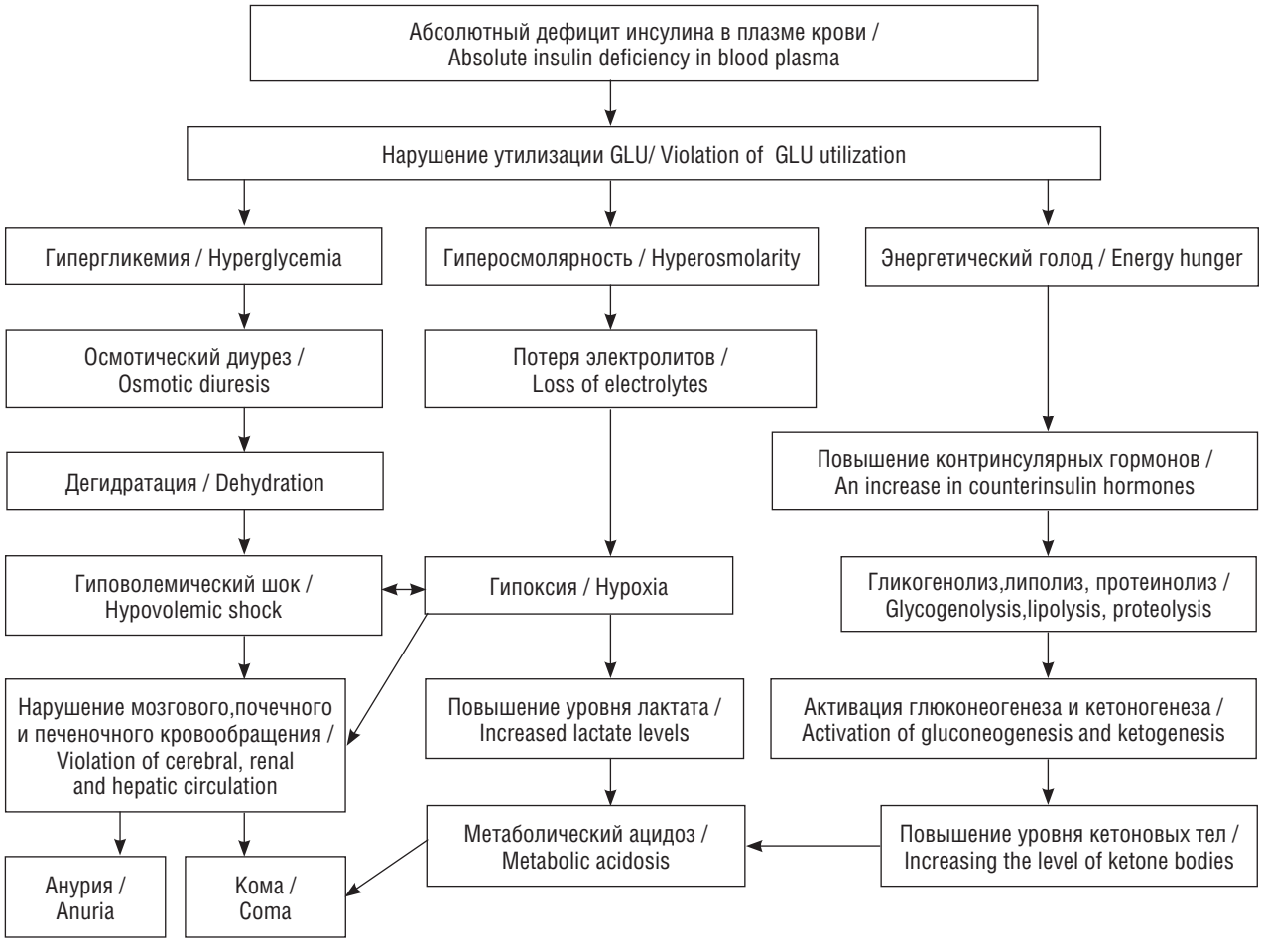

Fig. 1. The mechanism of development of diabetic encephalopathy in DM1

Рис. 1. Механизм развития диабетической энцефалопатии при СД1

cotropic hormone (ACTH), somatotropic hormone (STH)). In the body, lipolysis, glycolysis and proteolysis are activated, which leads to the formation of substrates for gluconeogenesis in the liver and kidneys. Gluconeogenesis in combination with impaired glucose utilization by tissues is the most important cause of rapidly increasing hyperglycemia, the increase in plasma osmolarity, intracellular dehydration, and osmotic diuresis [10, 11, 13].

In turn, activation of lipolysis leads to the liver not using fatty acids for triglyceride synthesis. As a result, some fatty acids are included in beta oxidation and ketogenesis. Ketone body synthesis occurs from amino acids such as isoleucine, leucine and valine, which accumulate as a result of excessive proteolysis. Accumulation of acetyl-CoA, acetoacetate and beta-hydroxybutyrate leads to depletion of alkali reserve in the blood and the development of metabolic acidosis. Synthesis of ketones by the body is higher than their consumption and utilization during excretion in urine, which also leads to metabolic acidosis (diabetic coma) [15].

Proteolysis disrupts the nitrogen balance and azotemia develops. Intracellular dehydration is replaced first by extracellular and then by general dehydration of the body. There is a reduction in tissue and renal blood flow, a deficiency of electrolytes Na^+, K^+, Cl^- is observed. Dehydration leads to hypovolemia, which is the cause of a reduction in cerebral, renal and peripheral blood flow. This intensified the already existing hypoxia in CNS and peripheral tissues. Tissue hypoxia promotes in these tissues the activation of anaerobic glycolysis and the accumulation of lactic acid, which can cause lactic acidosis [10, 11, 17].

Thus, the severity of the patient's condition is due to active dehydration of the body, decompensated metabolic acidosis, electrolyte deficiency, hypoxia, hyperosmolarity and can be complicated by diabetic encephalopathy and, in serious cases, coma [1, 4, 8].

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The pathogenesis of DE is associated with two main types of disorders: metabolic and hypoxic. The development of microangiopathy is mediated by the accumulation of low-density lipoproteins (LDL) in the blood vessel wall, activation of lipid peroxidation (LPO) processes, increased formation of free radicals, and suppression of the synthesis of prostacyclin, which has an antiplatelet and vasodilatory effect. The progression of microangiopathy leads to a reduction in endoneurial blood flow with the development of hypoxia, which contributes to the switching of the energy metabolism of the nervous tissue to ineffective anaerobic glycolysis, during which only two molecules of adenosine triphosphate (ATP) are formed from one molecule of glucose, while in the reaction of aerobic glycolysis — 38 molecules. As a result, the concentration of phosphocreatinine in neurons decreases, the lactate content increases, which leads to the development of oxygen and energy starvation of the nervous tissue. The reduction in endoneurial microcirculation and aggravation of nerve fiber function disorders contribute to a decrease in production and an increase in destruction of nitric oxide (NO), which has a vasodilatory effect, which can become one of the causes of the development of arterial spasm, that is an important pathogenetic mechanism for the development of arterial hypertension in diabetes mellitus [3, 4, 8, 10, 11]. In addition to the pathogenetic significance of endoneurial blood flow disturbances, metabolic disorders also play an important role. It has been established that the decrease in the impulse conduction velocity in myelinated nerve fibers is caused by a pathologically high intra-axonal concentration of Na^+ ions, in the development of which the main role belongs to a decreased Na^+/K^+-ATPase activity, which causes secondary vascular diseases, neurotrophic disorders, neurotoxicosis and, as a consequence, structural changes in neurons, as well as a violation of nerve conduction velocity. Diabetes mellitus has a huge impact on the white matter loss of the brain [8, 13, 15].

CLINICAL CASE

A girl, 5 years 7 months old, was admitted to the emergency department in clinic of the hospital No. 1 with classic symptoms of diabetes mellitus and ketoacidosis, as well as complaints of weakness and sluggishness. Due to the untimely seeking medical help, the patient's condition upon admission was extremely serious. Laboratory data: hyperglycemia (25 mmol/l), ketoacidosis, increased glycated hemoglobin, glucosuria. On the third day, against the background of the administration of high doses of insulin, clinical death was recorded due to a sharp fall in blood glucose levels with the subsequent formation of brain herniation. A nasogastric tube was inserted into the patient. On the 4th day from the onset of the disease, the girl was transferred to the clinic of hospital No. 2 in extremely serious condition. The level of disorders of consciousness: grade II deep coma. Early anamnesis without features. The patient was not registered with medical specialists. A brain magnetic resonance imaging (MRI) was performed: signs of hypoxic-ischemic encephalopathy in the form of diffuse edema in the white matter of the brain, ischemic/necrotic changes in the basal ganglia on both sides, multifocal cortical laminar necrosis. Expansion of the external and internal cerebrospinal fluid spaces. According to the results of multispiral computed tomography of the brain, atrophic changes in the brain and diffuse ischemia were observed. Triventricular hydrocephalus was noted.

Three months later, the patient was transferred to hospital 3 with the diagnosis: mixed encephalopathy, organic brain injury of mixed genesis (hypoxic-metabolic), decerebrate rigidity, structural metabolic epilepsy, type 1 diabetes mellitus, severe protein-energy malnutrition.

Comprehensive drug treatment was carried out, which included intensive insulin therapy (levemir, novorapid), anticonvulsants (keppra) and antiepileptic (clonazepam, convulex) drugs, muscle relaxants (baclosan), anxiolytics (relanium), carminatives (espumisan baby), enzymes (creon), a strict diet using nutrient mixtures (clinutren+Hipp HA1).

Against the background of a properly selected diet and drug treatment, positive dynamics were noted in leveling the correlation between the expected and obtained results of BMI from 11,75 to 14,49 (Fig. 2); the child's weight from 15 to 19,5 kg (Fig. 3, a, b), fat mass from 2,28 to 3,23 kg (Fig. 4); fat-free mass from 12,72 to 14,21 kg (Fig. 5), total water from 9,31 to 10,4 l (Fig. 6), basic exchange from 982 to 1031 kcal (Fig. 7).

During the treatment, an increase in glucose levels was periodically noted, which was stopped by timely administration of insulin in an appropriate dose (Fig. 8).

By the age of 5 years and 10 months, positive dynamics in the patient's physical development were revealed: she grew by 3 cm, gained 4,5 kg of body mass. A decrease in body fat mass and a compensatory increase in basic exchange were noted.

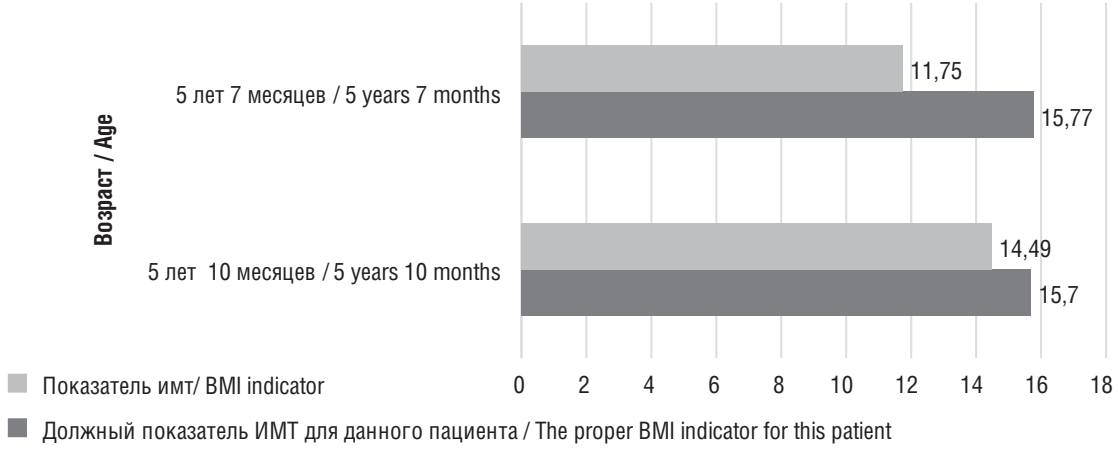
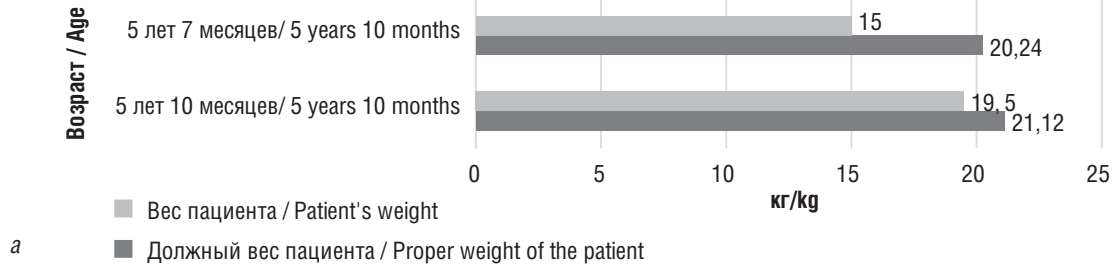


Рис. 2. График соотношения имеющегося индекса массы тела с должным

Fig. 2. A graph of the ratio of the available body mass index to the proper one



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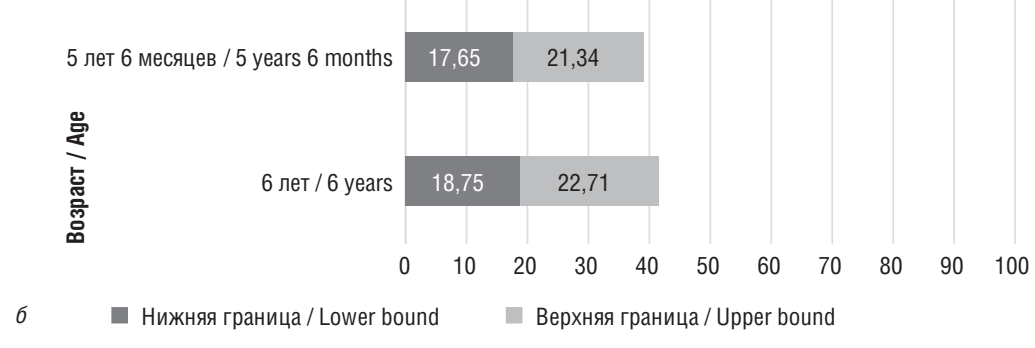

б

Fig. 3. Graph of weight dynamics (*a*), A graph of the patient's body weight compared to the norm corresponding to a given age (*b*)

Рис. 3. График динамики массы (*а*), график массы тела пациента в сравнению с нормой, соответствующей данному возрасту (*б*)

The girl could independently swallow pureed food, suck from a bottle, and her mother sometimes gave her additional water from a cup. The child was discharged from the hospital with recommendations under the supervision of a pediatric endocrinologist at her place of residence.

CONCLUSION

The uniqueness of this case is that it is necessary to take into account the possible acute development of DE at the onset of the disease. In this regard, an individual approach to the treatment of such children is needed in a specialized hospital under the supervision of a group of medical specialists (endocrinologist, gastroenterologist, neurologist, nutritionist). Probably, the most effective treatment of diabetes mellitus in these conditions is the installation of an insulin pump and non-invasive devices for monitoring blood glycemia. The success of therapy also depends on the patient's

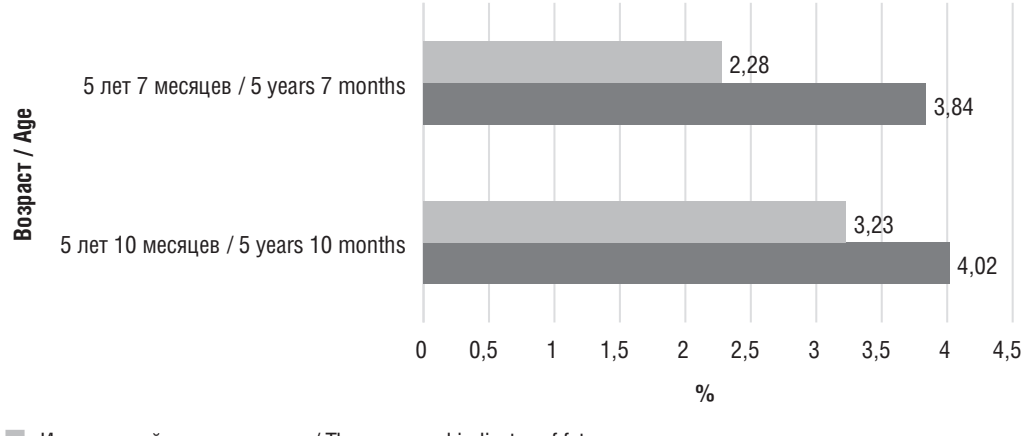

Fig. 4. A graph of the dynamics of fat mass

Рис. 4. График динамики жировой массы

Fig. 5. Graph of the dynamics of fat-free mass

Рис. 5. График динамики безжировой массы

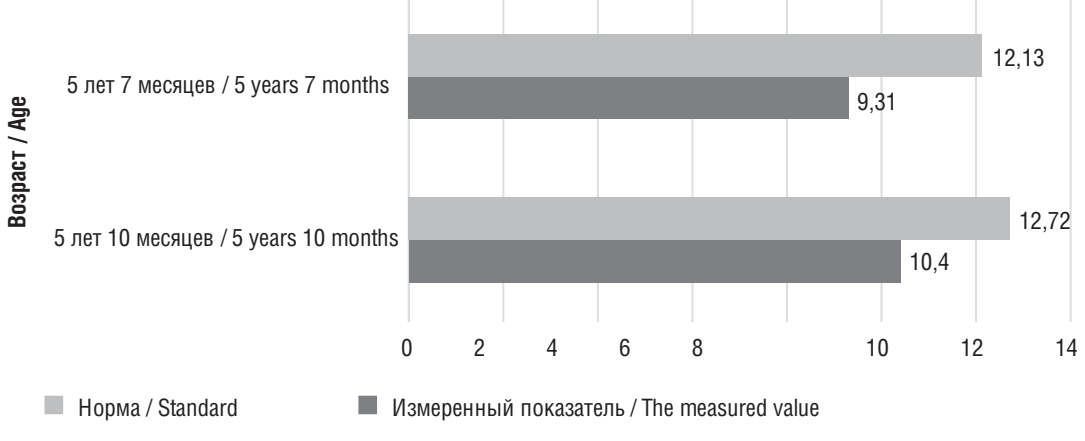

Fig. 6. A graph of the ratio of the amount of total water in the norm and in this patient

Рис. 6. График соотношения количества общей воды в норме и у данного пациента

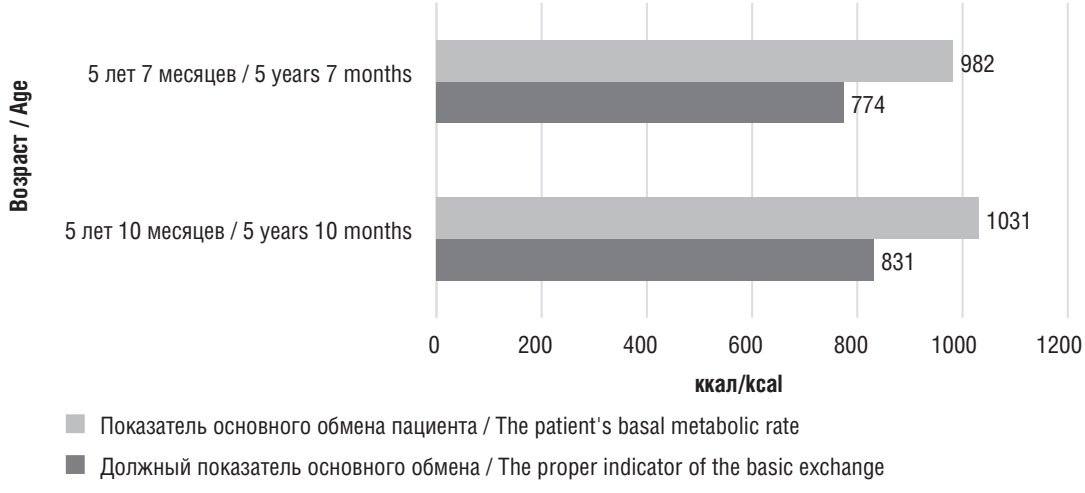

Fig. 7. The dynamics of changes in the basic exchange

Рис. 7. Динамика изменений основного обмена

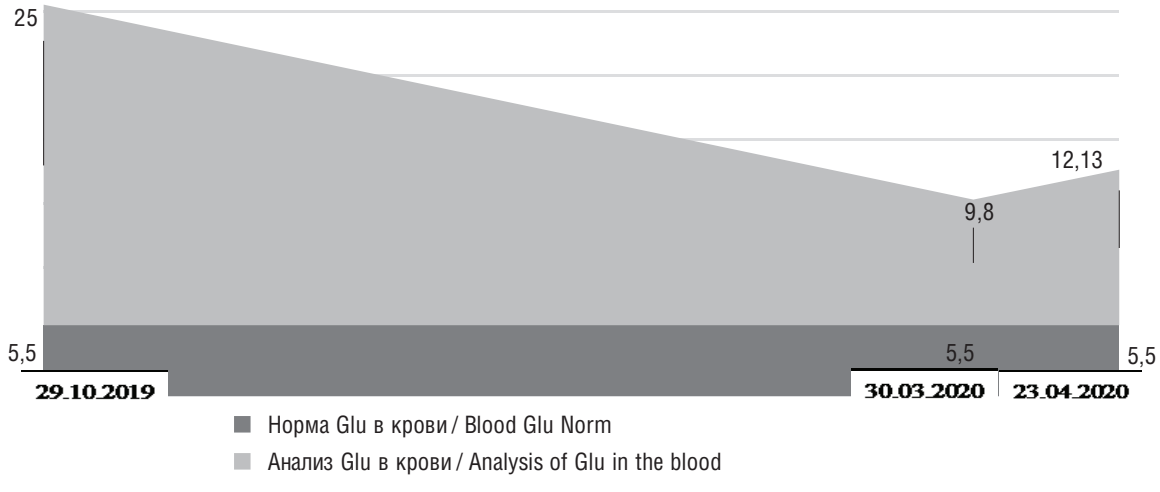

Fig. 8. Dynamics of changes in the concentration of GLU in the blood

Рис. 8. Динамика изменения концентрации GLU в крови

nutrition, which can be ensured by insertion a gastrostomy. The child's parents should be clearly informed about the correct gastrostomy care.

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.

Competing interests. The authors declare that they have no competing interests.

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Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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