Possible manifestations of cognitive impairment in children suffering from pancreatic dysfunction

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Abstract

The article investigates possible manifestations of cognitive impairment in children suffering from pancreatic dysfunction. The authors point out that improving blood glucose control in patients with type I diabetes mellitus is an important factor in reducing cognitive impairment, especially in children. At the present stage, the treatment of cognitive dysfunction has become an interdisciplinary multidisciplinary complex treatment, which in the future will not only improve the quality of life of patients, but also minimize the above-mentioned dysfunction as such.

Keywords

Cognitive impairment, Pancreas, Functional disorder, Ketoacidosis, Type 1 diabetes mellitus

Introduction

Cognition is the process of obtaining new knowledge by a person, the discovery of previously unknown. Cognitive functions are involved in the act of cognition, by which it is customary to understand the most complex functions of the brain, with the help of which the process of rational cognition of the world is carried out [1]. Under certain conditions, cognitive disorders may occur in the human body, which lead to a decrease in memory, mental performance and other cognitive functions compared to the baseline level (individual norm).

It is believed that the underlying mechanisms of cognitive impairment (CI) include insulin resistance, inflammation, oxidative stress and neurovascular dysfunction [2]. CI is increasingly recognized as the main complication of diabetes and is associated with complications associated with the treatment of diabetes. Diabetes is a group of metabolic diseases characterized by high blood glucose levels. In particular, the onset of type 1 diabetes mellitus (DM1) is relatively rapid, there is absolutely not enough insulin in the body, and ketoacidosis may occur.

Type 1 diabetes mellitus (DM1) is one of the most common chronic diseases diagnosed in childhood. Treatment of diabetes in young children is associated with a number of problems, as they are more prone to sharp fluctuations in glucose levels at a time when their developing brain is undergoing large-scale changes in the process of maturation [3]. The peculiarities of the formation of the main mechanisms of the nervous system in early childhood are expressed in the fact that the developing brain can be especially vulnerable to extreme glycemic indicators, which has a long-term impact on its development and cognition associated with it. The introduction of new diabetic technologies can reduce these complications.

The aim of the study is to study possible manifestations of cognitive impairment in children suffering from pancreatic dysfunction.

Materials and methods

When writing the paper, a study of sources describing in detail the mechanism and features of the development of cognitive impairment in children and adolescents suffering from diseases caused by disorders of the pancreas – in particular, type 1 diabetes mellitus, as well as works that identify areas for the development of new diabetic technologies that can reduce the level of possible complications in such patients. The data obtained were described and systematized using comparative and analytical research methods.

Results

Diabetes mellitus (DM) is a heterogeneous chronic metabolic disorder characterized by hyperglycemia, which is a global epidemic public health problem [4].
Premature mortality from diabetes is caused by long-term diabetic complications, including retinopathy, nephropathy, peripheral vascular diseases and heart diseases (micro- and macrovascular diseases).

Hyperglycemia combines type 1 and type 2 diabetes mellitus, the two most common forms of DM, differing both in epidemiology and etiology. Type 1 diabetes mellitus (DM1) most often occurs in adolescence due to autoimmune destruction by beta cells of the pancreas, which leads to an absolute deficiency in insulin production. Type 2 diabetes (DM2) includes 90-95% of cases of diabetes mellitus and is a pathology characteristic of the elderly, as a result of insulin resistance, accompanied by a progressive deficiency of beta cells.

Epidemiological studies have shown that diabetes is associated with an increased risk of dementia and the occurrence of serious cognitive dysfunction.

The severity of cognitive deficits depends on the type of diabetes, the age of onset of the disease and concomitant diseases. Patients with early onset of the disease, aged 4 to 6 years, have a potential clinically significant picture of impairment of all cognitive functions, including intelligence and memory. On the contrary, children diagnosed after 6 or 7 years are associated only with changes in verbal intelligence and the speed of psychomotor reactions, and sometimes executive functions, but there are no negative changes in the mechanisms responsible for learning and memory [5]. For example, in a sample of patients diagnosed with DM1 and monitored for 18 years, there was a moderate long-term decline in cognitive function [6].

The process of synaptic brain development and the level of metabolism are most active in childhood. There is an increase in synapse density during early postnatal cortical development, followed by a discrete period of synaptic contraction, which usually occurs in adolescence [7]. During the same period, there is an active increase in brain volume, which by the age of 6 corresponds to 90% of the adult brain volume [8].

Also, before the child reaches the age of 9-10 years, there is an increase in the volume of gray matter, the volume of the cortex and the average thickness of the cortex, after which, due to the reduction of synapses, the process of their reduction begins. If we talk about the volume of white matter, it gradually increases in childhood, adolescence and even in early adulthood [9]. In addition, it should be noted that at the age of 2 to 3 months and up to 4 years, the consumption of glucose by the brain increases sharply, this process is active in the first decade of life, after which it decreases to the level of an adult [10].

Specialists who compared the brain structure and neuropsychological functioning in young children with DM1 and a control group of the same age noted a change in the brain structure in children with DM1 [11]. Another group of specialists was looking for an answer to the question of whether the previously described brain and cognitive differences in children with DM1 persist, worsen or improve as children grow up to puberty, and the links with hyperglycemia were studied. The results showed that the total brain volume, gray and white matter volumes, as well as full-scale verbal IQ were lower in the group with DM1 at the age of 6, 8, 10 and 12 years. Brain volumes and cognitive indicators had a negative correlation with glycemic control (HbA1c and glucose sensor) [12].

Evaluation of the brain structure of young people who were diagnosed with DM1 in childhood was also carried out using MRI. In addition, cognitive abilities were assessed in this group also through neuropsychological tests. The results of the study showed that the volumes of the lateral ventricles were 37% larger, and ventricular atrophy was more common in the group with early onset of DM1 compared with the group with late onset of DM1 [13]. Also, the results of the above study did not indicate that the intellectual level of young people with early diabetes is much lower than that of their peers who were diagnosed with diabetes later. It should be assumed that diabetes with early onset may adversely affect the development of the nervous system.

A study of a separate group of children suffering from DM1 by calculating the values of fractional anisotropy (FA) and apparent diffusion coefficient (ADC) showed that all participants had significant changes in the values of FA and ADC in large areas of the brain. Such changes may be early signs of damage to myelin fibers or axon degeneration [14].

Another group of researchers evaluated the correlates of cognitive abilities and microstructural changes in WM in young children with DM1 using diffusion tensor imaging (DTI) compared with healthy people of the appropriate age and gender in the control group. DTI provides a quantitative assessment of the integrity of WM by measuring the diffusion of water molecules in brain tissue. The authors found that compared with healthy controls, children with DM1 had significantly
lower values of axial diffusion in the temporal and parietal regions without significant differences between the groups in FA and radial diffusion. They found a significant positive correlation between HbA1c levels and structural differences in BV (measured by radial diffusion). A higher HbA1c value significantly correlated with lower overall intellectual functioning measured using a full-scale intelligence quotient [15].

In general, the researchers conclude that children and adolescents with DM1 are more likely to cope worse with tasks that require constant attention, fast data processing speed, memory and visual-spatial functioning, compared with their peers who do not suffer from diabetes. However, it is believed that despite the equivalent cognitive and behavioral functioning of children with DM1 and the control group of the same age without diabetes, young children with DM1 showed increased activation in the areas of executive control (for example, in the dorsal anterior cingulate cortex, lower frontal gyrus, cerebellum and supramarginal gyrus) during the task requiring attention. The magnitude of this increase was significantly correlated with the lack of deactivation of the posterior node of the default mode network, which indicates the supposed compensatory role of brain function in DM1, whereby higher activation in task-related areas acted as compensation for DM1-related disturbances in the default mode network function and contribute to levels of behavioral performance, equivalent to the levels of their non-diabetic peers [16].

Discussion
Children's patients who have been diagnosed with DM1 are at risk of developing hypoglycemia. Since children lack expressive speech skills and have cognitive immaturity, they cannot always identify the first signs of hypoglycemia and inform adults about it.

Several studies of patients with DM1 in childhood have documented an association between severe hypoglycemia (with seizures or loss of consciousness) and brain changes. For example, one group of researchers found significant differences between young patients with DM1 and healthy control groups with respect to the total volume of gray matter or myelination of white matter. However, in the diabetic group, a history of severe hypoglycemia was associated with a smaller volume of gray matter in the left upper temporal region [17]. Another group of authors concluded that patients with DM1 with early onset diabetes had lower levels of gray matter volume density associated with poorer glycemic control and a higher frequency of repeated severe hypoglycemic events [18].

Many studies have assessed the extent and nature of cognitive dysfunction in children with DM1 and the possible effects associated with severe hypoglycemia and poor cognitive outcomes, but the results of such studies have often been controversial. Thus, individual cross-sectional studies have shown that the effect of severe hypoglycemia on cognitive dysfunction was significant; however, longitudinal studies have shown that severe episodes of hypoglycemia were not associated with cognitive dysfunction. Accordingly, it can be concluded that severe hypoglycemia may be a likely cause of cognitive decline in children with DM1. However, the long-term effects of severe hypoglycemia on cognitive dysfunction require additional confirmation.

As for hyperglycemia, there is an opinion in the literature that its chronic effects can also affect the brain of young patients. According to the authors who conducted the study of such patients by MRI, the relationship between the variability of glycemia, especially hyperglycemia, and cognitive function is more pronounced in young children with earlier onset and longer duration of diabetes, which further emphasizes the vulnerability of the brain in this age group.

Also in this context, it was reported that there are trends in the relationship between executive functioning, learning, memory and hyperglycemia, suggesting that structural brain changes in young people with diabetes have a subtle but measurable effect on cognitive functions already 2 years after the onset of DM1. These data indicate that dysregulation or variability of glycemia has serious consequences for young children, as well as for the structure and functions of the brain.

A large group of young children (aged 4 to < 10 years) with DM1 was compared by individual specialists with a control group of healthy people of the same age [19]. The results showed that diabetes with early onset significantly affected the development of general and regional volumes of gray matter, while the differences between the groups increased over time. Notably, in the diabetic group, slower growth was most closely associated with hyperglycemia and glycemic variability, as measured by several indicators, including glycated hemoglobin and extensive quarterly continuous glucose monitoring (CGM) data.

Chronic hyperglycemia can lead to the formation of glycation end products and their receptors, nu-
clear factor-kB, increased oxidative stress and even neurodegeneration [20]. These glycemic correlations confirm the opinion that increased glucose variability can damage developing neurons and myelin in children with DM1, and are consistent with observations in animal models of streptozotocin-induced diabetes, which demonstrate in vivo degenerative changes in neurons and glia, a violation of myelin sheaths and a decrease in myelin content in hyperglycemia.

Changes in the composition of brain sphingolipids (ceramides and sphingomyelin) caused by hyperglycemia can also provoke membrane rearrangement in some cell populations, which can disrupt the transmission of cellular signals and cause damage to brain tissue. The final mechanism of the observed changes is multifactorial.

The development of the processes of central nervous system damage in children with early diabetes may have a delayed, progressive and cumulative effect on neuropsychological outcomes and cognitive functions over time. These results may be subtle in terms of cognition, but they are likely to be reflected in the future.

Extreme glycemic indices are associated with a deterioration in general cognition, as well as with a decrease in memory performance [21]. A history of chronic hyperglycemia turns out to be more dangerous than previously thought. Neurocognitive deficits manifest themselves in many cognitive areas, including executive function and information processing speed. One study showed that variability in glucose levels may have a greater adverse effect on the developing brain than prolonged high or low glucose levels [22]. According to previous studies, there were 2 possible mechanisms by which variability in blood glucose levels leads to cognitive dysfunction. Thus, it was found that glycemic variability is associated with increased production of reactive oxygen species, which can damage the central nervous system [23]. Another mechanism has shown that fluctuating glucose levels can have a more toxic effect on the occurrence of oxidative stress than constant high glucose levels, which can lead to mitochondrial dysfunction and damage to neurons [24].

Minor brain damage can directly affect the psychological and mental consequences. Impaired executive function and mental health, in turn, can affect patients’ commitment and their ability to adapt to the world around them.

As a serious and special complication of DM1, diabetic ketoacidosis can cause serious physical and psychological damage to patients, including cognitive decline. Diabetic ketoacidosis is a typical and extremely serious complication of severe hyperglycemia in DM1, which could lead to coma or death. Meanwhile, both hyperglycemia and diabetic ketoacidosis can affect cognitive functions [25].

Diabetic ketoacidosis is a high risk factor for CI in patients with DM1. The study reported that cognitive dysfunction was associated not only with chronic hyperglycemia, but also with acute metabolic brain damage – diabetic ketoacidosis causes similar brain damage [26]. It is important to note that the neuroinflammatory reaction caused by diabetic ketoacidosis is of a long-term nature, which suggests that diabetic ketoacidosis may contribute to long-term cognitive decline in patients with diabetes. Although the underlying mechanisms have yet to be elucidated, as a serious complication of hyperglycemia, it has been suggested that diabetic ketoacidosis plays an important role in the cognitive decline associated with diabetes.

Advanced technologies have become an integral part of the treatment of DM1 with the potential to improve glycemic parameters and their consequences, as well as quality of life. These include continuous subcutaneous insulin delivery, glycemic control devices, sensory-augmented pumps, low-glucose predictive insulin suspension, and closed-loop systems that automate the administration of insulin depending on glucose levels (artificial pancreas).

The use of a glycemic control device in very young children is possible and reduces both the time spent in a state of hypoglycemia and the variability of glucose levels. Continuous subcutaneous insulin delivery reduces the incidence of severe hypoglycemia compared to multiple daily injections [27]. The use of a glycemic control device with sensory-augmented pumps can further limit the duration and severity of hypoglycemia, since a number of systems can detect and in some cases affect the impending and prevailing low blood glucose levels without significantly affecting metabolic control and without causing diabetic ketoacidosis [28].

Current studies of the home use of closed-loop insulin delivery systems “day-night” in children under one year with DM1 have proven that the system is feasible and safe, with extended time in the range of target glucose levels and without associated severe hypoglycemia or diabetic ketoacidosis [29].
Conclusions

Treatment of DM1 in young children is a difficult task for both parents and guardians. Hypoglycemia is a burden on the well-being of young children with DM1 and can have a serious impact on their brain development and cognitive functions. However, in recent years, several studies have reported that chronic exposure to hyperglycemia and increased glucose variability can also have significant consequences for brain structure and function in children with DM1. Thus, the improved and new technologies of insulin delivery and glucose monitoring introduced in recent years are aimed at increasing the flexibility of treatment and optimizing glycemic control, trying to ensure a “normal” life with less damage to the developing brain and neurocognitive function.

References

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