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Review

Brain functional and structural changes in diabetic children. How can intellectual development be optimized in type 1 diabetes?

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***Abstract*:** The neuropsychological functioning of people with type 1 diabetes (T1D) is of key importance to the effectiveness of the therapy, which, in its complexity, requires a great deal of knowledge, attention, and commitment. Intellectual limitations make it difficult to achieve the optimal metabolic balance, and a lack of this alignment can contribute to the further deterioration of cognitive functions. The aim of this study was to provide a narrative review of the current state of knowledge regarding the influence of diabetes on brain structure and functions during childhood and also to present possible actions to optimize intellectual development in children with T1D. Scopus, PubMed, and Web of Science databases were searched for relevant literature using selected keywords. The results were summarized using a narrative synthesis. Disturbances in glucose metabolism during childhood may have a lasting negative effect on the development of the brain and related cognitive functions. To optimize intellectual development in children with diabetes, it is essential to prevent disorders of the central nervous system by maintaining peri-normal glycemic levels. Based on the performed literature review, it seems necessary to take additional actions, including repeated neuropsychological evaluation with early detection of any cognitive dysfunctions, followed by the development of individual management strategies and the training of appropriate skills, together with complex, multidirectional environmental support.

Plain language summary

Intellectual development in children with type 1 diabetes

Disturbances in glucose metabolism during childhood may have a lasting negative effect on the development of the brain and related cognitive functions. To optimize intellectual development in children with type 1 diabetes, it is essential to prevent disorders of the central nervous system by maintaining close to normal glycemic levels. Based on the performed literature review, it seems necessary to take additional actions, including repeated neuropsychological evaluation with early detection of cognitive dysfunctions, followed by the development of individual management strategies, and the training of appropriate skills, together with complex, multidirectional environmental support.

Keywords: brain, children, cognitive functions, type 1 diabetes

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Introduction

The onset of type 1 diabetes (T1D) and the chronic course of the disease are significant factors that affect the child's development on many levels, including the cognitive function level.

Nerve cell growth, differentiation, and synaptogenesis are life-long processes but are most active in the prenatal period and during the first years of a child's life.[1]

Childhood and adolescence are periods of major neurodevelopmental changes.[2] Disturbances in glucose metabolism in these sensitive developmental periods may have a lasting negative impact on the development of the brain and related cognitive functions.

The neuropsychological functioning of a patient with T1D is of key importance for the course and effectiveness of the therapy, which, in its complexity, requires a great deal of knowledge, attention, and commitment. Intellectual limitations can make it difficult to achieve optimal metabolic balance, and this misalignment will then contribute to the further deterioration of cognitive functions, driving a vicious circle.

For a number of years, an increasing number of T1D cases have been observed in the general population; significantly, this increase is most pronounced among children under the age of 5. Additionally, the treatment of the disease is changing, with significant advances in insulin therapy and glycemic control. A growing number of children use insulin pumps and glucose monitoring systems, which contribute to quality of life but also seem to have an effect on cognitive development. However, despite the availability of better tools for controlling and regulating blood glucose levels, the number of pediatric patients with good metabolic disease management is still unsatisfactorily low.[3,4]

The aim of this study was to review the current state of knowledge regarding the possible influence of diabetes on brain structure and functions during childhood and also to present possible actions to optimize intellectual development in children with T1D. Scopus, PubMed, and Web of Science databases were searched for appropriate literature. The search was carried out with the use of Medical Subject Headings synonyms. The following terms were used: 'type 1 diabetes' AND 'brain functions'; 'type 1 diabetes' AND 'brain structure'; 'type 1 diabetes' AND 'intellectual development'; 'type 1 diabetes' AND 'cognitive functions'. The results were summarized using a narrative synthesis.

Brain functions and diabetes

Cognitive functions, as an activity of the nervous system, are responsible for receiving, processing, and storing information. They are of a complex and hierarchically organized nature. Neuropsychological concepts of human development suggest that how these are shaped in the early developmental period affects the ways they are regulated in adolescence and adulthood.[5] Motor and sensory systems (visual, auditory, and sensory), being modally specific, develop according to genetically determined stages, but the factors modulating this development also include external environmental factors, as well as educational interactions and specific self-activity. Cognitive functions are those mental activities that help people orient themselves in the environment, obtain information about themselves and their bodies, analyze situations, formulate conclusions, make decisions, and act. Cognitive processes include perceptual processes, attention, learning, memory, executive functions, and language. Difficulties associated with them may thus generate a number of difficulties in social, emotional, and somatic functioning.[5,6]

The occurrence of chronic disease in childhood may itself constitute a risk factor for the development of neuropsychological deficits of varying extent and severity. In children and adolescents, the nature of changes can be difficult to notice, as the first symptoms of the disease appear in children in different stages of psychosocial development, and the children themselves may react and experience their illness in different ways. Moreover, when the disease is diagnosed, children usually have different resources and receive various forms of support from the family environment.

The relationship between diabetes and cognitive functioning was first noted at the beginning of the twentieth century when Mills and Root demonstrated that people with diabetes had poorer memory, difficulties in performing arithmetic

tasks, and lower psychomotor skills than healthy people. The term 'diabetic encephalopathy' was introduced in 1950 to describe central nervous system (CNS) related complications of diabetes. Other terms, such as functional cerebral impairment and central neuropathy, have also been used in literature to describe diabetes-related cognitive dysfunction.[7,8]

It is known that children and adolescents with T1D perform tasks requiring constant attention, rapid processing, memory, and visuospatial functioning slightly worse than their nondiabetic peers.[9,10] This is particularly true of executive functions, including processes such as working memory, attention, and inhibition of reactions.[11]

Neuropsychological examination in children with T1D

Despite enormous advances in brain imaging technology, it is not possible to predict all the psychological effects of a child's chronic somatic disease on brain development solely from neuroradiological or neurophysiological images. A great deal of information regarding cognitive and behavioral problems can only be obtained on the basis of a psychological assessment.

Neuropsychological diagnosis requires the use of appropriately standardized, possibly accurate, and reliable diagnostic tools, the development of which uses theoretical concepts explaining structure–function relationships and theories of the effects of damage to the CNS. A number of neuropsychological tests and trials are used to diagnose cognitive functions.[1,5,12]

The aim of such analysis in children with T1D is to obtain specific information on the functioning of the CNS in this chronic disease:

(1) Finding and excluding features of dysfunctions in brain development.
(2) Determining the nature and severity of cognitive impairment in the child.
(3) Determining the practical impact of the identified cognitive disorders on the everyday life of children and adolescents with T1D: here, it is particularly important to take into account the potential impact that these disorders have on the course of the disease on the planning and implementation of diabetes therapy, and education.
(4) Observation of changes in individual cognitive functions over time, along with the duration of the disease.
(5) An attempt to find a relationship between these abnormalities and the observed changes in brain activation, behavior, or parameters related to the course of the disease, including dysglycemia.

It seems that the knowledge obtained in this way about the interrelationships between diabetes and CNS functions would help in planning activities aimed at optimizing intellectual development in affected children.[5,9,12]

The neuropsychological analysis of young people with T1D should be a complementary tool to the diabetologist's examination, providing a full picture of the patient's functioning. Describing the cognitive functioning of the patient allows the identification of difficulties that may arise in the treatment process, and this, in turn, enables the therapy to be adjusted.

The essence of neuropsychological analysis is to perform a detailed assessment of the development of specific cognitive processes. Such an analysis allows the profile of cognitive functioning to be determined; this may be characteristic of children and adolescents suffering from T1D. Many research reports show that the neuronal connections between individual centers of the brain develop in different ways in diabetes; this may be the reason for the different functional organization of the brain and, thus, also for changes in cognitive functions. The image of cognitive dysfunction may vary with the clinical course and outcomes of the disease and treatment.[12]

Neuropsychological testing can accurately determine dysfunctions in terms of cognitive abilities. This allows planning interventions, as well as predicting difficulties in the treatment process and the everyday functioning of children and adolescents with T1D. Understanding the specific symptoms, behaviors, and needs of people with diabetes is necessary to plan effective therapy and to adequately optimize development.

During the neuropsychological examination, the examinee performs a number of psychometric

and manual tasks. This diagnostic process is time-consuming, involving many meetings and requiring increased intellectual effort from the patient. Testing in children with diabetes can be disrupted by many different factors, so in order to obtain reliable data, it is necessary to verify:

- visual functions, as they may be disturbed in the course of the disease;
- blood glucose levels; if they are too low or too high at the time of an assessment, they can interfere with cognitive skills;
- motivation to cooperate with the examiner.[12]

The neuropsychological assessment of a child takes place over several stages, has its own specific nature, and involves the analysis of a number of functions: working, episodic, prospective, and autobiographical memory, communication skills, speech efficiency, verbalization, and attention capacity.[11]

The concept of 'intelligence', the most complex mental function, occupies a special place here. It requires the proper development of all brain regions, the individual parts of which are responsible for cognitive functions. Wechsler in his 1939 article, 'The nature of intelligence', emphasizes the adaptive functions of intelligence, believing that it determines the ability to use mental abilities to act effectively and to respond to the demands of the environment.

Neuropsychological research indicates that intelligence as a function is generally difficult to destroy through brain injury or pathophysiological processes in the CNS.[1] This is associated with the phenomenon of plasticity in the nervous system. The factor most sensitive to pathophysiological processes in the CNS is memory.[1]

A child may be very intelligent, but success or failure in diabetes management is determined, in addition to the intelligence quotient (IQ), by more subtle factors, such as developed cognitive strategies, knowledge and its proper use, the ability to assess a problem situation, the ability to predict consequences, as well as planning and reflecting on the direction of intellectual research. When examining children with diabetes, the IQ is thus important, as is the precise measurement of individual cognitive functions, in order to capture the relationship between the disease and its effects on the developing cognitive processes. Intelligence in diabetes is also associated with decision-making and the ability to adjust therapy to the changing conditions of everyday life, the aim of which is proper metabolic control. The probability of making right decisions each day is associated with education, one of the basic elements of diabetes therapy.[10,13] Understanding, remembering, and putting into practice the knowledge passed on during education is closely related to the neuropsychological efficiency of a particular patient.

Brain structure and diabetes

Studies examining cognitive processes as another complication of diabetes have initially focused solely on the analysis of neuropsychological tests. Research using modern neurophysiological and neuroimaging techniques of the nervous system has become more frequent. It has been established that, in the course of diabetes, there are structural and electrophysiological changes, as well as disturbances in neurotransmission, in the form of diabetic encephalopathy.[9,14]

An altered brain structure has been observed in children with T1D in comparison to age and sex-matched healthy controls.[15–18] Cross-sectional studies indicate that abnormalities may appear soon after diagnosis and persist into adulthood.[19,20] The severity of clinical symptoms seems to be important in predicting brain structural differences in adolescents approximately 3 months after diagnosis.[17] The severity of clinical presentation in youth with T1D is associated with differences in brain structure.[17,18]

Differences in the regional morphology of the brain have been demonstrated in diabetic children; these differences affect the regions underlying executive functions, such as the prefrontal cortex and the anterior insula, as well as the occipital cortex and cerebellum,[21] as well as changes in white matter.[18,21,22]

The risk of structural changes in the magnetic resonance imaging image, most often related to the atrophy of the white matter, the cerebral cortex, and subcortical areas, is greatest in people with long duration of the disease and severe episodes of hypoglycemia.[23]

The decreased volume of white matter observed in the brain is associated with the impairment of various cognitive aspects,[7,18] including information processing speed, psychomotor performance, vocabulary development, general intelligence, motor coordination, executive functions,[24] psychomotor functions, and memory.[11,18,25,26] These changes in white matter are associated with hyperglycemia[27] and may reflect vascular abnormalities in interstitial cerebral arterioles.[28]

Compared to the nondiabetic control group, people with diabetes also had a lower gray matter density, mainly in the posterior, temporal, and cerebellar regions of the brain.[21,22] Other studies have shown an increased volume of gray matter in the left superior dorsolateral gyrus and middle frontal gyrus but a decreased volume of gray matter in the right lingual gyrus, cerebellum, preclinic, left inferior temporal gyrus, and middle temporal gyrus.[29]

Considering the changes in brain structure observed in adolescents with T1D, it is surprising that the cognitive impairment observed in this group is not more severe. One mechanism that may act to maintain normal (or close to normal) neurocognitive functions despite altered brain structures is a compensatory increase in brain activation. It appears that increased brain activation in T1D may temporarily counteract negative cognitive effects.[30,31]

Children with T1D seem to show increased activation in executive control regions (dorsolateral prefrontal and supramarginal gyri) and reduced suppression of activation in the posterior node of the default mode network. Associations have also been found between activation patterns and behavior with clinical disease courses. These data support a neural model in which a compensatory increase in the activation of executive control networks can temporarily counteract T1D-related abnormalities in brain structure and default mode functioning to facilitate normative cognitive and behavioral.[32]

Research data suggest that compensatory increased brain activation may occur in the early stages of T1D and can persist into adulthood. However, this compensatory increase in brain function seems to be a finite phenomenon that eventually disappears as the disease progresses.[30,33]

The structural changes observed in the brain are linked to developing changes in microcirculation in the brain.

Diabetic microangiopathy refers to functional disorders of capillaries with precapillary and postcapillary vessels. It is characterized by increased permeability and remodeling of the blood vessel wall, increased angiogenesis, and inflammatory changes. Diabetic functional and structural disorders occurring in the microcirculation can cause impaired flow in the vascular bed, increasing blood clotting and consequently causing hypoxia and damage to the surrounding tissues. In endothelial cells, the system of glucose transporters (GLUT2) is not downregulated, so even a slight increase in glucose concentration increases intracellular metabolism and interferes with mitochondrial function. Due to the inability to metabolize the excess glucose in endothelial cells, additional pathways are activated: the protein glycation pathway, the hexosamine pathway, and the polyol pathway. These lead to an increase in the production of free oxygen radicals, the development of oxidative stress, and endothelial cell apoptosis.[34–38] The structural and functional interaction of neurons with the surrounding vascular system is crucial for the proper functioning of the CNS.[39]

Cerebrovascular disease in people with T1D causes vascular cognitive decline that mainly occurs in two periods: the first 5–7 years of life, when the brain develops, and the period when the brain undergoes neurodegenerative changes due to aging (age over 65).[36]

What factors relate to the damage?

Cognitive impairment in children with diabetes may go unnoticed for a long time, and progressive changes may be difficult to diagnose due to the development of the disease and the unpredictability of developmental changes in children.

The greatest dynamics of cognitive impairment in the course of diabetes occur in people with intense development of the CNS, that is, during the first 5–7 years of life.[7,9,18,20] This period is associated

with intense myelination, high metabolic activity in nerve cells, and a greater demand for oxygen,[40] as well as persistently elevated glucose values.[9]

The factors that determine the development of the CNS and cognitive functions in children with T1D and which are most often considered in the literature are:

- the child's age at diagnosis,
- duration of the disease,
- dysglycemia: hypoglycemia and hyperglycemia, as well as fluctuations in glucose levels,
- wide recognition of environmental factors.

Child's age at diagnosis and disease duration

The child's age at diagnosis and the duration of the disease are nonmodifiable factors.

In younger children with T1D, it is difficult to predict and recognize all symptoms of hypoglycemia and hyperglycemia due to their unpredictable activity and appetite. However, glucose control in this period of life is crucial as it determines the development of the CNS.[30,41] Early childhood is a period of rapid and dynamic neuronal changes, including myelination and the formation of synaptic connections. Frequent glycemic imbalance may thus lead to permanent neurocognitive deficits.[1]

Younger age at the onset of T1D has long been recognized as one of the strongest risk factors associated with cognitive impairment, ranging from poorer overall mental performance[18,42] to specific deficits in the performance of tasks that assess visuospatial and executive functions, attention, memory, and speed of information processing.[7,42,43] Children diagnosed in early childhood, especially before the age of 5, also have poorer results in terms of school achievement, motor skills, and hand coordination. Similar results have been reported in many studies.[7,9,44]

The developing nervous system of young children is very sensitive, especially to hypoglycemic episodes, and the adrenergic response in this age group is less mature than in older children and adults. Hence, frequent exposure to hypoglycemia in childhood may lead to neurological deficits. The higher energy requirements of children make them more sensitive to glucose fluctuations in the brain, which may be detrimental to the optimal growth and development of the brain. A number of studies have shown evidence of selective neuropsychological dysfunctions, especially in children with early onset disease or in children who have experienced severe metabolic crises.[7,18,42]

Cognitive impairment may occur early, about 2 years after the diagnosis of diabetes in a child.[24] Studies of newly diagnosed diabetes cases show moderate deficits that include slower information processing rates and lower scores on subtests that measure reasoning and learning.[45] Similar cognitive deficits in children, even 2 years after the diagnosis, have been described by Northam *et al.*, who found that such patients achieved lower results for intelligence, vocabulary, visuomotor coordination, speed of mental processes, and learning.[24,42,46] Six years after the diagnosis, scores for these subtests showed progressive deterioration in function; compared to the control group, the following were also found to weaken: general intelligence, attention, speed of mental processes, long-term memory, and executive functions.[42]

Poor glycemic control: hypoglycemia, hyperglycemia, and glucose fluctuations

Achieving blood glucose levels in the normal range (perinormoglycemia) remains one of the main goals of intense insulin therapy. But such therapy also carries a greater risk of hypoglycemia. Because the brain relies predominantly on glucose as an energy source, the effect of hypoglycemia on brain function is of great physiological and clinical importance. The potential cognitive consequences of severe hypoglycemia, which include coma, are a key issue for physicians, patients, and their families. Many studies have clearly shown that prolonged and recurrent hypoglycemia can damage the CNS. Brain tissues require a constant supply of glucose because glucose reserves are vanishingly small, and under normal conditions, the brain uses keto acids as a source of energy only marginally.[47] Hypoglycemia can disrupt cognitive processes as it alters blood circulation in the brain, especially in the frontal part of the hippocampus,[48] which may lead to a temporary decline in mental performance. It may take about 1.5 days for intellectual functions to return to the state before an episode of hypoglycemia.[24,49]

Severe hypoglycemia leads to the uncontrolled release of excitatory amino acids, such as glutamate and aspartate, triggering a cascade of events that can cause neuronal damage.[50] In the acute phase of hypoglycemia, transient disturbances in the functions of the CNS, abnormal electroencephalographic recordings, and disturbances in regional cerebral blood flow are found. Recurrent hypoglycemic states can lead to persistent neuropsychological deficits.[51] These are associated with reduced memory and learning capacity.[51] Rovet *et al.*,[52] during a 7-year follow-up of children aged 1–11.7 with episodes of neuroglycopenia, found a reduced ability to concentrate and remember, as well as impaired motor coordination. It is worth noting that hypoglycemic episodes themselves often present with symptoms of brain dysfunctions, such as behavioral disorders, redundant reactions, mood lability (which can generate a number of interpersonal conflicts and learning difficulties), and periodic or permanent focal neurological disorders.[53] Symptoms related to the insufficient use of glucose in brain tissue are associated with mental functions and include an inability to concentrate and remember, attacks of aggression and cheerfulness, or difficulty interacting with the environment. Later neurological disorders can include severe headache, visual disturbances (spatial, color, and shape), impaired motor coordination, slurred speech, difficulty in thinking, uncoordinated eye movements, nystagmus, impaired consciousness, loss of consciousness, and convulsions. The most dangerous symptom is hypoglycemic coma.[18,53]

Severe hypoglycemia resulting from the administration of too much insulin may lead to changes in the CNS, with necrosis in the cerebral cortex, accompanied by glial growth in other areas of the brain, including in the limbic structures responsible for emotions and memory, such as the hippocampus.[18,51]

However, growing evidence shows that decreased cognitive performance in T1D patients is primarily associated with chronic hyperglycemic states.[10,53]

Chronic hyperglycemia is associated with the loss of neurons and a slowdown in nerve conduction.[18,51,53] Cato *et al.*[10] have indicated that there are significant differences in cognitive functioning, especially between groups with good and poor glycemic control. In the study of McCarthy *et al.*[54] worse school results were obtained in children with chronic metabolic maladjustment. In the study of Perantie *et al.*,[55] lower verbal intelligence was found in children with diabetes than in healthy children, and lower verbal intelligence was more common in children with chronic hyperglycemia. Other authors have pointed to deficits in the development of visual abilities, attention, processing speed, memory, learning, and executive functions.[7] The frontal and temporal areas of the brain have proved to be particularly sensitive to the effects of blood glucose levels.[7,10,18] Chronic hyperglycemia in diabetic patients can also cause memory impairment, problems with remembering and learning, attention disorders, and neuropathy. It negatively affects the processes of brain plasticity as well as the maturation and density of synapses, resulting in retinopathy and gray matter atrophy and affecting the metabolism of neurotransmitters.[18,24] Malone *et al.*[56] hypothesized that chronic hyperglycemia induces greater structural changes in neurons than hypoglycemia and consequently leads to cognitive impairment of a greater extent than hypoglycemia.

Acute hyperglycemia significantly reduces working memory capacity in adolescents and lowers IQ scores in children with T1D.[28,57] Working memory stores information that needs to be readily available and is crucial for goal-directed behavior.[58] As acute hyperglycemia results in a lower working memory capacity, it has a direct clinical impact on school performance and leads to other cognitive challenges in this sensitive diabetic population.[57]

The 18-year-long observations of the Diabetes Control and Complications Trial showed that diabetic patients, whose mean glycosylated hemoglobin (HbA1c) was less than 7.4%, obtained significantly better results on tests of mental processing speed and visuomotor coordination than those in whom the mean HbA1c was greater than 8.8%.[59] The higher the HbA1c value, the lower the general cognitive functioning results.[22]

Hyperglycemia in brain tissues leads to accelerated formation of glycation end products, the accumulation of potentially toxic glucose metabolites, oxidative stress, and microvascular changes in the brain.[60]

Oxidative stress seems to be a key phenomenon in the pathophysiology of diabetic complications, including those affecting the brain.[60,61] Under hyperglycemia, there is increased production of superoxide anions, which causes intracellular oxidation–reduction imbalances. The existing oxidative stress and persistent hyperglycemia intensify the metabolism of glucose through metabolic pathways (including the polyol, pentose, and hexosamine pathways), the stimulation of which additionally intensifies the developing disorders of the oxidation–reduction balance. Under hyperglycemia, the nonenzymatic glycation of proteins with the accompanying oxidation of glucose also increases. The oxygen free radicals created in this reaction additionally strengthen ionic imbalance. It is oxidative stress and the resulting low-intensity inflammation that connect chronic hyperglycemia and diabetes complications, including loss of neurons and damage to Schwann cells, which directly translate into the effects on cognitive functions.[60,62,63]

The increased production of free radicals in brain tissues is also observed in the case of hypoglycemia. Imbalances in ion homeostasis during hypoglycemia lead to depolarization of the cell membrane and the massive release of neurotransmitters, including glutamate, which, in the course of further processes, leads to an increase in free oxygen radicals and local inflammation.[61,62,64]

However, both clinical and experimental studies have indicated that glucose fluctuations may be even more harmful than the states of chronic hyperglycemia or acute hypoglycemia. Increased glycemic variability is associated with microvascular and macrovascular diabetic complications, including higher incidence of cerebrovascular events, as well as white matter hyperintensities and cognitive decline.[65] Mismatches in the brain between altered glucose transporters and acute glucose fluctuations can contribute to neuronal damage. In this process, oxidative stress plays a significant role as a pathophysiological factor in glucose neurotoxicity.[66]

Another matter is that diabetes mellitus, as a significant metabolic distress for cells, also induces chronic activation of the hypothalamus–pituitary–adrenocortical axis. Glucose is a key energy substrate for almost all cells; therefore, rapid glycemic changes are strong cellular stressors. It seems that patients with poor glycemic control show diurnal hypersecretion of glucocorticoids and altered regulation of the hypothalamus–pituitary–adrenocortical axis, with impaired stress-related adaptation. Observed dysregulation probably involves complex interactions between the decreased sensitivity to the negative glucocorticoid feedback and hyperinsulinemia or hypoleptinemia, which may enhance the central drive of the axis.[67]

New technologies offer promising prospects for improving glycemic control in children with diabetes, and thus, they would play an important role in optimizing the functions of the CNS. The use of devices such as insulin pumps and glucose monitoring systems allows to achieve long-term near-normal glycemic levels, but they still require the user's conscious participation in their efficient operation.

Environmental factors

The course of diabetes is influenced by a number of obvious environmental factors. Many of these conditions can have a lasting impact on growing children and adolescents.

Of particular importance in this regard are:

- the psychological support provided in the environment (family, school), and the impact of stress, broadly understood, along with comorbid mental disorders;
- nutrition;
- physical activity.

Environmental support and the impact of stress. Family support may seem obvious.[3,4] However, while the responsibility for treating young children falls on parents and guardians, from school age onward, due to the increasing amount of time spent by the child outside the home, expectations increase that children and adolescents will be able to manage the disease on their own, leading support to turn into a claim.

Childhood and adolescence are periods in which individuals complete their developmental tasks, gaining a sense of autonomy and competence, developing diligence, and shaping realistic self-esteem. These tasks require the child to be successful in the psychological and social spheres. A

failure to solve the developmental crisis leads to a feeling of inferiority, incompetence, mismatch, low self-esteem, and the experience of rejection by the peer group. Children and adolescents suffering from diabetes for a long time develop chronic fatigue, a depressed mood that negatively affects motivation and interest in learning. If this is combined with absences from school due to hospitalization, a lack of understanding of the specificity of the disease by teachers and peers, and numerous learning backlogs, accumulated stress may also overlap with school and cognitive difficulties.[68] The somatization of stress accompanying a chronic disease results from the intensity of emotions that cause prolonged changes in the activity of the vegetative, endocrine, and immune systems, along with organ responses.[69] As a consequence, long-term dysregulation, suppression, and the persistence of emotions such as sadness, anger, guilt, and anxiety can lead to changes in the normal functioning of the body and, consequently, to the intensification of pathological changes.

Research indicates that environmentally conditioned mental stimuli alter the activity of the cortical, subcortical, and limbic structures and, thus, the regulation of vegetative and endocrine functions. As a consequence, this translates into the functioning of the morphological–functional system that controls motivational behavior, learning and memory, regulation of sleep and wakefulness, as well as emotional excitability.[69] It is known that the effectiveness of treatment is weaker in patients experiencing greater stress[70] and a lack of support, which is associated with worse glycemic control [70,71] and can lead to the use of strategies based on emotions and avoidance.

The coexistence of any mental disorder with diabetes not only worsens the mental functioning of the patient but also carries with it somatic complications that are associated with worse glycemic control and recurrent episodes of ketoacidosis.[72] At the same time, depression most often affects children and adolescents with worse metabolic control, especially those who are hospitalized.[73] Depressive symptoms were observed in 1 out of 12 T1D children in a primary school and 1 out of 5 teenagers. Depressive symptoms may affect metabolic control and quality of life.[74] Depression in children with diabetes is two or three times more common, depending on the age of the child.[73] The risk of suicidal thoughts or attempts increases tenfold, which may be particularly dangerous for diabetic patients with access to insulin.[75]

One other important component in chronic disease is fatigue, associated with the inhibition of emotions and physical fitness, limitation of life activity, problems with memory and attention, sleep disorders, and undefined head, abdominal, and muscle pain.

Neuropsychological examination can help determine the probable cause of symptoms in patients with damage to the CNS. It can be used to distinguish between, for example, post-traumatic stress disorder, depressive disorder, and simple simulation: the symptoms in this context may be externally similar, but their quality is different. For example, problems with memory may be identified as a lack of concentration (as new information does not reach the memory), difficulty actualizing the knowledge (information is stored in memory but cannot be extracted), a symptom of depression (the patient is then not motivated to answer the questions), or a symptom of post-traumatic stress (psychogenic amnesia may occur, as a result of which the patient cannot recall some events from memory). Each of these symptoms requires a different treatment.

Nutrition and its significance for the brains of children with diabetes. A properly designed and (most importantly) properly adhered-to diet can be an important tool to support the development and functions of the brain in children.

Nutrition should be considered here in terms of three basic aspects: ensuring the optimal balance of nutrients for the developing brain of a child, preventing dysglycemia, and potential anti-inflammatory effect of the diet to counteract oxidative damage to the brain structures.

Diet for optimal development of brain structure and function. From the very beginning, a child's brain requires an adequate supply of substrates for the proper development of synapses, for the process of myelination, and for the synthesis of neurotransmitters.[76,77] One way to optimize the development of the brain structure and function in children, including those with T1D, is to provide a complete set of nutrients necessary for

these processes. A properly balanced diet can prevent qualitative malnutrition, which would be an additional stressor for the brain of a child with type-1 diabetes, quite apart from disturbances in glycemic levels. This support for the development of cognitive functions is especially important in children who become ill at a younger age.[76]

In the context of proper brain structure and function, the most important nutrients seem to be high-quality protein, long-chain fatty acids from the omega-3 family, vitamin B_{12}, folic acid, zinc, iron, and iodine. Deficiencies in these nutrients, especially in the early developmental period, but also later, can aggravate disorders that result from diabetes.[76,77]

Diet to prevent glucose fluctuations. The recommendations of scientific societies for the health of children and adolescents with T1D indicate that their diet should include grain products that are a source of complex carbohydrates, as well as an adequate amount of fiber, vegetables, fruit (especially raw fruit), high-quality dairy products, and lean meat.[78] Additionally, diabetics are advised not to consume products rich in simple carbohydrates and products with a high glycemic index and load. It has been shown that this type of eating, as opposed to a highly processed diet, will result in more stable serum glucose levels and fewer episodes of hypoglycemia and hyperglycemia. In addition, exercise can increase the sensitivity of tissues to insulin, and when performed immediately after a meal, permits better postprandial glucose serum levels to be reached.[78–80]

Anti-inflammatory diet in the prevention of oxidative damage to brain structures. As mentioned above, oxidation–reduction imbalance and the accompanying inflammation are key problems in people with T1D and are a consequence of disturbances in glycemic levels.[60,61] An anti-inflammatory diet might be an interesting nutritional strategy to help optimize the development of brain structures and functions in affected children.

An anti-inflammatory diet is rich in nutrients that have been proven to eliminate free radicals. Its principles include the consumption of the proper amount and quality of fatty acids, especially unsaturated fatty acids, with an emphasis on the correct ratio between the omega-3 and omega-6 families. An anti-inflammatory diet promotes the consumption of a large amount of different colored vegetables and fruits, as the natural colors in food (flavonoids) have strong antioxidant and anti-inflammatory effects. This nutritional strategy also uses low-processed cereal products with low glycemic indices and high fiber. Additionally, when using this method of nutrition, the dietary intake of substances with proven proinflammatory effects should be limited. These include saturated fatty acids, *trans* isomers of unsaturated fatty acids, excess sodium, and foods characteristic of a Western processed diet, such as refined products and those with low fiber and a large amount of simple sugars.[81,82]

Anti-inflammatory diets have been the subject of many studies, which have indicated that the higher the dietary inflammatory index (DII),[83] the higher the risk of diseases of civilization, such as obesity[84–86] and its complications,[87,88] as well as neurodegenerative diseases[89] and cognitive loss.[90] Increased consumption of proinflammatory foods (as measured by DII) has been shown to have a negative effect on children's and adolescent's learning performance.[91]

Although there is a shortage of studies on the anti-inflammatory diet and cognitive function in children and adolescents with T1D, using the principles of this diet could be beneficial as:

- the anti-inflammatory diet is a rich source of the substrates necessary for the proper development of the brain's structure and function in children and adolescents[77,81];
- the anti-inflammatory diet has a low glycemic index,[81,92] so it can help reduce the risk of hypoglycemic and hyperglycemic episodes while increasing the chances of better metabolic control;
- adherence to the anti-inflammatory diet, as measured by DII, is associated with the proper development of cognitive functions in both children and adults and a reduced risk of loss of these functions and neurodegeneration[89–91];
- if the oxidative stress accompanying glycemic fluctuations is one of the reasons for cognitive decline in children with T1D,[60,61] an anti-inflammatory diet as a free radical scavenging nutritional strategy could reduce the negative effects of these events.[64,81]

Physical activity. Physical activity is essential to the proper course of children's development in general. At the same time, the multidirectional benefits it brings make it an integral part of the comprehensive management of diabetes. Regular, sufficient, planned, and balanced physical exercise positively influences weight control, insulin sensitivity, glycemic balance, and lipid profile.[93] In the case of diabetes, the duration and intensity of exercise must, of course, depend not only on the child's abilities but also on his or her current metabolic status.

In terms of brain functions, physical activity also has a positive effect on the CNS, as it improves cognitive functions, improves memory, and reduces the risk of dementia. Research has increasingly focused on the analysis of neurotrophic factors, such as brain-derived neurotrophic factor and insulin-like growth factor-1. It seems that the regular repetition of significant physical activity may be a promising strategy for brain health in people with T1D.[93,94]

Social determinants of health. Differences in diabetes outcomes can result from multiple contributors, including biological, clinical, and nonclinical factors. There is scientific evidence suggesting that socioeconomic status, neighborhood and physical environment, food environment, health care, and social conditions are associated with diabetes-related outcomes. Inequities in living conditions and environments affect biological and behavioral aspects in the course of diabetes and the incidence of its complications. Social and environmental factors combined are known as social determinants of health and together account for 50–60% of general health outcomes.[95] Globally, social determinants are responsible for most childhood diseases and deaths, affecting the child's health through a complex inter-relationship of various factors such as income, education, health-related behaviors, environmental conditions, and others. They constitute socially related risk and protective exposures – 'causes of causes' acting over the course of an individual life, where distal factors influence more proximal factors in causal pathways to health outcomes. In child populations, social determinants are usually identified as health inequities, inequalities that are unfair, unjust, avoidable, and unnecessary.[96,97] In case of T1D, proper education, stable financial situation, and access to health care are crucial for effective treatment and, therefore, better health.

Summary

The lack of prospects for recovery, the risk of complications, and the need to take responsibility for the course of the disease in T1D form a heavy burden for children and their families. The disease can interfere with the emotional and cognitive development of a child and affect family relationships. The daily effort of treatment rests mainly on the child and his or her family, who must attend to dietary requirements, measuring glucose levels several times a day, administering insulin, and adjusting doses to the patient's current situation, all of which may lead to permanent tension and, consequently, a feeling of exhaustion, fatigue, sadness, and anger.

Understanding the mechanisms underlying these changes is important, given the high cognitive load required for optimal adherence to a complex treatment regimen.

Diabetes mellitus is a disease that can, to some extent, be managed. Optimizing treatment requires the doctor to cooperate with the patient in order to determine the treatment process and the effects of the patient's self-care and to prepare for what will inevitably happen during the disease process.

Care for a child with diabetes presently requires continuous training adapted to the successive stages of the disease and the patient's development. Health education, which is crucial for success, should be preceded by an individual assessment of the child's needs and the setting of individual goals, adjusted to the child's age, knowledge, the most common somatic and psychological problems, and the family situation. This requires the involvement of both the family and school environment. Such repetitive re-education needs to be adjusted to the developmental age and changing health situation of the patient.

To optimize intellectual development in children with diabetes, the prevention of CNS disorders through careful maintenance of perinormoglycemia is essential.

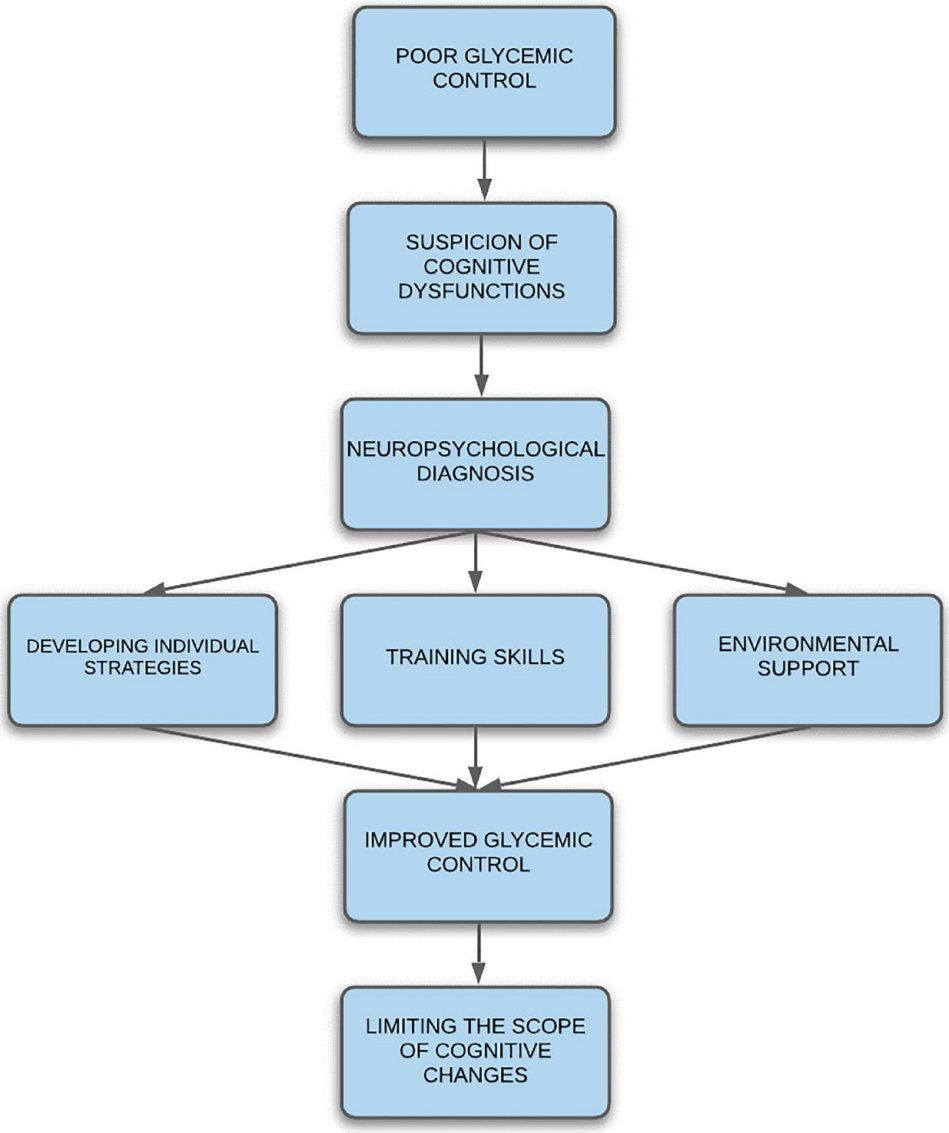

Figure 1. The role of neuropsychological diagnosis in diabetes care during childhood and adolescence.

However, it is precisely glycemic control that proves to be the greatest challenge for patients in practice. In the overwhelming majority of cases, perinormoglycemia is an unattainable goal, especially in the youngest children. Therefore, it seems necessary to take actions such as:

(1) Repeated neuropsychological diagnostics to detect any cognitive dysfunctions that arise early.
(2) Limiting the impact of the dysfunctions on the course of diabetes treatment by determining their specific nature and then developing an individual management strategy, appropriate skills training, and appropriate support for the family and school environment (Figure 1).
(3) Dietary care with the development of a nutrition plan that takes into account not only typical diabetic aspects but also elements supporting the development of the CNS and recommendations of an anti-inflammatory diet.
(4) Physical activity that is both regular and adapted to age and abilities, with appropriate protection against glycemic fluctuations.

From the moment of diagnosis, a child with diabetes is working for his or her future health; the child needs to be intellectually fit, well-motivated, and able to consistently apply good self-control. We should remember that self-treatment of diabetes is lifelong and requires the patient to maintain mental fitness. Without this, even modern technological devices, such as personal insulin pumps or glycemic monitoring systems, will not be effective.

Conclusion

Disturbances in glucose metabolism during childhood may have a lasting negative effect on the development of the brain and related cognitive functions. To optimize intellectual development in children with T1D, it is essential to prevent disorders of the CNS by maintaining close to normal glycemic levels. Based on the performed literature review, it seems necessary to take additional actions, including repeated neuropsychological evaluation with early detection of cognitive dysfunctions, followed by the development of individual management strategies and the training of appropriate skills, together with complex, multidirectional environmental support.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

Maia Stanisławska-Kubiak: Conceptualization; Methodology; Project administration; Resources; Validation; Writing – original draft; Writing – review & editing.

Katarzyna Anna Majewska: Conceptualization; Data curation; Formal analysis; Methodology; Resources; Writing – review & editing.

Agata Krasińska: Conceptualization; Data curation; Investigation; Validation.

Paulina Wais: Conceptualization; Data curation; Investigation; Methodology; Validation.

Dominik Majewski: Conceptualization; Data curation; Formal analysis; Investigation; Resources; Software.

Ewa Mojs: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Writing – review & editing.

Andrzej Kędzia: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Resources; Validation.

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