REVIEW ARTICLE

Optic Nerve and Cerebral Edema in the Course of Diabetic Ketoacidosis

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Abstract: In the recent years we have been observing an increased incidence of type 1 diabetes in children and adolescents. This leads to a more frequent acute complication of type 1 diabetes among children with hyperglycemia. The most common of these is diabetic ketoacidosis (DKA), while cerebral edema is the most dangerous. In children with DKA, cerebral edema most often presents with clinical symptoms but may also appear in the so-called "subclinical" form. That is why the search continues for new methods of assessing and monitoring cerebral edema in the course of DKA treatment. Ultrasonographic optic nerve sheath diameter (US ONSD) assessment is performed in various clinical scenarios when cerebral edema is suspected. It is most often performed in adult patients but increasingly often in children. US ONSD assessment is useful in the treatment of DKA in children with type 1 diabetes. This manuscript provides an overview of research results available in PubMed and other available databases on the course of treatment of DKA in children with type 1 diabetes.

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Current Neuropharmacology

INTRODUCTION

Epidemiology of Type 1 Diabetes

Type 1 diabetes is an increasing problem among children due to the dramatically rising incidence [1, 2]. In the recent years we have been observing an increased incidence of type 1 diabetes in children and adolescents. According to the International Diabetes Federation (IDF) data from 2006, about 440,000 children suffered from type 1 diabetes worldwide and 70,000 new cases were reported that year [3]. Whereas the 2013 data from the IDF show an estimated type 1 diabetes prevalence of 497,000 children and an estimated incidence of 79,100 new cases in children under 15 years of age. The largest populations of children with type 1 diabetes live in Europe (26%) and North America with the Carribean region (together about 22%) [4]. The most dynamic increase in type 1 diabetes incidence, over 9% annually, is noted in the North-Eastern Europe with Poland leading in the statistics [5]. This is more than triple the global average incidence which remains at the level of 3% annually [3, 4].

Diabetic Ketoacidosis (DKA)

The constantly increasing incidence of type 1 diabetes, particularly among the small children, leads to an increase in acute complications of this disease. According to the International Society for Pediatric and Adolescent Diabetes (ISPAD), diabetic ketoacidosis is the most frequent of the acute complications of diabetes type 1 [6]. The frequency of DKA at diagnosis around the world ranges from 12.8% to 80%. The highest frequencies are noted in the United Arab Emirates, Saudi Arabia and Romania, whereas the lowest in Sweden, the Slovak Republic and Canada [7]. Rewers *et al*. estimated that DKA prevalence was significantly higher in patients with type 1 diabetes (29.4%) rather than in those with type 2 diabetes (9.7%) and the prevalence decreased with age from 37.3% in children aged 0-4 years to 14.7% in those 15-19 years old [8]. Olak-Bialon *et al*. reported similar results, estimating DKA in 33% of children upon diagnosis of type 1 diabetes. Significantly higher incidence of diabetes in children with diabetes type 1 was also noted in children under 4 years of age [9]. In retrospective studies of 585 patients under 15 years of age diagnosed with newly-diagnosed type 1 diabetes Hekkala *et al*. demonstrated that the overall frequency of DKA decreased over a 20-year period in northern Finland. However, children aged <2 years were still at high risk for DKA upon diagnosis [10]. According to Ciechanowska *et al*. despite the increasing incidence of DKA over the last 20 years in Poland, the frequency of DKA in this patient group remains stable at about 26% [11]. As demonstrated by Maniatis *et al*., the children who are at the highest risk of DKA are: under 4 years of age, come from families without history of type 1 diabetes, come from low-income families, have less access

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to primary care and live in regions with low type 1 diabetes incidence [12].

The frequency of DKA in children already treated for type 1 diabetes is around 1-10% annually [13, 14]. In this patient group, those who are at risk of DKA have a chronic metabolic imbalance, come from pathological social groups or do not take insulin regularly [11]. Patients who are treated with continuous subcutaneous insulin infusion (insulin pump therapy) with rapid-acting insulin analogues are at particular risk of developing DKA. In this patient group DKA may develop in as little as 6-10 hours, often due to the clogging of the infusion line, pump failure or the accidental removal of the infusion set during physical activity or sleep [11].

Death is the most serious complication associated with DKA and it occurs in 0.15-0.30% of children with type 1 diabetes [6]. The most common cause of death in the course of DKA in these patients is cerebral edema. Although the mortality due to cerebral edema is constantly decreasing, it still is the cause of 60-90% of deaths among children with type 1 diabetes [6]. The other causes of death in the course of DKA are: hypokalemia, hypocalcemia, hypomagnesemia, severe hypophosphatemia, hypoglycemia, cerebral venous sinus thrombosis, basal artery thrombosis, intracerebral hemorrhage, ischemic stroke, venous thrombosis, pulmonary embolism. The less frequent causes of death in the course of DKA are also: sepsis, mucormycosis, aspiration pneumonia, pulmonary edema, adult respiratory distress syndrome (ARDS), pneumothorax, rhabdomyolysis, ischemic bowel necrosis, acute renal failure and acute pancreatitis [6].

CEREBRAL EDEMA IN THE COURSE OF DKA

The frequency of cerebral edema in children with DKA is estimated at 0,7-1:100 and is higher in the at-risk groups such as children: <5 years of age, in whom DKA is the first symptom of type 1 diabetes, with long history of hyperglycemia, with high blood urea nitrogen concentration, with metabolic acidosis and low partial pressure of carbon dioxide (pCO_2) upon DKA diagnosis [15, 16]. In addition, higher risk of cerebral edema is connected with therapeutic errors, e.g. administration of bicarbonate, excess intravenous fluid administered in the first 4 hours of treatment or administering insulin in the first hour of fluid therapy [16-18].

Cerebral edema in the course of DKA is most frequent within 12 hours of starting the intravenous insulin therapy and rarely occurs before the start of treatment or late in the treatment (24-48 hours). Children without neurological symptoms during DKA might have subtle signs of brain injury such as memory deficits [6]. This might be caused by the so-called "sublinical" cerebral edema which has been confirmed by the magnetic resonance (MR) and computer tomography (CT) imaging of the central nervous system (CNS) in majority of children with DKA [15, 19-21]. The "subclinical" cerebral edema is a state of increased fluid retention in brain tissue without causing the classic symptoms due to increased intracranial pressure (ICP) [19-21]. The daily clinical practice has been to exclude cerebral edema *via* fundoscopy. In exceptional situations it is recommended to perform CNS imaging, but this requires the

patient to be in stable enough for transport to the imaging lab, which by itself can be risky [22].

Mechanism of Cerebral Edema in the Course of DKA

The pathophysiology of cerebral edema in the course of DKA is still debated and three potential etiologies are under scrutiny: 1) blood-brain barrier and vascular disturbances, 2) astrocyte edema and cytotoxic edema and 3) disturbances of cell membrane function [23-25]. The vascular cause appears to be the most likely, suggesting that cerebral edema is the outcome of an initial extracellular hypoperfusion of the brain before the start of DKA treatment and the subsequent hyperperfusion during treatment. This hypothesis is confirmed by the fact that the severity of dehydration and hyperventilation have more influence on cerebral edema than the initial osmolality or the changes in serum osmolality [16]. Diffusion-weighted MR imaging shows that the fluid surrounding the cells is more important in the formation of cerebral edema than the osmotic edema of the cells themselves [16, 27].

Signs of Cerebral Edema

The most common signs suggesting cerebral edema in the course of DKA in children with diabetes type 1 include: headache, vomiting, slowing of heart rate, rising blood pressure and decreased oxygen saturation. In the course of DKA warning symptoms of cerebral edema are neurological changes that can be either general (such as restlessness, irritability, increased drowsiness, incontinence) or specific (paresis or paralysis of cranial nerves (most often CN III, IV or VI)) and respiratory disturbances [6].

Treatment of Cerebral Edema in the Course of DKA in Children with Type 1 Diabetes

According to the Polish Diabetes Association (PDA) and ISPAD guidelines, treatment of suspected cerebral edema must be started as soon as possible. The rate of fluid administration should be reduced by one-third and mannitol should be administered in dose 0.5-1g/kg body mass over 10-15 min. If no response to the initial dose, a second dose of mannitol should be repeated in 30-120 minutes. Hypertonic (3%) NaCl solution is a possible alternative to mannitol (2.5-5 ml/kg over 10-15 minutes), particularly in case of no response to the initial dose of mannitol. However, further studies are needed to confirm the safety of this hypertonic agent. During the treatment, the patient's head should be elevated at 30°. The staff should be prepared to intubate in case of respiratory disturbances. After stabilizing the patient's condition imaging should be considered in order to exclude intracranial hemorrhage or cerebral vessel thrombosis [6, 22].

DIAGNOSING CEREBRAL EDEMA

Fundoscopic Assessment in Cerebral Edema

Fundoscopy is widely performed in daily clinical practice and it is the recommended examination in case of suspected cerebral edema [28]. Fundus of the eye is a common term for the posterior pole of the eyeball, where the retina, blood vessels and the disc of the optic nerve are visible. This

examination is performed using an ophthalmoscope and requires the dilation of the patient's pupils using eyerops [28].

Fundoscopy has fundamental importance in the ongoing assessment of chronic complications - such examination is focused on the blood vessels and the retina with macula [29]. Whereas in emergency situations, the fundoscopic examination is focused on the disk of the optic nerve. In case of increased intracranial pressure, the optic nerve is herniating into the posterior chamber of the eye and the borders of the optic disk are blurred. This is caused by the increased cerebro-spinal fluid pressure and the sudden widening of the subarachnoid space. Due to the stiffness of the dura mater, the optic nerve is compressed. This leads to the herniation of the optic nerve into the posterior chamber of the eye, folding of the retina around the optic nerve and the widening of the transverse dimension of optic nerve [28]. According to the literature, the blurring of the optic disk's borders is a rather late sign [28].

Fundoscopy is widely used in the assessment of cerebral edema due to its non-invasiveness, easy repetition and many decades of experience in performing it. However the definite disadvantages of fundoscopy are: its subjectivenss, the need of preparation to the examination, and the fact that it is qualitative assessment which does not allow precise monitoring of the changes [28]. Preparation for the fundoscopy involves the administration of mydriatic drops, which can cause blurred vision afterwards and difficulties in assessing the pupil responses. In the pediatric population, fundoscopy is further hampered by the patient's resistance due to irritability and fear [28]. Therefore, other methods are frequently needed to detect cerebral edema.

Central Nervous System Imaging in Cerebral Edema

The ISPAD and PDA guidelines recommend CNS imaging in case of suspected cerebral edema in children with type 1 diabetes in order to exclude intracranial hemorrhage or cerebral vessel thrombosis [6, 22, 26]. In the early phase of generalized cerebral edema, CNS imaging confirms effacement of the sulci and basilar cisternal spaces (especially the suprasellar, quadrigeminal plate and ambient cisterns), compression and decrease of cerebral ventricle size and reduction of the gray-white matter differentiation. Over the course of the edema, the supratentorial space becomes uniformly hypodense in comparison to the relatively hyperdense cerebellum. Next, subfalcine or transtentorial herniation can occur [26]. An additional advantage of the MRI is the possibility to assess perfusion and perform spectroscopic analysis of particular elements of the CNS or diffusion-weighted imaging [31]. However, the major disadvantages of these imaging techniques are the need to achieve a stable clinical status before the examination, the need to transport and sedate the pediatric patient and in the case of CT, exposure to ionizing radiation [32].

Ultrasonography of the Optic Nerve Sheath Diameter in Cerebral Edema

The ultrasonographic (US) assessment of the optic nerve sheath diameter (ONSD) is usually performed in adults but increasingly in the pediatric population as well. Our experience shows that it can be successfully performed in children with DKA [33-36]. The optic nerve is technically part of the CNS and is ensheathed in the meninges. Changes in the cerebro-spinal fluid (CSF) volume and ICP cause changes in the width of the optic nerve itself as well as of the CSF-filled space under the optic nerve sheath [30].

The US assessment of the optic nerve and ONSD is most often performed using a linear probe (7.5-10 MHz or greater). The probe is placed lightly on the closed upper eyelid in patient in supine position, applying small amount of ultrasound gel. However, it is possible to assess the ONSD using a convex or endocavital probe. The ONSD is measured 3 mm posterior to the globe in the transverse plane [30, 37-42].

ONSD Assessment in Adults

One of the first report of US measurement of ONSD was published in the 1970's by Boynton *et al*. who compared ultrasound of ONSD to CT [43]. In the adult population this method is used in clinical scenarios with an underlying increase of intracranial pressure, such as severe head trauma, subarachnoid hemorrhage, intracranial hematoma or stroke [44-49]. The pathological ONSD is not unequivocally established: some authors suggest 5mm whereas others indicate 5.7-5.9mm as abnormal [46-51]. Our study of young adults (19 to 26 years) defines the normal ONSD as 4.2 ± 0.3mm [30].

In one study of patients admitted to the intensive therapy unit, the sensitivity and specificity of US assessment of ONSD in detecting increased ICP (in comparison to direct/invasive method) was respectively 88% and 93% (with the norm set at 5mm), whereas it was 74% and 100% with the norm set at 5.7mm [45, 47]. Despite using different values to define the normal ONSD, Kimberly *et al*., Soldatos *et al*. and Geeraerts *et al*. all demonstrated very strong correlations between the direct/invasive ICP measurement and US assessment of ONSD in patients with head trauma (correlation coefficients r=0.59, r=0.68, r=0.71, respectively). Furthermore, Geeraerts *et al*. found a strong correlation between the changes in ICP and US ONSD (r=0.73) [45-47]. A significant usefulness of ultrasound in comparison to CT was also found in head trauma patients - according to various authors the sensitivity of US assessment of ONSD was 74-98.6% and specificity was 65-92.8% [48-50]. A meta-analysis comparing the direct/invasive ICP measurement and US ONSD reveals that the total diagnostic odds ratio is as much as 51 (95% CI, 22-121) in other words indicating a 51x greater likelihood of diagnosing wide ONSD in patients with increased intracranial pressure than in those with normal ICP [42].

ONSD Assessment in Children

Using the keywords "optic nerve sheath diameter ultrasound" or "optic nerve sheath diameter ultrasonography" and the additional filter "Child: birth-18 years," in late July 2015 we retrieved 144 articles from PubMed, of which only 27 were relevant to the pediatric population. The scant literature confirms the diagnostic value of US assessment of ONSD in children with hydrocephalus, craniosynostosis, head trauma,

liver failure, metabolic disease (e.g. mucopolysaccharidosis) and congenital malformations [28, 37-39, 51-54]. In a recent study Haratz *et al*. assessed ONSD by ultrasound *in utero* in cases of suspected increased ICP [55].

It is accepted that in healthy children <1 year of age the ONSD should not exceed 4.0mm [37, 51, 53, 56]. Some authors indicate that ONSD should remain at <4mm up until 4 years of age [39, 56]. It is suggested to apply rigorous criteria and to consider ONSD >4.0mm as pathological [41]. In children >1 year of age (or according to some authors above age 4) ONSD should not exceed 4.5mm as in Fig. **1** [37, 51, 53, 56].
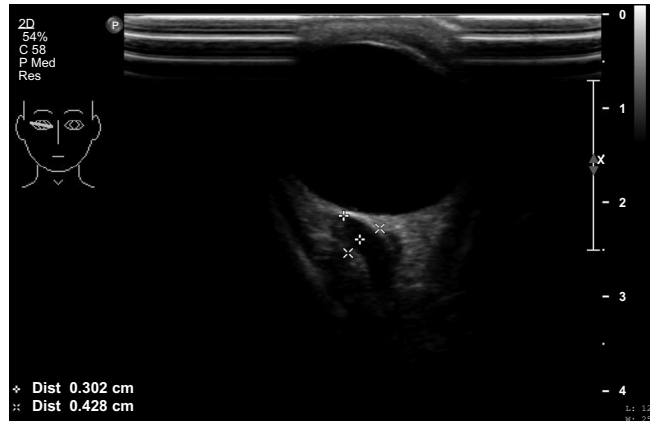

Fig. (1). Normal optic nerve sheath diameter.

If ONSD exceed 4.5mm it is a pathology and always requires further investigation, seen on Fig. **2** [56, 57]. Some authors indicate that ONSD between 4.5 and 5.0mm is a borderline value and only values >5.0mm should be regarded as increased ICP [39]. However the studies by Steinborn *et al*. and Hall *et al*. cast doubt on the previously-accepted norms as too low [58, 59].
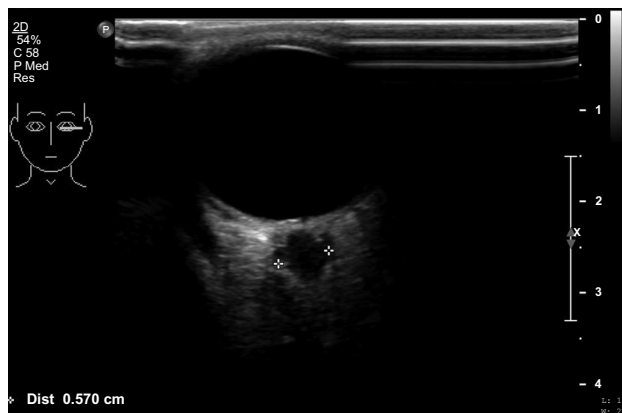

Fig. (2). Increased optic nerve sheath diameter.

The sensitivity and specificity of US assessment of ONSD in children has been assessed only in very few studies [28, 51, 60]. Le *et al*. demonstrated high sensitivity and low specificity of US ONSD in the assessment of intracranial pressure, respectively 83% (95% CI 0.60 to 0.94) and 38% (95% CI 0.23 to 0.54). A satisfactory reliability has been demonstrated between the assessments performed by an emergency department pediatrician, a sonographer specializing in ophthalmologic pathologies (kappa 0.52) and a pediatric ophthalmologist (kappa 0.64) [51]. Even better results were reported by Beare *et al*. who set 4.2mm as the borderline diameter and demonstrated the sensitivity and specificity of the US ONSD of respectively 100% and 86% [60]. Contrasting results were reported by Driessen *et al*. who compared the US assessments with CT and fundoscopy in children with craniosynostosis. They demonstrated a statistically significant correlation between the US ONSD assessment with CT (r = 0.41, p<0.001), however in comparison to fundoscopy the sensitivity of the ultrasound was low (11%) with high specificity (97%). The authors concluded that US ONSD is valuable in the quantitative assessment and monitoring of the ONSD in this patient group but fundoscopy is necessary [28].

Steinborn *et al*. suggested higher normal values of the US ONSD, on average 5.86 ± 0.71 mm. They demonstrated very high correlation with ONSD assessment *via* MRI, which on average was 5.86 ± 0.66 mm. In addition, those authors indicated high concordance correlation (CCC) between the examiners performing ultrasound (CCC = 0.93) and MR (CCC = 0.9). The differences between the results might be due to the use of a high-frequency (17 MHz) probe [61]. Similar normal values of the ONSD were noted by Hall *et al*. in their analysis of patients with ventriculoperitoneal shunt (VPS) insufficiency, also using a high-frequency (14 MHz) probe. Among the patients with VPS insufficiency, the ONSD was 4.5 ± 0.9mm, whereas in children with a correctly functioning VPS it was 5.0 ± 0.6 mm. In this study, the sensitivity of the US ONSD assessment in diagnosing VPS insufficiency was 61.1 % (95 % CI 35.7-82.7) and specificity 22.2 % (95 % CI 6.4-47.6 %) [59]. To our knowledge, currently there is no published meta-analysis regarding the use of US ONSD assessment in children.

Pros and Cons of Ultrasound Assessment of ONSD

As indicated earlier, the edema of the optic nerve disk results from the following sequence of events: widening of the optic nerve, protrusion of the optic disk and edema of the optic disk [62]. Therefore, the US assessment of a widening ONSD might be an earlier sign of increased intracranial pressure than the edema of the optic nerve disk seen in fundoscopy [37, 62]. This fact might be very useful in the management of patients in whom changes of clinical state and homeostasis disturbances occur very quickly, as in the case of children with DM1 suffering from DKA [6]. A study by Newman *et al*. indicates the possibility of monitoring the changes of intracranial pressure *via* ultrasonography of ONSD. The authors demonstrated a correlation between the changes in intracranial pressure and ONSD during several days and even months of follow-up [37]. The results by Driessen *et al*. in children with craniosynostosis indicates that ultrasound assessment of ONSD correlates with direct measurement of ICP and might change dynamically even during the night [63].

CT or MR studies of children with DKA confirmed the existence of the so-called "subclinical" cerebral edema [19-21]. It appears that the increased water retention in the CNS

tissue in the course of DKA and the associated subclinical cerebral edema might also be correlated with an increased ONSD. However, MR and CT have their limitations. They often require sedation of small children and this additional procedure might cause complications in the intensive therapy of life-threatening metabolic imbalances, one of which is DKA in the course of type 1 diabetes in children. Another limitation of those imaging techniques is the need for patient transport to the imaging lab [51]. In the case of CT scans, one must keep in mind the harms of exposing a child to ionizing radiation.

It is noteworthy that fundoscopy is a qualitative examination whereas US ONSD is quantitative, thus making it much easier to objectively monitor changes in the optic nerve and its sheath [28]. Another advantage of ultrasonography is its simplicity and ease of use. Le *et al*. analyzed children admitted to the pediatric emergency department due to suspected increase in intracranial pressure and demonstrated a high correlation between the measurements obtained by a pediatrician assessing the US ONSD, an ultrasonographer specializing in ophthalmic pathologies and a pediatric ophthalmologist. Such results indicate that a trained physician will correctly assess the ONSD using ultrasound [51]. Our earlier study indicated that even when using different probes (linear and convex), the ONSD measurements obtained by inexperienced examiners were not statistically different [30].

Furthermore, the US assessment of ONSD is relatively cheap, non-invasive, does not require patient transport (can be easily performed at the bedside), is not dependent on the patient's position (such as supine vs half-seated), does not require preparation before the examination (mydriatic drops, contrast agents), is performed quickly (less than one minute) and can be reproduced as often as needed which is of paramount importance in monitoring DKA treatment in children with type 1 diabetes [28, 49, 50, 56, 60, 64].

ONSD IN CHILDREN WITH TYPE 1 DIABETES

Literature about the US assessment of ONSD in type 1 diabetes patients with DKA are limited to preliminary findings and single patient case reports [33-36, 51]. Preliminary reports indicate a statistically significant difference in ONSD on admission vs after correcting the metabolic parameters (3.69 ± 0.59mm and 3.31 ± 0.33mm (p=0.001), respectively) in a group of 24 children age 8.1 ± 4.0 with a new diagnosis of type 1 diabetes (6 with DKA, one in hyperglycemic hyperosmolar state (HHS) and 17 without DKA). In the group without DKA, a statistically significant difference in the ONSD measurements was noted (3.64 ± 0.40mm *vs* 3.39 ± 0.32 (p=0,0209)). Whereas in the group with DKA the difference in ONSD measurements was on the border of statistical significance ($3,74 \pm 0,96$mm *vs* $3,12 \pm 0,32$mm (p=0,0581)) (Table **1**) [35].

Table 1. Results of ultrasound-based optic nerve sheath diameter measurements.

Patient Group	No. of Patients	ONSD on Admission [mm]	ONSD after Treatment [mm]	p values
without DKA	17	3.64 ± 0.40	3.39 ± 0.32	P=0.020
DKA	6	3.74 ± 0.96	3.12 ± 0.32	P=0.058
HHS	1	4.2	3.25	n/s
TOTAL	24	3.69 ± 0.59	3.31 ± 0.33	P=0.001

DKA - diabetic ketoacidosis, HHS - hyperglycemic hyperosmolar state, ONSD - optic nerve sheath diameter.
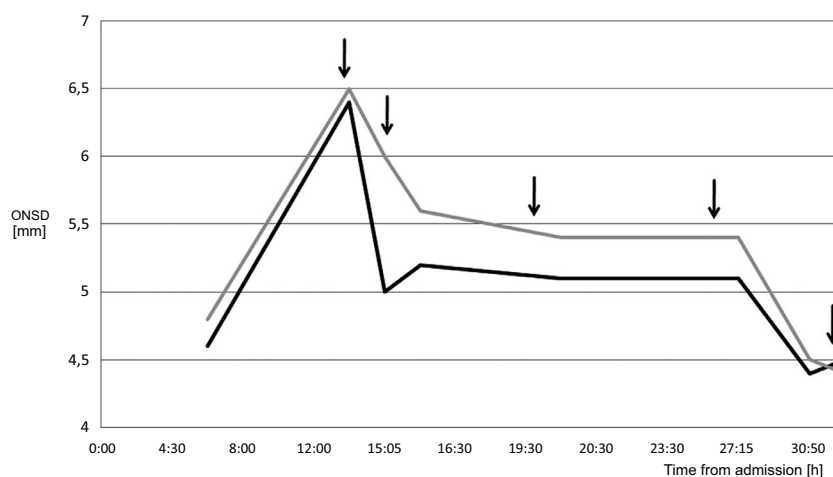

Fig. (3). Changes in the ONSD in course of DKA treatment of a single patient. ONSD of the right eye (black line) and ONSD of the left eye (grey line) in the course of DKA treatment. Time when mannitol was administered intravenously (black arrows).

In children already treated for type 1 diabetes and admitted to the hospital due to DKA, the ONSD has been noted to change during aggressive intravenous treatment with peaks and troughs between 4.5mm and 6.5mm in as little as 7 hours. Such changes in the diameters are correlated with the changes in the biochemical and clinical parameters as well as the treatment of edema (Fig. **3**) [33].

SUMMARY

In summary, our institution's experiences and the case reports in literature are not sufficient to draw far-reaching conclusions about the usefulness of the US assessment of ONSD in the course of DKA treatment in children with type 1 diabetes. However, the literature regarding cerebral edema in children and adults indicate that the US assessment of ONSD is an additional tool for assessing the risk of cerebral edema. The US assessment of ONSD might be particularly useful in monitoring the effectiveness of DKA treatment in children and in prevention of cerebral edema and other acute complications of type 1 diabetes.

CONFLICTS OF INTEREST

The authors do not have any conflicts of interest to report.

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