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Diabetic ketoacidosis and cognitive impairment in children and adolescents

Magomedova K.Sh.[1], Bykov Yu.V.[2,3], Baturin V.A.[2]

[1] *Stepnovskaya District Hospital*
52a, Dodonova Str., Stepnoye village, Stavropol Region, 357930, Russian Federation

[2] *Stavropol State Medical University*
310, Mira Str., Stavropol, 355017, Russian Federation

[3] *Children's City Clinical Hospital named G. K. Filippsky*
5, Ponomareva Str., Stavropol, 355002, Russian Federation

ABSTRACT

The aim of the literature review was to highlight modern scientific sources on the formation and clinical manifestations of cognitive impairment in children and adolescents with type 1 diabetes mellitus (DM) after diabetic ketoacidosis (DKA). Type 1 DM is one of the most prevalent endocrine disorders in childhood and adolescence. DKA is the most common acute complication of type 1 DM that may cause cognitive impairment. Cerebral edema is the main cause of cerebral vascular insufficiency in patients with DKA. However, the mechanisms underlying the development of cognitive dysfunction in DKA have not been fully elucidated.

The leading hypotheses include development of neuroinflammation, oxidative stress, disruption of neurogenesis, and neurodegeneration. Hypoxic – ischemic injury and changes in the brain neuroanatomy may also cause cognitive dysfunction. Disruption of some brain structures has been reported after DKA episodes, primarily affecting the white matter. Clinical studies in the pediatric population support the presence of a correlation between the severity and frequency of DKA and the severity of cognitive impairment. Cognitive dysfunction in children and adolescents after a DKA episode can manifest through decreased attention, impaired memory and executive function, and reduced IQ. The earliest possible diagnosis of cognitive impairment in pediatric patients with symptoms of DKA in the context of type 1 DM can improve the treatment prognosis for this endocrinopathy.

Keywords: type 1 diabetes mellitus, diabetic ketoacidosis, cognitive impairment, children and adolescents

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✉ *Bykov Yuri V.,* yubykov@gmail.com

Диабетический кетоацидоз и когнитивные нарушения у детей и подростков

Магомедова К.Ш.[1], Быков Ю.В.[2, 3], Батурин В.А.[2]

[1] *Степновская районная больница*
Россия, 357930, Ставропольский край, Степновский район, с. Степное, ул. Додонова, 52а

[2] *Ставропольский государственный медицинский университет (СтГМУ)*
Россия, 355017, г. Ставрополь, ул. Мира, 310

[3] *Детская городская клиническая больница им. Г.К. Филиппского*
Россия, 355002, г. Ставрополь, ул. Пономарева, 5

РЕЗЮМЕ

Цель исследования – освещение современных научных источников по вопросам формирования и клиническим проявлениям когнитивных нарушений у детей и подростков с сахарным диабетом (СД) 1-го типа после перенесенного диабетического кетоацидоза (ДКА). СД 1-го типа является одним из распространенных эндокринных заболеваний в детском и подростковом возрасте. ДКА – наиболее частое острое осложнение СД 1-го типа, который может вызывать когнитивные нарушения. Отек головного мозга при ДКА является основной причиной, приводящей к церебральной недостаточности. Механизмы формирования когнитивной дисфункции при ДКА полностью не выяснены.

Ведущими гипотезами являются: возникновение нейровоспаления, оксидативный стресс, нарушение процессов нейрогенеза и нейродегенерация. Гипоксически-ишемические нарушения и изменения в нейроанатомии головного мозга также могут являться причинами когнитивной дисфункции. Отмечено нарушение некоторых структур головного мозга после ДКА, в первую очередь белого вещества. Клинические исследования, проведенные в педиатрической популяции, подтверждают корреляцию между тяжестью и частотой ДКА и выраженностью когнитивных нарушений. Когнитивная дисфункция у детей и подростков после ДКА может проявляться в снижении внимания, нарушении памяти и исполнительной функции, а также в низком уровне IQ. Максимально ранняя диагностика когнитивных нарушений в педиатрической практике при СД 1-го типа с проявлениями ДКА может улучшить терапевтический прогноз при лечении данной эндокринопатии.

Ключевые слова: сахарный диабет 1-го типа, диабетический кетоацидоз, когнитивные нарушения, дети и подростки

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

Источник финансирования. Авторы заявляют об отсутствии финансирования при проведении исследования.

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INTRODUCTION

Type 1 diabetes mellitus (DM), one of the most prevalent metabolic disorders in children, presents an important public healthcare problem due to its rapidly increasing incidence [1–3]. According to available data, almost 15 million children across the globe have type 1 DM, with its prevalence growing steadily (by 2–5% each year), especially in the developing countries [3, 4]. The steadily growing prevalence of this endocrinopathy, especially among young children, leads to an increase in its acute complications [4].

According to the International Society for Pediatric and Adolescent Diabetes (ISPAD), diabetic ketoacidosis (DKA) is the most prevalent acute complication of type 1 DM [5–9]. The prevalence of DKA at the time of diagnosis in pediatric practice ranges from 12.8 to 80%, with the mean of 38.8% [4,

10–12]. DKA is the most frequent cause of death in children with type 1 DM, while the mortality rate for DKA is 0.3–0.5% in developed countries and much higher (about 10%) in developing countries [13–16].

DKA occurs due to the interaction between insulin (deficiency) and counterregulatory hormones (excessive concentrations) [13, 17]. While insulin deficiency leads to hyperglycemia and ketosis, an excess of counterregulatory hormones (epinephrine, cortisol, and growth hormone), which are produced in large amounts during stress, exacerbates hyperglycemia by suppressing the effect of insulin and increasing glycogenolysis in the liver [7, 17]. The characteristic manifestations of DKA are hyperglycemia, ketosis, and metabolic acidosis [7, 18]. DKA may be the primary manifestation of type 1 DM, but it may also develop further along the course of the disease and presents a serious relapsing issue in children and adolescents [5]. It has been demonstrated that 25–40% of children with newly diagnosed type 1 DM are also diagnosed with DKA, and in patients with a chronic disease course, DKA may develop due to poor compliance with treatment guidelines or malfunction of equipment used for DM treatment (for instance, failure of an insulin pump) [19]. According to the published data, the severity of DKA at the time of diagnosis affects the long-term clinical course of type 1 DM: children with DKA and newly diagnosed type 1 DM have poorer glycemic control and lower residual β-cell function for 2 years after the diagnosis, as well as a lower remission rate [20–22].

Cerebral circulation insufficiency is the most prevalent complication of DKA in children and adolescents with type 1 DM [12, 23]. Cerebral edema (CE) associated with serious neurological impairments has long been acknowledged as a rare but severe complication of DKA in children [24]. Severe, clinically evident manifestations of CE occur in about 1% of DKA episodes and often lead to death or persistent, chronic neurological symptoms [19, 24–26]. Insignificant (subclinical) manifestations of CE can be observed in the majority of children with DKA, even in cases when the clinical changes in the neurological status are minimal or absent [19, 27, 28]. It has been shown that changes in brain MRI in children and adolescents persist for 3 months after CE is diagnosed in patients with a DKA episode in the medical history [9].

This review describes cognitive impairments accompanying DKA in patients with type 1 DM as a pathological condition, with statistically significant differences in cognitive function compared to healthy children and adolescents.

PATHOPHYSIOLOGICAL MECHANISMS OF THE DEVELOPMENT OF COGNITIVE IMPAIRMENTS IN DK

The mechanisms leading to brain damage in DKA with subsequent development of cognitive impairments are not yet fully understood and currently remain a field of active research [19, 29]. Animal research experiments and clinical studies in the pediatric population have demonstrated that DKA may result in damage to neurons and astrocytes in patients with neuroinflammation [30, 31], apoptosis [32, 33], and impaired processes that suppress proliferation of neuronal cells (neurogenesis) [34, 35] and neurodegeneration [36]. Acute hyperglycemia which accompanies DKA may exacerbate oxidative stress, which could also trigger the development of cognitive deficits in children and adolescents with type 1 DM [37–39]. Data suggest that pathophysiological changes accompanying DKA adversely affect the brain, initiating an inflammatory response and development of vasogenic cerebral edema, which may trigger the development of cognitive dysfunction [29]. Animal studies have shown that DKA causes reactive astrogliosis and microglia activation in the brain, and these changes were most evident within the first 24 hours after the onset of DKA, although some inflammatory changes remained even 72 hours after the onset of DKA [29]. These persistent inflammatory disorders suggest ongoing brain damage even after DKA resolution [29].

Some authors reported the identification of specific biomarkers that indicate brain damage in children and adolescents with DKA [40]. S.T. Nett et al. [41] showed elevated plasma levels of interleukin (IL)-6 and tumor necrosis factor alpha (TNFα), a key indicator of astrocyte reactivity and neurodegeneration, in 45% of children with DKA, which had a positive correlation with the impairment in consciousness, indicating that systemic inflammation accompanies brain dysfunction in decompensated type 1 DM. Calcium-binding protein (S100β) secreted by astrocytes was elevated in DKA and was considered as an indicator of neuronal death, including one occurring during the inflammatory response [42].

S. Hamed et al. [43] observed elevated levels of neuron-specific enolase (NSE) in children with DKA at baseline and 12 and 24 hours after the initiation of DKA treatment in type 1 DM. The authors concluded

that the serum level of NSE was elevated on day 1 after the onset of DKA and correlated with the severity of hyperglycemia, ketosis, and acidosis [43]. S.L. Wootton-Gorges et al. [44] reported neuronal damage in DKA evidenced by a reduced N-acetylaspartate-to-creatine ratio (NAA / Cr), one of the markers of viability and normal functioning of neurons. Another inflammation marker in DKA is the kynurenine pathway with its kynurenine / tryptophan ratio, which may be elevated before DKA treatment in children and adolescents [45]. The elevated kynurenine / tryptophan ratio may result in excessive production of neurotoxins, which exacerbate cerebral circulation insufficiency [45].

It has been shown that ketone bodies can have a differential effect on brain capillary endothelial cells and increase the release of vasoactive peptides, for instance, endothelin-1 (ET-1) and vascular endothelial growth factor (VEGF), which adversely affect the cognitive function [46]. Development of hyperlipoproteinemia and emergence of toxic products of tryptophan catabolism are additional side effects stemming from dysregulation of metabolism in DKA, and they can have an adverse effect on cognitive functions [47].

Diabetic vasculopathy or angiopathy has long been considered as the cause of brain damage in DKA patients with subsequent development of cognitive dysfunction [48, 49]. DKA is known to cause CE and a decrease in cerebral blood flow with a potential long-term adverse effect on brain development in children and adolescents [23]. MRI-based studies in children and animal models demonstrate the impaired blood supply to the brain and metabolism alteration patterns accompanying DKA that are similar to the changes often observed in hypoxic – ischemic brain injury [19, 50]. It has been shown that cerebral hypoxia and / or ischemia associated with other conditions (for instance, altitude sickness, cardiac arrest or pediatric sleep-disordered breathing) may be linked to the development of cognitive impairments, which provides additional evidence for the involvement of hypoxic – ischemic disorders in the pathophysiology of cerebral circulation insufficiency in children and adolescents with DKA [51].

Acute hyperglycemia accompanying DKA may damage developing neurons and myelin in children with type 1 DM, which is consistent with data obtained in experimental models of DM that demonstrate degenerative changes in neurons and glial cells *in vivo*, along with disruption of myelin sheaths and a decrease in myelin in hyperglycemia [39]. Changes in the composition of brain sphingolipids (ceramides and sphingomyelin) caused by DKA may also trigger membrane remodeling in some cell populations, which may disrupt cell – cell interaction and result in brain tissue damage [52].

DKA also leads to changes in the neuroanatomy of the brain [19, 53]. Published MRI data reveal abnormalities in the gray and white matter of the brain in children and adolescents who previously had an episode of DKA [19]. The most pronounced changes were observed in the white matter of the brain, especially in the frontal lobes and are most noticeable in younger children who had the most severe acidemia that accompanied DKA [54]. Other authors report on persisting brain abnormalities in patients, detectable even 3 months after an acute DKA episode [9, 55]. Significant correlations have been reported between the decline in the overall volume of the gray and white matter of the brain and delayed memory at initial presentation, as well as subsequent impairment of sustained attention 6 months after the diagnosis of DKA [19].

F.J. Cameron et al. [54] investigated brain morphology and cognitive functions in children aged 6–18 years with and without DKA at presentation and at four time points: 48 hours, 5 days, 28 days, and 6 months after it. They demonstrated a significant correlation between changes in the brain morphology and the cognitive deficits observed at different time points. Another study [55] assessed whether the severity of clinical symptoms (presence of DKA at the time of diagnosis) corresponded to the differences in patients' cognitive functions and brain structure. The results showed a lower volume of the left temporo – parieto – occipital cortex in children with type 1 DM compared to the control group, which correlated with the severity of cognitive impairments. M.J. Marzelli et al. [56] discovered that young children with type 1 DM and frequent episodes of DKA in their medical history had decreased volumes of brain matter in key regions of the brain associated with cognitive functioning, compared to healthy individuals in the control group.

Thus, it may be said that the duration of post-DKA morphological and functional disorders of the CNS in children and adolescents may vary from 48 hours to 6 months. However, the time frames during which peak damage occurs and during which changes may be reversed remain unknown, which requires additional research [57]. Therefore, cognitive functions should be studied starting at 48 hours after a DKA episode with an almost six-month follow-up period [57].

CLINICAL MANIFESTATIONS OF COGNITIVE IMPAIRMENTS IN DKA

An assessment of cognitive impairments has been the subject of numerous studies, some of which reported a significant correlation between type 1 DM and a decline in cognitive function in children and adolescents, including those having DKA [40, 41, 53, 58, 59]. In a meta-analysis aimed at assessing the association between type 1 DM and cognitive function, P.A. Gaudieri et al. [60] concluded that this endocrine disease adversely affects various cognitive spheres in childhood and adolescence. The authors also reported that this correlation was more noticeable in children with an early onset of type 1 DM (an onset in early childhood) [60]. A different group of authors showed that children with type 1 DM have a lower level of intelligence compared to healthy children without DM [58, 59].

DKA often leads to morphological and functional changes in the brain which are associated with adverse neurocognitive outcomes [40, 53]. It has been shown that 40–70% of children with type 1 DM complicated by DKA exhibit diverse types of cognitive deficits, such as decreased attention, poor memory, impaired executive function, and low IQ [41]. According to several clinical, neuroimaging, and experimental studies, DKA may cause both light and severe cognitive impairments over the course of the disease, and these impairments develop even in the absence of subclinical manifestations of CE during decompensation [18, 40]. According to some studies, there is a trend in pediatric patients with newly diagnosed type 1 DM and DKA toward a decline in cognitive functions along the course of the disease compared to patients of the same age with type 1 DM and no symptoms of DKA [9]. For instance, children and adolescents with type 1 DM complicated by DKA at presentation coped worse with mathematical tasks than their siblings without DM in the control group [61]. S. Ghetti et al. [57] estimated whether an episode of DKA which occurred when type 1 DM was diagnosed or later, along the course of the disease, affects cognitive function in children and adolescents. The study involved 758 children with DKA and 376 children in the control group (with type 1 DM without DKA) aged 6–18 years. The authors demonstrated a correlation between the severe course of DKA and a lower coefficient of mental development [57].

The presence of DKA episodes in the medical history also correlated with a lower verbal intelligence quotient in children with type 1 DM and a decline in cognitive function [9, 61–63]. This study revealed memory deficits in children with type 1 DM and a history of DKA compared to children with a similar duration of DM and similar glycemic control, but without a history of DKA [64]. M.A. Cato et al. [65] reported a correlation between learning and memory impairment and a history of DKA in patients who had their first DKA episode 2 years prior to the assessment.

At the moment, it is not clear whether a single episode of DKA causes a long-term decline in cognitive functions in children and adolescents with type 1 DM [57]. However, it has been proven that the clinical severity of a DKA episode correlates with the severity of cognitive dysfunction 6 months after the diagnosis; therefore, DKA severity may be associated with the degree of CNS damage [54]. Still, not all clinical studies reveal an association between a history of DKA and cognitive dysfunction. For instance, a study revealed that children with type 1 DM and DKA were not cognitively impaired compared to children with type 1 DM and no DKA [66]. Therefore, based on the described clinical studies, it is possible to assume a relationship between DKA and the severity of cognitive impairments in children and adolescents with type 1 DM.

ASPECTS OF DIAGNOSIS AND MANAGEMENT OF COGNITIVE IMPAIRMENTS IN DKA

Cognitive dysfunction after an episode of DKA can be diagnosed using specialized neurophysiological methods adapted for children and adolescents and used in practical management of type 1 DM [67, 68]. For instance, the Wechsler Intelligence Scale for Children (WISC) is used to detect impairments of general intellectual ability and its components including verbal and non-verbal intelligence [69]. The Benton Visual Retention Test is used to measure visual perception and visual memory in children aged 8 years and older [70]. The Wisconsin Card Sorting Test is used to assess clinically important aspects of attention deficits [71]. The Stroop Color and Word Test is used to assess cognitive dysfunction in children and adolescents [72].

At present, despite the discovery of numerous pathophysiological mechanisms which may underpin the development of cognitive deficits after an episode of DKA, no specific (etiotropic) treatment has been developed for this cerebral dysfunction [73]. The following pharmacological agents can be potentially used to treat this condition: polypeptide

drug cortexin [74], hopantenic acid preparations [75], and memantine, a NMDA receptor antagonist [76], but the efficacy of these drugs in treating DKA in patients with type 1 DM has yet to be demonstrated in controlled studies. The possible non-pharmacological interventions include regular physical exercise and athletic activities, which have shown their efficacy in ameliorating mild cognitive impairment in adolescents with type 1 DM [77]. Much emphasis is placed on preventive measures aimed at maintaining a normal glycemic profile in order to reduce the risk of a DKA episode, and, as a consequence, minimize cognitive impairment [78].

CONCLUSION

DKA in children with type 1 DM is the most prevalent acute complication that can be an important trigger of cerebral circulation insufficiency further along the course of the disease. The pathophysiology of cognitive impairments in DKA remains understudied, even though children and adolescents with DKA are precisely the group of patients requiring special attention due to the severity of their disease, with a complicated and often negative prognosis in terms of brain dysfunction. Therefore, the search for new possible mechanisms underlying the development of cognitive deficits in this complication of type 1 DM in children and adolescents is a promising area of research in modern endocrinology.

Another major issue is that the theories about mechanisms of cerebral circulation insufficiency in children with DKA involve a wide variety of factors and the presumed mechanisms are of different nature and include neuroinflammation, apoptosis, disruption of neurogenesis, and neurodegeneration. Many research questions exist in relation to the duration of the formation of functional and morphological CNS impairments after a DKA episode in children and adolescents. The time periods during which the manifestations of cognitive dysfunction are at their peak and the aspects of potential reversibility of these impairments are still understudied. Furthermore, not all clinical studies reveal an association between a history of DKA and cognitive dysfunction.

Thus, the pathophysiological mechanisms that cause cerebral circulation insufficiency, along with the clinical manifestations of this pathology, are far from being fully understood, and further studies are needed in this direction within evidence-based medicine. At the same time, it can already be clearly assumed that timely and the earliest possible diagnosis of cognitive dysfunction during treatment of type 1 DM complicated by DKA may improve therapeutic approaches to this disease.

REFERENCES

1. Ji X., Wang Y., Saylor J. Sleep and Type 1 Diabetes Mellitus Management Among Children, Adolescents, and Emerging Young Adults: A Systematic Review. *J. Pediatr. Nurs*. 2021;61:245–253. DOI: 10.1016/j.pedn.2021.06.010.
2. Bhutta Z.A., Salam R.A., Gomber A., Lewis-Watts L., Narang T., Mbanya J.C. et al. A century past the discovery of insulin: global progress and challenges for type 1 diabetes among children and adolescents in low-income and middle-income countries. *Lancet.* 2021;398(10313):1837–1850. DOI: 10.1016/S0140-6736(21)02247-9.
3. Pourabbasi A., Tehrani-Doost M., Ebrahimi Qavam S., Larijani B. Evaluation of the correlation between type 1 diabetes and cognitive function in children and adolescents,and comparison of this correlation with structural changes in the central nervous system: a study protocol. *BMJ Open*. 2016;6(4):e007917. DOI: 10.1136/bmjopen-2015-007917.
4. Szmygel Ł., Kosiak W., Zorena K., Myśliwiec M. Optic nerve and cerebral edema in the course of diabetic cetoacidosis. *Curr. Neuropharmacol*. 2016;14(8):784–791. DOI: 10.2174/1570159x14666160225155151.
5. Frontino G., Di Tonno R., Castorani V., Rigamonti A., Morotti E., Sandullo F. et al. Non-occlusive mesenteric ischemia in children with diabetic ketoacidosis: case report and review of literature. *Front. Endocrinol. (Lausanne).* 2022;13:900325. DOI: 10.3389/fendo.2022.900325.
6. Wolfsdorf J.I., Allgrove J., Craig M.E., Edge J., Glaser N., Jain V. et al. Diabetic ketoacidosis and hyper-glycemic hypersmolar state ISPAD Clinical Practice Consensus Guidelines 2014. *Pediatr. Diabetes.* 2014;15(20):154–179. DOI: 10.1111/pedi.12165.
7. Unal E., Pirinccioglu A.G., Yanmaz S.Y., Yılmaz K., Taşkesen M., Haspolat Y.K. A different perspective of elevated lactate in pediatric patients with diabetic ketoacidosis. *Acta. Endocrinol. (Buchar.).* 2020;16(1):114–117. DOI: 10.4183/aeb.2020.114.
8. Dabelea D., Rewers A., Stafford J.M., Standiford D.A., Lawrence J.M., Saydah S. et al. Trends in the prevalence of ketoacidosis at diabetes diagnosis: the SEARCH for Diabetes in Youth Study. *Pediatrics.* 2014;133(4):e938–945. DOI: 10.1542/peds.2013-2795.
9. Jessup A.B., Grimley M.B., Meyer E., Passmore G.P., Belger A., Hoffman W.H. Effects of diabetic ketoacidosis on visual and verbal neurocognitive function in young patients presenting with new-onset type 1 diabetes. *J. Clin. Res. Pediatr. Endocrinol.* 2015;7(3):203–210. DOI: 10.4274/jcrpe.2158.
10. Al-Zubeidi H., Leon-Chi L., Newfield R.S. Low vitamin D level in pediatric patients with new onset Type 1 diabetes is common, especially if in ketoacidosis. *Pediatr. Diabetes.* 2016;17(8):592–598. DOI: 111/pedi.12342.
11. Hong J., Jalaludin M.Y., Mohamad Adam B., Fuziah M.Z., Wu L.L., Rasat R. et al. Affiliations expand. Diabetic ketoacido-

sis at diagnosis of type 1 diabetes mellitus in Malaysian children and adolescents. *Malays. Fam. Physician.* 2015;10(3):11–18.
12. Usher-Smith J.A., Thompson M.J., Sharp S.J, Walter F.M. Factors associated with the presence of diabetic ketoacidosis at diagnosis of diabetes in children and young adults: a systematic review. *BMJ.* 2011;343:d4092. DOI: 10.1136/bmj.d4092.
13. Li W., Huang E., Gao S. Type 1 Diabetes Mellitus and Cognitive Impairments: A Systematic Review. *J. Alzheimers Dis.* 2017;57(1):29–36. DOI: 10.3233/JAD-161250.
14. Jayashree M., Singhi S. Diabetic ketoacidosis: predictors of outcome in a pediatric intensive care unit of a developing country. *Pediatr. Crit. Care Med.* 2004;5(5):427–433. DOI: 10.1097/01.PCC.0000137987.74235.5E.
15. Benoit S.R., Zhang Y., Geiss L.S., Gregg E.W., Albright A. Trends in diabetic ketoacidosis hospitalizations and in-hospital mortality – United States, 2000–2014. *MMWR Morb. Mortal. Wkly Rep.* 2018;67(12):362–365. DOI: 10.15585/mmwr.mm6712a3.
16. DiLiberti J.H., Lorenz R.A. Long-term trends in childhood diabetes mortality: 1968–1998. *Diabetes Care.* 2001;24(8):1348–1352. DOI: 10.2337/diacare.24.8.1348.
17. Wolfsdorf J., Craig M.E., Daneman D., Dunger D., Edge J., Lee W. et al. Diabetic ketoacidosis in children and adolescents with diabetes. *Pediatr. Diabetes.* 2009;10(12):118–133. DOI: 10.1111/j.1399-5448.2009.00569.x.
18. Bialo S.R., Agrawal S., Boney C.M., Quintos J.B. Rare complications of pediatric diabetic ketoacidosis. *World J. Diabetes.* 2015;6(1):167–174. DOI: 10.4239/wjd.v6.i1.167.
19. Wootton-Gorges S.L., Buonocore M.H., Kuppermann N., Marcin J.P., Barnes P.D., Neely E.K. et al. Cerebral proton magnetic resonance spectroscopy in children with diabetic ketoacidosis. *AJNR Am. J. Neuroradiol.* 2007;28(5):895–899.
20. Bowden S.A., Duck M.M., Hoffman R.P. Young children (<5 yr) and adolescents (>12 yr) with type 1 diabetes mellitus have low rate of partial remission: diabetic ketoacidosis is an important risk factor. *Pediatr. Diabetes.* 2008;9(3):197–201. DOI: 10.1111/j.1399-5448.2008.00376.x
21. Abdul-Rasoul M., Habib H., Al-Khouly M. "The honeymoon phase" in children with type 1 diabetes mellitus: frequency, duration, and influential factors. *Pediatr. Diabetes*. 2006;7(2):101–107. DOI: 10.1111/j.1399-543X.2006.00155.x.
22. Duca L.M., Reboussin B.A., Pihoker C., Imperatore G., Saydah S., Mayer-Davis E. et al. Diabetic ketoacidosis at diagnosis of type 1 diabetes and glycemic control over time: The SEARCH for diabetes in youth study. *Pediatr. Diabetes.* 2019;20(2):172–179. DOI: 10.1111/pedi.12809.
23. Glaser N., Anderson S., Leong W., Tancredi D., O'Donnell M. Cognitive dysfunction associated with diabetic ketoacidosis in rats. *Neurosci. Lett.* 2012;510(2):110–114. DOI: 10.1016/j.neulet.2012.01.014.
24. Glaser N., Barnett P., McCaslin I., Nelson D., Trainor J., Louie J. et al. Risk factors for cerebral edema in children with diabetic ketoacidosis. *N. Engl. J. Med.* 2001;344(4):264–269. DOI: 10.1056/NEJM200101253440404.
25. Edge J., Hawkins M., Winter D., Dunger D. The risk and outcome of cerebral oedema developing during diabetic ketoacidosis. *Arch. Dis. Child.* 2001;85(1):16–22. DOI: 10.1136/adc.85.1.16.
26. González Pannia P., Balboa R., Navarro R., Nocita M.F., Ferraro M., Mannucci C. Prevalence of cerebral edema among diabetic ketoacidosis patients. [Article in English, Spanish]. *Arch. Argent Pediatr.* 2020;118(5):332–336. DOI: 10.5546/aap.2020.eng.332.
27. Glaser N., Gorges S., Marcin J., Buonocore M., DiCarlo J., Neely E. et al. Mechanism of cerebral edema in children with diabetic ketoacidosis. *J. Pediatr.* 2004;145(2):164–171. DOI: 10.1016/j.jpeds.2004.03.045.
28. Glaser N., Wooton-Gorges S., Buonocore M., Marcin J., Rewers A., Strain J., DiCarlo J., Neely E.K., Barnes P., Kuppermann N. Frequency of sub-clinical cerebral edema in children with diabetic ketoacidosis. *Pediatr. Diab.* 2006;7(2):75–80. DOI: 10.1111/j.1399-543X.2006.00156.x.
29. Glaser N., Sasaki-Russell J., Cohen M., Little C., O'Donnell M., Sall J. Histological and cognitive alterations in adult diabetic rats following an episode of juvenile diabetic ketoacidosis: Evidence of permanent cerebral injury. *Neurosci. Lett.* 2017;650:161–167. DOI: 10.1016/j.neulet.2017.04.035.
30. Zhou X., Zhang F., Hu X., Chen J., Wen X., Sun Y. et al. Inhibition of inflammation by astaxanthin alleviates cognition deficits in diabetic mice. *Physiol. Behav.* 2015;151:412–420. DOI: 10.1016/j.physbeh.2015.08.015.
31. Xu L., Zhu J., Yin W., Ding X. Astaxanthin improves cognitive deficits from oxidative stress, nitric oxide synthase and inflammation through upregulation of PI3K/Akt in diabetes rat. *Int. J. Clin. Exp. Pathol.* 2015;8(6):6083–6094.
32. Sun L.J., Hou X.H., Xue S.H., Yan F., Dai Y.J., Zhao C.H. Oil modulates glycogen synthase kinase-3 signaling pathway in diabetes-induced hippocampal neurons apoptosis. *Brain Res.* 2014;1574:37–49. DOI: 10.1016/j.brainres.2014.05.050.
33. Yonguc G.N., Dodurga Y., Adiguzel E., Gundogdu G., Kucukatay V., Ozbal S. et al. Grape seed extract has superior beneficial effects than Vitamin E on oxidative stress and apoptosis in the hippocampus of streptozotocin induced diabetic rats. *Gene.* 2015;555(2):119–126.DOI: 10.1016/j.gene.2014.10.052.
34. Zhang L., Chopp M., Zhang Y., Xiong Y., Li C., Sadry N. et al. Diabetes mellitus impairs cognitive function in middle-aged rats and neurological recovery in middle-aged rats after stroke. *Stroke.* 2016;47(8):2112–2118. DOI: 10.1161/STROKEAHA.115.012578.
35. Nakano M., Nagaishi K., Konari N., Saito Y., Chikenji T., Mizuete Y. Bone marrow-derived mesenchymal stem cells improve diabetes-induced cognitive impairment by exosome transfer into damaged neurons and astrocytes. *Sci. Rep.* 2016;6:24805. DOI: 10.1038/srep24805.
36. Moran C., Beare R., Phan T.G., Bruce D.G., Callisaya M.L., Srikanth V. Alzheimer's Disease Neuroimaging Initiative (ADNI). Type 2 diabetes mellitus and biomarkers of neurodegeneration. *Neurology.* 2015;85(13):1123–1130. DOI: 10.1212/WNL.0000000000001982.
37. Aragno M., Mastrocola R., Medana C., Restivo F., Catalano M.G., Pons N. et al. Up-regulation of advanced glycated products receptors in the brain of diabetic rats is prevented by antioxidant treatment. *Endocrinology.* 2005;146(12):5561–5567. DOI: 10.1210/en.2005-0712.
38. King G.L., Loeken M.R. Hyperglycemia-induced oxida-

tive stress in diabetic complications. *Histochem. Cell Biol.* 2004;122(4):333–338. DOI: 10.1007/s00418-004-0678-9.
39. Wang X., Yu S., Hu J.P., Wang C.Y., Wang Y., Liu H.X. Streptozotocin-induced diabetes increases amyloid plaque deposition in AD transgenic mice through modulating AGEs/RAGE/NF-κB pathway. *Int. J. Neurosci.* 2014;124(8):601–608. DOI: 10.3109/00207454.2013.866110.
40. Hamed S.A. Brain injury with diabetes mellitus: evidence, mechanisms and treatment implications. *Expert Rev. Clin. Pharmacol.* 2017;10(4):409–428. DOI: 10.1080/17512433.2017.1293521.
41. Nett S.T., Noble J.A., Levin D.L., Cvijanovich N.Z., Vavilala M.S., Jarviset J.D. Biomarkers and genetics of brain injury risk in diabetic ketoacidosis: A pilot study. *J. Pediatr. Intensive Care.* 2014;3(2):59–66. DOI: 10.3233/PIC-14091.
42. Albuerne M., Mammola C.L., Naves F.J., Levanti B., Germanà G., Vega J.A. Immunohistochemical localization of S100 proteins in dorsal root, sympathetic and enteric ganglia of several mammalian species, including man. *J. Peripher. Nerv. Syst.* 1998;3(4):243–253.
43. Hamed S., Metwally K.A., Farghaly H.S., Sherief T. Serum levels of neuronspecific enolase in children with diabetic ketoacidosis. *J. Child. Neurol.* 2017(a);32(5):475–481. DOI: 10.1177/0883073816686718.
44. Wootton-Gorges S.L., Buonocore M.H., Caltagirone R.A., Kuppermann N., Glaser N.S. Progressive decrease in N-acetylaspartate/Creatine ratio in a teenager with type 1 diabetes and repeated episodes of ketoacidosis without clinically apparent cerebral edema: evidence for permanent brain injury. *AJNR Am. J. Neuroradiol.* 2010;31(4):780–781. DOI: 10.3174/ajnr.A1829.
45. Hoffman W.H., Whelan S.A., Lee N. Tryptophan, kynurenine pathway, and diabetic ketoacidosis in type 1 diabetes. *PLoS One.* 2021;16(7):e0254116. DOI: 10.1371/journal.pone.0254116.
46. Close T.E., Cepinskas G., Omatsu T., Rose K.L., Summers K., Patterson E.K. et al. Diabetic ketoacidosis elicits systemic inflammation associated with cerebrovascular endothelial dysfunction. *Microcirculation.* 2013;20(6):534–543. DOI: 10.1111/micc.12053.
47. Kommer T.N., Dik M.G., Comijs H.C., Jonker C., Deeg D.J. Role of lipoproteins and inflammation in cognitive decline: do they interact? *Neurobiol. Aging*. 2012;33(1):196–196. DOI: 10.1016/j.neurobiolaging.2010.05.024.
48. Siqueira L.F. Cerebrovascular complications of diabetic ketoacidosis in children. *Arq. Bras. Endocrinol. Metabol.* 2011;55(4):288–290. DOI: 10.1590/s0004-27302011000400009.
49. Bekyarova G.Y., Ivanova D.G., Madjova V.H. Molecular mechanisms associating oxidative stress with endothelial dysfunction in the development of various vascular complications in diabetes mellitus. *Folia Med. (Plovdiv).* 2007;49(3–4):13–19.
50. Yuen N., Anderson S.E., Glaser N.S., O'Donnell M.E. Cerebral blood flow and cerebral edema in ratswith diabetic ketoacidosis. *Diabetes.* 2008;57(10):2588–2594. DOI: 10.2337/db07-1410.
51. Suratt P.M., Peruggia M., D'Andrea L., Diamond R., Barth J.T., Nikova M. et al. Cognitive function and behavior of children with adenotonsillar hypertrophy suspected of having obstructive sleep-disordered breathing. *Pediatrics.* 2006;118(3):771–781. DOI: 10.1542/peds.2006-0173.
52. Fiedorowicz A., Prokopiuk S., Zendzian-Piotrowska M., Chabowski A., Car H. Sphingolipid profiles are altered in prefrontal cortex of rats under acute hyperglycemia. *Neuroscience.* 2014;256:282–291. DOI: 10.1016/j.neuroscience.2013.10.022.
53. Mackay M.T., Molesworth C., Northam E.A., Inder T.E., Cameron F.J., DKA Brain Injury Study Group. Diabetic ketoacidosis and electroencephalographic changes in newly diagnosed pediatric patients. *Pediatr. Diabetes.* 2016;17(4):244–248. DOI: 10.1111/pedi.12284.
54. Cameron F.J., Scratch S.E., Nadebaum C., Northam E.A., Koves I., Jennings J. et al. Neurological consequences of diabetic ketoacidosis at initial presentation of type 1 diabetes in a prospective cohort study of children. *Diabetes Care.* 2014;37(6):1554–1562. DOI: 10.2337/dc13-1904.
55. Siller A.F., Lugar H., Rutlin J., Koller J.M., Semenkovich K., White N.H. et al. Severity of clinical presentation in youth with type 1 diabetes is associated with differences in brain structure. *Pediatr. Diabetes.* 2017;18(8):686–695. DOI: 10.1111/pedi.12420.
56. Marzelli M.J., Mazaika P.K., Barnea-Goraly N., Hershey T., Tsalikian E., Tamborlane W. et al. Neuroanatomical correlates of dysglycemia in young children with type 1 diabetes. *Diabetes.* 2014;63(1):343–353. DOI: 10.2337/db13-0179.
57. Ghetti S., Kuppermann N., Rewers A., Myers S.R., Schunk J.E., Stoner M.J. et al. Cognitive function following diabetic ketoacidosis in children with new-onset or previously diagnosed type 1 diabetes. *Diabetes Care.* 2020;43(11):2768–2775. DOI: 10.2337/dc20-0187.
58. Hannonen R., Tupola S., Ahonen T., Riikonen R. Neurocognitive functioning in children with type-1 diabetes with and without episodes of severe hypoglycaemia. *Dev. Med. Child Neurol.* 2003;45(4):262–268. DOI: 10.1017/s0012162203000501.
59. Northam E.A., Rankins D., Lin A.R., Wellard M., Pell G.S., Finch S.J. Central nervous system function in youth with type 1 diabetes 12 years after disease onset. *Diabetes Care.* 2009;32(3):445–50. DOI: 10.2337/dc08-1657.
60. Gaudieri P.A., Chen R., Greer T.F., Holmes C.S. Cognitive function in children with type 1 diabetes: a meta-analysis. *Diabetes Care.* 2008;31(9):1892–1897. DOI: 10.2337/dc07-2132.
61. Semenkovich K., Bischoff A., Doty T., Nelson S., Siller A.F., Hershey T. Clinical presentation and memory function in youth with type 1 diabetes. *Pediatr. Diabetes.* 2016;17(7):492–499. DOI: 10.1111/pedi.12314.
62. Cato M.A., Mauras N., Mazaika P., Kollman C., Cheng P., Aye T. et al. Longitudinal evaluation of cognitive functioning in young children with Type 1 diabetes over 18 months. *J. Int. Neuropsychol. Soc.* 2016;22(3):293–302. DOI: 10.1017/S1355617715001289.
63. Nadebaum C., Scratch S.E., Northam E.A., Cameron F.J. Diabetic Ketoacidosis and Brain Injury Study Group. Clinical utility of mental state screening as a predictor of intellectual outcomes 6 months after diagnosis of type 1 diabetes. *Pedi-*

atr. Diabetes. 2012;13(8):632–637. DOI:10.1111/j.1399-5448.2012.00870.x.
64. Ghetti S., Lee J., Holtpatrick C., DeMaster D., Glaser N. Diabetic ketoacidosis and memory impariment in children with Type 1 diabetes. *J. Pediatr*. 2009;156(1):109–114. DOI:10.1016/j.jpeds.2009.07.054.
65. Cato M.A., Mauras N., Ambrosino J., Bondurant A., Conrad A.L., Kollman C. et al. Cognitive functioning in young children with type 1 diabetes. *J. Int. Neuropsychol. Soc.* 2014;20(2):238–47. DOI: 10.1017/S1355617713001434.
66. Skipper N., Gaulke A., Sildorf S.M., Eriksen T.M., Nielsen N.F., Svensson J. Association of type 1 diabetes with standardized test scores of Danish schoolchildren. *JAMA.* 2019;321(5):484–492. DOI: 10.1001/jama.2018.21819.
67. Ohmann S., Popow C., Rami B., König M., Blaas S., Fliri C. et al. Cognitive functions and glycemic control in children and adolescents with type 1 diabetes. *Psychol. Med.* 2010;40(1):95–103. DOI: 10.1017/S0033291709005777.
68. Abo-El-Asrar M., Andrawes N.G., Rabie M.A., Aly El-Gabry D., Khalifa A., El-Sherif M et al. Cognitive functions in children and adolescents with early-onset diabetes mellitus in Egypt. *Appl. Neuropsychol. Child.* 2018;7(1):21–30. DOI: 10.1080/21622965.2016.1224186.
69. Na S.D., Burns T.G. Wechsler Intelligence Scale for Children-V: Test Review. *Appl. Neuropsychol. Child.* 2016;5(2):156–160. DOI: 10.1080/21622965.2015.1015337.
70. Segabinazi J.D., Pawlowski J., Zanini A.M., Wagner G.P., Sbicigo J.B., Trentini C.M. et al. Age, education and intellectual quotient influences: structural equation modeling on the study of Benton Visual Retention Test (BVRT). *Span J. Psychol.* 2020;23:e27. DOI: 10.1017/sjp.2020.30.
71. Miles S., Howlett C.A., Berryman C., Nedeljkovic M., Moseley G.L., Phillipou A. Considerations for using the Wisconsin Card Sorting Test to assess cognitive flexibility. *Behav. Res. Methods.* 2021;53(5):2083–2091. DOI: 10.3758/s13428-021-01551-3.
72. Scarpina F., Tagini S. The Stroop Color and Word Test. *Front. Psychol*. 2017;8:557. DOI: 10.3389/fpsyg.2017.00557.eCollection 2017.
73. Xourgia E., Papazafiropoulou A., Melidonis A. Antidiabetic treatment on memory and spatial learning: From the pancreas to the neuron. *World J. Diabetes*. 2019;10(3):169–180. DOI: 10.4239/wjd.v10.i3.169
74. Chutko L.S., Surushkina S.I., Iakovenko E.A., Bykova I.L., Nikishena I.S. Efficacy of cortexin in the treatment of memory disorders in children. [In Russ.]. *Zh. Nevrol. Psikhiatr. Im. S. S. Korsakova.* 2011;111(9Pt2):37–40.
75. Batysheva T.T., Platonova A.N., Chebanenko N.V., Bykova O.V. Management of cognitive impairment in children and adolescents with cerebral palsy treated with pantocalcin. [In Russ.]. *Zh. Nevrol. Psikhiatr. Im. S.S. Korsakova.* 2013;113(9):48–53.
76. Karahmadi M., Salehi M., Rezayi M., Mahaki B. Study of the effect of Memantine therapy on the treatment of dyslexia in children. *J. Res. Med. Sci.* 2017;22:137. DOI: 10.4103/jrms.JRMS_250_17. eCollection 2017.
77. Fiatarone Singh M.A., Gates N., Saigal N., Wilson G.C., Meiklejohn J., Brodaty H. et al.. The Study of Mental and Resistance Training (SMART) study-resistance training and/or cognitive training in mild cognitive impairment: a randomized, double-blind, double-sham controlled trial. *J. Am. Med. Dir. Assoc.* 2014;15(12):873–880. DOI: 10.1016/j.jamda.2014.09.010.
78. Biessels G.J., Kerssen A., de Haan E.H., Kappelle L.J. Cognitive dysfunction and diabetes: implications for primary care. *Prim. Care Diabetes.* 2007;1(4):187–193. DOI: 10.1016/j.pcd.2007.10.002

Authors' information

Magomedova Kamila Sh. – General Practitioner, Stepnovskaya District Hospital, Stavropol Region, Stepnovsky District, Stepnoye Village, kamilla.2017@bk.ru, http://orcid.org/0000-0003-1167-907 - 4

Bykov Yuri V. – Cand. Sci. (Med.), Teaching Assistant, Department of Anesthesiology and Resuscitation with the Course of Further Vocational Education, Stavropol State Medical University, Stavropol; Children's City Clinical Hospital named G. K. Filippsky, Stavropol, yubykov@gmail.com, http://orcid.org/0000-0003-4705-3823

Baturin Vladimir A. – Dr. Sci. (Med.), Professor, Department of Clinical Pharmacology with the Course of Further Vocational Education, Stavropol State Medical University, Stavropol, prof.baturin@gmail.com, http://orcid.org / 0000-0002-6892-3552

(✉) **Bykov Yuri V.,** yubykov@gmail.com

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