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CAN BRAIN EDEMA BE PREDICTED WITH OPTIC NERVE SHEATH DIAMETER MEASUREMENT IN CASES WITH DIABETIC KETOACIDOSIS?: A PRELIMINARY STUDY

DİYABETİK KETOASİDOZLU OLGULARDA OPTİK SİNİR KILIF ÇAPI ÖLÇÜMÜ İLE BEYİN ÖDEMİ ÖNGÖRÜLEBİLİR Mİ?: BİR ÖNCÜL ÇALIŞMA

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ABSTRACT

Objective: The clinical signs and symptoms of brain edema resulting from diabetic ketoacidosis (DKA) may not always be obvious. When the intracranial pressure increases, the optic nerve sheath diameter (ONSD) simultaneously increases and can be imaged with ultrasonography. We aimed to discuss the determinative features of ONSD measurements in brain edema (BE) in DKA.

Materials and Methods: Patients who were classified as having mild, moderate and severe DKA were included in the study. Transorbital ultrasonography was performed during the first two hours of treatment while the patients remained in the supine neutral position with their eyes closed. The optic nerve sheath diameters, which appeared as a hypoechoic double-edged line 3 mm deep to the globe, were measured. The same measurements were repeated in outpatient clinic controls. The ONSD values and metabolic, neurological conditions of the patients were compared.

Results: Eight patients with a mean age of 8.8±3 (Standard Deviation (SD)) years were included in the study. Seven of them presented with moderate to severe DKA. Two patients suffering from headaches were found to have mild BE according to the brain computerized tomography (CT). The ONSD was 5.7±0.93

ÖZET

Amaç: Diyabetik ketoasidozda (DKA) beyin ödeminin klinik belirti ve semptomları her zaman açık olmayabilir. İntrakraniyal basınç arttığında, optik sinir kılıfı çapı (OSKÇ) aynı anda artar ve ultrasonografi ile görüntülenebilir. Bu çalışmada, DKA'da beyin ödemi (BÖ) varlığında OSKÇ değerlerinin belirleyici özelliklerinin tartışılması amaçlandı.

Gereç ve Yöntem: Çalışmaya hafif, orta ve şiddetli DKA tanılı hastalar dahil edildi. Tedavinin ilk iki saatinde hastanın gözleri kapalı, sırtüstü nötral pozisyonda yatarken transorbital ultrasonografi uygulandı. Globun 3 mm derinliğinde hipoekoik çift kenarlı bir çizgi olarak görünen optik sinir kılıf çapları ölçüldü. Poliklinik kontrollerinde de aynı ölçümler tekrarlandı. Hastaların OSKÇ değerleri ile metabolik ve nörolojik durumları karşılaştırıldı.

Bulgular: Yaş ortalaması 8,8±3 (SS) yıl olan sekiz hasta çalışmaya dahil edildi. Bunlardan yedisinde orta-şiddetli DKA vardı. Bilgisayarlı beyin tomografisinde (BT) baş ağrısı olan iki hastanın hafif BÖ olduğu görüldü. Orta-şiddetli DKA'lı hastalarda OSKÇ 5,7±0,93 mm (ortalama±SD (Standard Sapma)), hafif DKA'lı tek hastada ise 4 mm idi. BT'de BÖ'lü 2 hastanın OSKÇ'si 6,8 mm ve 5,9 mm idi. Şiddetli DKA'lı beş hastanın tedaviden bir hafta sonraki poliklinik kontrolünde ortalama OSKÇ 4,4±0,32 mm idi.

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mm (mean±SD) in the patients with moderate-severe DKA and 4 mm in the single patient with mild DKA. The ONSDs of the two patients with BE on the CT were 6.8 mm and 5.9 mm. The mean ONSD of the five patients with severe DKA was 4.4±0.32 mm in the outpatient clinic checks.

Conclusion: The measurement of ONSD by USG may be a supportive method for predicting BE in children with DKA.

Keywords: Diabetic ketoacidosis, optic nerve sheath diameter measurement, brain edema

Sonuç: USG ile OSKÇ ölçümü, DKA'lı çocuklarda BÖ'yü tahmin etmek için destekleyici bir yöntem olabilir.

Anahtar Kelimeler: Diyabetik ketoasidoz, optik sinir kılıf çapı ölçümü, beyin ödemi

INTRODUCTION

Diabetic ketoacidosis (DKA) is the most common complication of Type 1 Diabetes Mellitus (DM). It's clinical picture consists of ketonemia, ketonuria, hyperglycemia and acidosis (1-3). The first diagnosis of type 1 DM is with a DKA attack in 15-67% of the patients (4, 5).

Brain edema is the most severe complication of DKA attacks and is seen in less than 1% of patients but can be fatal. Clinical signs and symptoms may not always be obvious. The pathogenesis is still not clear and associations with dehydration, cerebral hypoperfusion or sudden changes in serum osmolality have been suggested (2).

Detecting the presence of a brain edema (BE) as early as possible and being able to predict the condition before obvious clinical symptoms develop are critical. An effective, non-invasive and method that can provide guidance and prevent secondary damage is not currently available.

The optic nerve extends from the intracranial subarachnoid space to the intraorbital area as an extension of the brain and is surrounded by layers of the meningeal membrane. When intracranial pressure (ICP) increases, the structure reflects this increased subarachnoid pressure from the intracranial area directly to the intraorbital area. Increased ICP is observed as a simultaneous increase in the optic nerve sheath diameter (ONSD). ONSD measurements can be easily performed with ultrasonography at the bedside. This method has been shown to be effective and reliable in the diagnosis of increased ICP (6-9). However, there are very limited studies on the practicality and power of this method in patients with DKA. Here, in this preliminary evaluation, we discuss the possibility of predicting the presence of brain edema during a DKA attack using ONSD measurements.

MATERIALS AND METHODS

We evaluated the data of the eight DKA patients, six of whom were newly diagnosed, seen at the Çukurova University School of Medicine's Pediatric Emergency Department and followed-up and treated in our unit. This study was approved by the Ethical Committee of the Çukurova University (Date: 09.08.2021, No: 113).

Patients diagnosed with DKA were included in the study. They had been treated according to our hospital DKA treatment protocols. Patients were included after providing written consent and after detailed information about the ultrasonographic ONSD measurement procedure was provided to the patient and family. Their ultrasonographic ONSD measurements were all conducted by the same pediatric emergency physician who was trained in ultrasonography and who had more than 2 years of experience. The procedure was performed within the first two hours of treatment. The ultrasonographic ONSD measurements were then repeated when the patient attended their routine out patient follow-up one week after the DKA treatment was completed.

Transorbital ultrasonography (USG) was performed on the horizontal and sagittal axes with a Sonosite Edge® USG device with a 6-15 MHz receiver using a method reported to have good reliability in previous studies (6, 7). The patient's eyes were kept closed while they were in the supine neutral position without sedation. Both globes and the optic nerve sheath diameters, which appeared as a hypoechoic double-edged line 3 mm deep at the optic nerve exit site, were imaged. The optic nerve sheath diameter at this point was measured in both the longitudinal and transverse sections in the frozen images. The mean of the four measurements was calculated and recorded.

The clinical and laboratory values at presentation and the characteristics of the treatment process were obtained from the patient records. Patients were classified as mild (venous pH 7.20-7.30, bicarbonate 10-15 mmol/L), moderate (venous pH 7.10-7.20, bicarbonate 5-10 mmol/L) and severe (venous pH <7.10, bicarbonate <5 mmol/L)) DKA according to their metabolic state at presentation (10).

Statistical analysis

Descriptive statistical analysis was performed. All analyses were performed using the IBM SPSS Statistics version 20.0 statistical software package. Normally distributed variables were expressed as mean±SD. The statistical level of significance for all tests was considered to be 0.05.

RESULTS

The eight patients, aged 5.5 to 13 years, consisted of four males and four females. They had presented at our

emergency department with symptoms of fatigue, nausea, and vomiting. One patient was diagnosed with mild DKA and all the others with moderate to severe DKA. The vital signs of the patients, aside from acidotic respiration, were consistent with age and all patients were hemodynamically stable. Ophthalmoscopic examination revealed no papillary stasis. Only two patients had headaches and their Glasgow Coma Scale (GCS) scores were 12 and 13. Their brain computed tomography (CT) investigations revealed mild brain edema. Demographic, clinical, and laboratory characteristics and the ONSD values are presented in Table 1 while ONSD examples are presented in Figures 1a and 1b.

Fluid and insulin treatment was started in accordance with the unit's DKA treatment protocol (10). Two patients were monitored in the pediatric intensive care unit and the others at the pediatric endocrinology department. All were discharged with full recovery and without a problem.

The initial mean (SD) value of ONSD of the seven patients with moderate-severe DKA was 5.7 (0.93) mm. The ONSD of the patient with mild DKA was 4 mm (Figure 1a, b). The ONSD values of the two patients showing brain edema on the CT were 6.8 mm and 5.9 mm, respectively. The

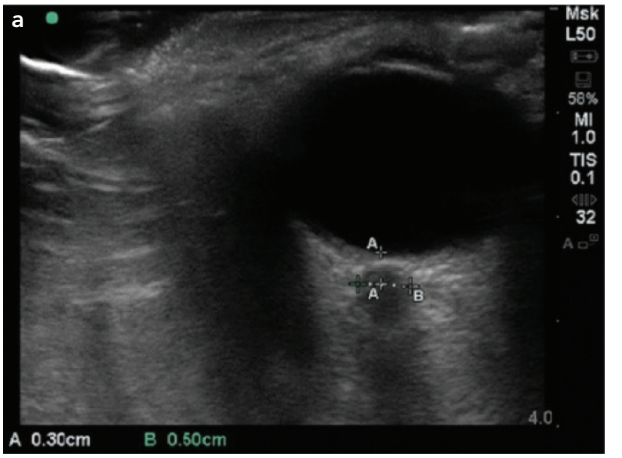

Figure 1a. A sample image from patients

mean (SD) ONSD of the five patients with moderate and severe DKA was 4.4(0.32) mm during the symptom-free follow-up one week after discharge and the difference was statistically significant (p: 0.008).

A high negative correlation was found between the ONSD and GCS values and the partial carbon dioxide ($PaCO_2$) levels in blood gases at admission (r: -0.859,

Table 1: Demographical, clinical, laboratory, and ONSD results of the patients

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Age (year)	12	13	6	6	7	13	8	6
Gender	M	F	F	F	F	M	M	M
Physical examination	Acidotic respiration	Acidotic respiration	Acidotic respiration	Acidotic respiration	Acidotic respiration	Acidotic respiration	Acidotic respiration	Acidotic respiration
GKS	15	15	12	13	13	15	13	14
Corrected Na	139	137	139	141	140	138	140	141
pH	7.0	7.09	6.8	7.08	7.1	7.2	7.1	7.17
HCO3	7	7.4	5	7.6	8.6	14	9	10
PaCO2	14	15	9	15	16	34	18	19
Blood sugar (mg/dl)	414	424	472	360	365	352	446	540
DM/year	6	6	New diagnosis	New diagnosis	New diagnosis	New diagnosis	New diagnosis	New diagnosis
Symptoms associated brain edema	Non	Non	Headache	Headache	Non	Non	Non	Non
DKA severity	Severe	Severe	Severe	Severe	Moderate	Mild	Moderate	Moderate
Braine edema at CT	Non applied	Non applied	+	+	Non applied	Non applied	Non applied	Non applied
Initial ONSD/mm	5.1	4.9	6.8	5.9	7.0	4	5.6	5.2
Control ONSD/mm	4.4	4	4.6	4.1	4.9	-	-	-

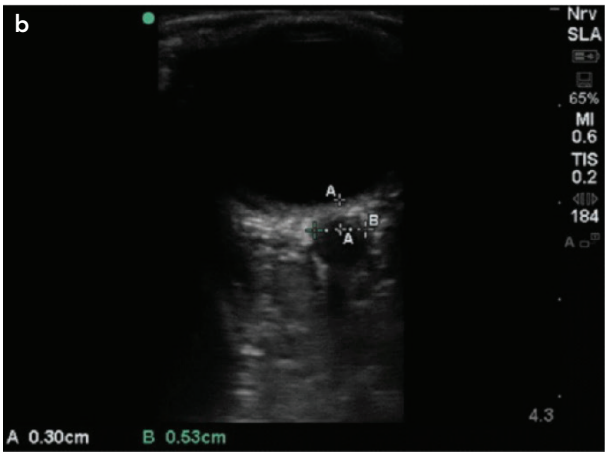

Figure 1b. A sample image from patients

p: 0.006 and r: -0.71, p: 0.04, respectively). A decrease in the GCS score from 15 was associated with an increase in ONSD measurements. This good level of correlation was statistically significant (r: 0.901 p: 0.02)

DISCUSSION

The results of this preliminary study suggest that the progress of clinical neurological findings and increased ONSD in children with moderate to severe DKA may be associated with the severity of the metabolic impairment and the presence of clinical and subclinical brain edema. Therefore, early diagnosis of BE is needed using a convenient method that is easy to administer at the bedside.

Detection of papillary stasis with fundoscopic examination is a late stage finding of brain edema and is therefore not reliable for early BE diagnosis. CT has risks such as radiation side effects and requires transport and sedation (8, 11, 12). Monitorization with invasive intracranial pressure measurement is the gold standard method for BE diagnosis but is not practical for emergencies (10).

The optic nerve sheath consists of three meningeal membranes. Fresh cadaver studies have shown that the cerebrospinal fluid circulates in the subarachnoid space and that the intracranial and intraorbital subarachnoid space pressure is the same (8, 12). It has been reported that the first marker in BE is an ONSD increase, and this is most prominently observed at a distance of 3 mm behind the globe (6-8). ONSD values measured with USG and Magnetic Resonance Imaging have been shown to be compatible in studies conducted in healthy children and adolescents (8, 12). Although a definite cut-off value has not been determined yet, an ONSD limit (cut-off) value with USG of 5.7-5.9 mm has been reported to have very high sensitivity (65-84%) and specificity (71-100%) when compared with the presence of brain edema on CT images (9, 13, 14).

The increase in ONSD as measured with USG has been shown to be useful in diagnosing BE early and monitoring the response to treatment in studies on patients with increased ICP due to traumatic or non-traumatic brain injury (6, 7, 9, 12-14).

A few studies have investigated the use of ultrasonographic ONSD measurements in the diagnosis and follow-up of BE in pediatric and adult hyperglycemia and in DKA patients. Bergman et al. found no statistically significant difference between the ONSD measurements in their study where they included patients aged 7-18 years with well-controlled DM, DKA and hyperglycemic non-DKA (15). Hensen et al. reported no significant difference between changes in ONSD during treatment in their pilot study on seven patients aged 4-17 years who were diagnosed with DKA without clinical suspicion of BE. They measured ONSD at the first hour, 8th hour and 24th hour of treatment (16). In our study the ONSDs of the seven patients with moderate and severe DKA were 4.9 to 7 mm (mean: 5.7±0.93 mm). The ONSD of our only patient with mild DKA was lower (4 mm). The ONSDs of two patients with severe DKA who underwent CT because they had headaches and low GCS scores (12 and 13) were 6.8 and 5.9 mm. These measurements were above the cut-off values that could indicate brain edema as reported in the literature, indicating that the DKA had become more severe. The ONSD increase also became significantly more pronounced (11, 13, 14).

The ONSD of these two patients measured at the symptom-free follow-up one week later was found to be 4.6 mm and 4.1 mm, respectively, and had decreased below the brain edema related cut-off values reported in the literature. A statistically significant difference was found between the mean ONSDs of the moderate to severe DKA patients measured at presentation and during the one-week follow-up. This change may indicate that the ONSD value is within normal limits when the children with DM are normoglycemic, but then increases compared to the basal values in the moderate to severe DKA state.

Another finding in our study, ONSD increase and/or brain edema in CT were present in patients with decreased GCS scores. There was a statistically significant negative correlation between the GCS values and the ONSD measurements of our patients. It can be recommended that evaluation of GCS at frequent intervals together with serial ONSD measurements in DKA patients with DKA may help in the early diagnosis of subclinical and clinical brain edema.

The results of this preliminary study suggest that the progress of clinical neurological findings and increased ONSD in children with moderate to severe DKA may be associated with the severity of the metabolic impairment and the presence of clinical and subclinical brain ede-

ma. However, prospective, and large-scale studies are required to determine the ONSD cut-off values that indicate the presence of clinically significant brain edema requiring intervention.

CONCLUSION

This study reveals that the measurement of ONSD using USG may be a supportive method for predicting BE in children with DKA. Prospective and large-scale studies are required.

Ethics Committee Approval: This study was approved by the Ethical Committee of the Çukurova University (Date: 09.08.2021, No: 113).

Informed Consent: Written consent was obtained from the participants.

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