CASE REPORT

Diffuse Intracranial Hemorrhages, Acute Peripheral Neuropathy, and Acute Kidney Injury in a Newly Diagnosed Diabetes Patient with Severe Diabetic Ketoacidosis: A Case Report and Literature Review

Yeon Ju Woo¹, Hyun Sook Hong², Soo Jeong Choi³, Young-Lim Shin¹

Departments of ¹Pediatrics and ²Radiology, ³Division of Nephrology, Department of Internal Medicine, Soonchunhyang University Bucheon Hospital, Soonchunhyang University College of Medicine, Bucheon, Korea

Diabetic ketoacidosis (DKA) is a common complication associated with pediatric type 1 diabetes mellitus (DM). Although cerebral edema is the major cause of death in DKA, there is a possibility of the occurrence of other dangerous complications involving multiple systems, thereby contributing to mortality and morbidity. Herein, we report the case of a 13-year-old girl with new-onset type 1 DM and severe DKA. Her condition was further complicated by the occurrence of diffuse intracranial hemorrhages, acute kidney injury requiring hemodialysis, and peripheral neuropathy. Patients with severe acidosis require careful monitoring of kidney function and neurological complications, and these conditions should be treated appropriately.

Keywords: Diabetic ketoacidosis; Hemorrhage; Acute kidney injury; Peripheral nervous system diseases

INTRODUCTION

Diabetic ketoacidosis (DKA) is an acute fatal complication associated with diabetes mellitus (DM) and is characterized by hyperglycemia, ketosis, and metabolic acidosis. The severity of DKA is classified as mild, moderate, or severe depending on the degree of acidosis (mild: venous pH < 7.3 or bicarbonate < 15 mmol/L; moderate: pH < 7.2, bicarbonate < 10 mmol/L; and severe: pH < 7.1, bicarbonate < 5 mmol/L) [1]. It contributes to mortality and morbidity in the affected individuals. The principal complications of DKA include cerebral edema, electrolyte imbalance, and hypoglycemia, of which cerebral edema is the leading cause of death. Moreover, rare complications involving various organ systems have also been reported to lead to mortality and morbidity in patients with DKA. These include neurologic complications other than cerebral edema, venous thrombosis, sepsis, pulmonary edema, rhabdomyolysis, and acute pancreatitis [2]. Furthermore, stroke accounts for approximately 10% of all intracranial complications of DKA and should be paid requisite attention because it can cause sudden

changes in consciousness, and the diagnosis could be mistaken for cerebral edema [3]. Peripheral neuropathy after ketoacidosis is another neurological complication of DKA. Although chronic progressive peripheral neuropathy is common in diabetes patients, acute peripheral neuropathy after ketoacidosis has been rarely reported, and the mechanism underlying the same remains unclear.

We, herein, report a case of DKA along with intracranial hemorrhage, acute peripheral neuropathy, and acute kidney injury (AKI). The patient underwent hemodialysis and presented rare complications of DKA, which is not usually manifested as one of the earliest consequences of type 1 DM.

CASE REPORT

A previously healthy 13-year-old girl visited the emergency room with abdominal pain and nausea that had begun a day earlier. She had been taking medicine prescribed for gastroenteritis at a primary hospital. At the initial presentation, her consciousness was clear, but she looked acutely ill with dehydrated lips and tongue. On

Correspondence to: Young-Lim Shin

Department of Pediatrics, Soonchunhyang University Bucheon Hospital, Soonchunhyang University College of Medicine, 170 Jomaru-ro, Wonmi-gu, Bucheon 14584, Korea

Tel: +82-32-621-5407, Fax: +82-32-621-5016, E-mail: ylshin@schmc.ac.kr

Received: Sep. 22, 2020 / Accepted after revision: Oct. 20, 2020

© 2020 Soonchunhyang Medical Research Institute

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<https://creativecommons.org/licenses/by-nc/4.0/>).

physical examination, her weight was 42 kg (10th–25th percentile), height was 155 cm (25th–50th percentile), and body mass index was 17.48 kg/m² (10th–25th percentile). Her body temperature was 37.2°C, blood pressure was 130/80 mm Hg, heart rate was 130 beats/min, and respiratory rate was 16 breaths/min. Her initial blood glucose level was 494 mg/dL, and further tests confirmed profound metabolic acidosis, ketonemia, and ketonuria (Table 1). As per the standard measures to be undertaken during the diagnosis of DM and severe DKA, normal saline was administered for hydration. She was admitted to the intensive care unit.

Two hours later, the patient became drowsy and the Glasgow Coma Scale (GCS) score decreased to 12 points. The patient has

Table 1. Initial laboratory data

Variable (reference range)	Value
Arterial blood gas analysis	
pH	7.01
pCO ₂ (mm Hg)	8
pO ₂ (mm Hg)	132
Bicarbonate (mmol/L)	2.0
Base excess (mmol/L)	-27.0
Anion gap	36.5
Blood glucose level (mg/dL)	494
Blood ketone (mmol/L)	5.4
Urine ketone	3+
Sodium (mmol/L)	136
Potassium (mmol/L)	3.5
Chloride (mmol/L)	96
Total CO ₂ (mmol/L)	3
Serum osmolality (mOsm/L)	335
Blood urea nitrogen (mg/dL)	16.6
Creatinine (mg/dL)	0.9
Hemoglobin A1c (%)	16.2
White blood cell (1,000/μL)	19.39
C-reactive protein (mg/dL)	0.12
Coagulation profile	
Platelet (150–450 10 ³ /μL)	383
PT (9.5–13.5 sec)	14.4
aPTT (23–35 sec)	29.9
Fibrinogen (170–410 mg/dL)	375
D-dimer (0–0.65 mg/L FEU)	1.96
Antithrombin III (75%–125%)	102.3
Free protein S (69.4%–138.3%)	68.4
Protein C (72%–160%)	44.4
Lupus anticoagulant (negative)	Negative
Von-Willebrand Ag (50%–160%)	276
Factor V Leiden mutation	Not detected

PT, prothrombin time; aPTT, activated partial thromboplastin time.

also had a manifestation of Kussmaul respiration. Despite adequate fluid resuscitation and continuous intravenous insulin injection, profound metabolic acidosis (pH < 7.0) persisted, and the subject developed a fever. Her consciousness deteriorated to 4 points on the GCS. Additionally, her blood pressure started to drop, and the urine output began to decrease. Computed tomography (CT) of the brain was performed immediately. Albeit the brain CT did not indicate any abnormalities, intravenous mannitol was initiated as cerebral edema was suspected. Furthermore, supplemental treatments including inotropes, broad-spectrum antibiotics, diuretics, and sodium bicarbonate were also given.

The blood sugar levels normalized while metabolic acidosis improved (from pH 6.68 to pH 7.26) over the 3rd day through aggressive treatments. However, the patient remained unconscious, and her renal function deteriorated gradually (Fig. 1). The creatinine levels gradually increased to 7.2 mg/dL, and metabolic acidosis deteriorated again (from pH 7.26 to pH 7.17). The patient was subjected to hemodialysis on the 4th day of hospitalization. On the 2nd day of hemodialysis, she had a 1-minute generalized tonic-clonic seizure during dialysis. A follow-up CT of the brain was conducted on the 5th day of hospitalization, and a newly developed focal hemorrhage on both the parietal lobes was observed (Fig. 2A). Brain magnetic resonance imaging (MRI) was performed on the same day and multiple hemorrhages on the right temporal, parietal lobes, basal ganglia, and cerebellum were observed (Fig. 2B, C). An anti-epileptic drug was initiated, and no additional seizures were observed.

Aggressive treatments including hemodialysis, continuous insulin, and mannitol were continued until the 7th day of hospital-

Fig. 1. Kidney function during hospitalization.

Fig. 2. (A–C) Brain imaging findings on the 5th day of hospitalization. (A) Brain computed tomography shows focal hemorrhage and surrounding edema in both parietal lobes. Nodular hemorrhage in right temporal (not shown) and both parietal lobes on T1-weighted image, and punctate microbleeds in entire brain including cerebellum, midbrain, both basal ganglia, and corpus callosum. (B) Brain MRI shows nodular hemorrhage in right temporal and both parietal lobes on T1-weighted sagittal image, and (C) punctate microbleeds in entire brain including cerebellum, midbrain, both basal ganglia, and corpus callosum on SWI. (D) Brain MRI scan after 4 months shows markedly improved, and still visible microbleeds on SWI. MRI, magnetic resonance imaging; SWI, susceptibility-weighted image.

ization, and the patient gradually improved. Her consciousness became alert, and renal function improved (Fig. 1). On the 10th day, we switched the treatment from an intravenous administration of insulin to subcutaneous administration. She started to sit and eat on her own. At first, she seemed to have no neurological sequelae, such as damage to her memory, motor, and sensory functions. However, she had difficulty in trying to walk and showed a steppage gait on the left side. She also felt a tingling sensation and hyperesthesia in her left leg below the knee. Electromyography, nerve conduction velocity, and left knee MRI were performed, and a left common peroneal nerve injury was diagnosed. She received electrical stimulation therapy and physical therapy. An additional problem that surfaced was pressure ulcers. She began to show non-

blanchable erythema (grade 1 pressure ulcer) on the coccyx, after half a day of hospitalization. It quickly deteriorated to a second grade despite every 2 hours of position change, air-filled mattresses, and protective barrier dressings. There were also ulcers on the occipital and left forearm within a week. Conservative treatments continued, and there was no further deterioration as metabolic acidosis improved, and she started ambulation. Thereafter, she underwent escharectomy, and the wound size reduced.

Another follow-up of the brain MRI was performed 4 months later. It showed partially improved thrombotic microangiopathy (Fig. 2D). There were no further neurological sequelae, and the neurologic symptoms of the left leg was improved, thereby minimizing the difficulty in walking then. Currently, she is being treat-

ed with multiple daily insulin injections, and her blood sugar level is being well controlled.

This study was approved by the Institutional Review Board of Soonchunhyang University Bucheon Hospital (IRB approval no., 2020-05-011). Written informed consent was obtained from the patient and her parents.

DISCUSSION

DKA is a serious acute complication associated with pediatric type 1 DM. Cerebral involvement is the leading cause of mortality in DKA, of which cerebral edema is the most common. The risk factors for cerebral edema include younger age, new-onset diabetes, longer duration of symptoms, severe acidosis, lower partial pressure of carbon dioxide, and high serum blood urea nitrogen [1,4]. In addition to cerebral edema, strokes account for approximately 10% of intracranial complications, causing neurological changes in patients with DKA. Stroke is classified into three categories: (1) ischemic stroke; (2) cerebral vein thrombosis; and (3) hemorrhagic infarction [3]. The pathophysiology of stroke in DKA is associated with a variety of factors. DKA is a pro-inflammatory response, as evident from the increase in inflammatory cytokines and inflammatory markers such as C-reactive protein and by the activation of complements [5-7]. This systemic inflammatory response in DKA causes vascular endothelial injury and subsequent hypercoagulability, which increases the risk of ischemic or hemorrhagic stroke. In addition, other factors such as oxidative stress due to hyperglycemia and ischemia by hypoperfusion are related to vascular injury. In addition, factors such as abnormalities in blood volume, viscosity, and cerebral autoregulation are also associated with coagulopathy, which can contribute to the risk of stroke [8,9].

Among the three categories classified above, our patient had hemorrhagic infarction. There are several reported cases of hemorrhagic infarction in pediatric DKA patients [9-14]. These appeared in various forms, ranging from large hematomas to microhemorrhage of the white matter, as summarized in Table 2. In most of these cases (except one patient), the DKA was in a severe category, and complications of other organs (AKI, acute peripheral neuropathy, elevation in pancreatic enzyme) were observed in 5 out of 9 patients. Mahmoud et al. [9] reported two cases of petechial brain hemorrhage in a newly diagnosed DKA patient, which is similar to the findings in our patient. Both corresponded to severe DKA and showed rapid neurologic deterioration. There was no cerebral

edema or other major cerebrovascular diseases upon radiologic examination, and for the patient, it was found to be normal in the coagulation test. The authors suggested that microhemorrhages were caused by small white matter vessel disruption due to cytotoxic injury and excluded other pathologies such as coagulopathy and hypoperfusion by biopsy. Although our patient had similarities with these two patients in that they showed diffuse microscopic hemorrhage, other pathophysiology, as described above should also be considered because our patient developed coagulopathy later and could not exclude ischemia and vascular injury due to hypotension and hypoperfusion.

Peripheral neuropathy is usually a chronic complication that occurs slowly due to continuous exposure to hyperglycemia in type 1 DM, but it occurred early in the present case. Acute neuropathy after ketoacidosis, such as in our patient, is extremely rare. Baszyńska-Wilk et al. [15] reported a case of peripheral paralysis of both legs and acute motor peripheral neuropathy in a 9-year-old girl who developed such a condition after severe DKA. The pathophysiology of these acute neuropathies is still unclear, and it is hypothesized that peripheral nerve ischemia caused by procoagulant status and hemodynamic and metabolic changes related to DKA are the major contributors to its genesis [15,16].

AKI is another fatal complication of DKA. It has been rarely reported despite the risk factors associated with it. Hursh et al. [17] examined the incidence of acute kidney damage in children with DKA. They reported that 64% of the hospitalized children with DKA met the AKI standards according to the Kidney Disease/Improving Global Outcomes serum creatinine criteria and suggested an association between severe AKI and the severity of acidosis or volume depletion. This result is much higher than that previously thought and suggests that AKI is underrecognized in DKA, and medical practitioners should be particularly alert to kidney injury in severe DKA. However, only two out of 195 patients needed hemodialysis, like the case in our study. In addition to this, only a few cases of severe AKI requiring dialysis have been reported in DKA [18,19]. They suggested that the etiology is multifactorial, mostly due to hypovolemia and hypotension. In this case, the patient showed severe dehydration and lethargy, but we could not find other causes of severe metabolic acidosis than other DKA patients.

Our patient also developed a pressure ulcer. There are many risk factors related to pressure ulcer, such as duration of pressure, friction, exposure to hospital devices, tissue perfusion, malnutrition, and immobility. In the case of our patient, ulcers progressed rap-

Table 2. Pediatric case reports of hemorrhagic stroke associated with diabetic ketoacidosis

Reference	Sex/age (yr)	Brain radiologic findings	Neurologic symptoms	DKA severity	Coagulation profile	Other complications
Aturu [10] (1986)	F/11	Multiple bilateral posterior temporal hematomas on day 4 CT	Behavioral disturbances, lethargy, unresponsive, generalized seizures	Severe	Normal PT and aPTT	AKI
Rogers et al. [11] (1990)	F/9	Hemorrhage into Rt. basal ganglia on day 12 CT, hemorrhage in Rt. caudate nucleus, anterior limb of internal capsule on day 21 CT	Ataxic gait, lethargic, only responded to pain, apnea, Rt. sided tonic seizure, decorticate posturing	Severe	Not reported	Not reported
	F/9	Hemorrhagic infarctions of the basal ganglia, upper brain stem, surrounding portions of the frontal, temporal occipital lobes on day 6 MRI	Only responded to deep pain, Lt. exotropia, papilledema	Severe	Not reported	Not reported
Atkin et al. [12] (1995)	F/15	Normal CT scan on day 1, multiple small hematomas predominantly in the parietal lobe on day 12 MRI	Unconscious but responding to pain, generalized hypotonia, areflexia	Severe	Platelet count ↓ (85,000/uL), normal coagulation test	AKI requiring HD, acute peripheral neuropathy (both forearm)
Mahmud et al. [9] (2007)	F/11	Not remarkable finding on CT and MRI; on autopsy, pin-point hemorrhages in the hemispheric white matter and scattered throughout the brain stem and spinal cord	Lethargy, rapid deterioration of consciousness	Severe	Normal coagulation test	AKI requiring HD
	F/14	Multiple petechial hemorrhages involving the subcortical white matter U-fibers bilaterally, genu of corpus callosum, and the posterior limb of the internal capsule bilaterally on MRI	Lethargic, unresponsive, and dyspneic	Severe	Normal coagulation test	AKI, transient elevation in amylase, lipase
Lin et al. [13] (2008)	F/5	Hematoma in the Lt. thalamus on day 11 MRI	Rt. central facial palsy, Rt. hemiplegia, positive Babinski sign on Rt.	Severe	Normal platelet count, PT, aPTT, protein C and S	Not reported
Azad et al. [14] (2017)	M/6	Hemorrhage in the midbrain area with obstructive hydrocephalus on CT	Altered sensorium, generalized tonic-clonic seizure, intermittent decorticate posturing, only responded to pain, pupil dilatation	Mild	Normal coagulation test	Normal kidney function at first test
Present case (2020)	F/13	Normal CT scan on day 1, multiple microhemorrhages in Rt. temporal, both parietal lobes, both basal ganglia and cerebellum on day 5 MRI	Worsening to unconsciousness	Severe	Near normal at initial test, platelet count ↓ (61,000/uL) and positive FDP, D-dimer on day 5 (appropriate for DIC)	AKI requiring HD, acute peripheral neuropathy (Lt. leg), multiple pressure ulcers

DKA, diabetic ketoacidosis; F, female; M, male; CT, computed tomography; PT, prothrombin time; aPTT, activated partial thromboplastin time; AKI, acute kidney injury; Rt., right; MRI, magnetic resonance imaging; Lt., left; HD, hemodialysis; FDP, fibrin degradation product; DIC, disseminated intravascular coagulation.

idly within a day even when proper precautions such as frequent position changes were practiced with utmost sincerity, and it seems to be caused by poor perfusion due to metabolic acidosis and hypotension.

In conclusion, we report a case in which a newly diagnosed patient with type 1 DM showed diffuse intracranial hemorrhage, acute peripheral neuropathy, severe AKI requiring hemodialysis, and pressure ulcers, which are rare complications of DKA. Although each mechanism has not been fully identified, these complications are thought to be related to factors such as cytotoxic injury, coagulopathy, hypoperfusion, and hypotension. The symptoms might be associated with the severity of acidosis, as most of these complications have been reported in patients with severe DKA. Therefore, patients with severe DKA should be carefully monitored for acute neurologic symptoms caused by various factors in addition to cerebral edema, renal function, and pressure sores to reduce mortality and morbidity.

REFERENCES

1. Wolfsdorf JL, Glaser N, Agus M, Fritsch M, Hanas R, Rewers A, et al. ISPAD clinical practice consensus guidelines 2018: diabetic ketoacidosis and the hyperglycemic hyperosmolar state. *Pediatr Diabetes* 2018;19 Suppl 27:155-77.
2. Bialo SR, Agrawal S, Boney CM, Quintos JB. Rare complications of pediatric diabetic ketoacidosis. *World J Diabetes* 2015;6:167-74.
3. Rosenbloom AL. Intracerebral crises during treatment of diabetic ketoacidosis. *Diabetes Care* 1990;13:22-33.
4. Dunger DB, Sperling MA, Acerini CL, Bohn DJ, Daneman D, Danne TP, et al. ESPE/LWPES consensus statement on diabetic ketoacidosis in children and adolescents. *Arch Dis Child* 2004;89:188-94.
5. Hoffman WH, Burek CL, Waller JL, Fisher LE, Khichi M, Mellick LB. Cytokine response to diabetic ketoacidosis and its treatment. *Clin Immunol* 2003;108:175-81.
6. Dalton RR, Hoffman WH, Passmore GG, Martin SL. Plasma C-reactive protein levels in severe diabetic ketoacidosis. *Ann Clin Lab Sci* 2003;33:435-42.
7. Hoffman WH, Cudrici CD, Zafranskaia E, Rus H. Complement activation in diabetic ketoacidosis brains. *Exp Mol Pathol* 2006;80:283-8.
8. Foster JR, Morrison G, Fraser DD. Diabetic ketoacidosis-associated stroke in children and youth. *Stroke Res Treat* 2011;2011:219706.
9. Mahmud FH, Ramsay DA, Levin SD, Singh RN, Kotylak T, Fraser DD. Coma with diffuse white matter hemorrhages in juvenile diabetic ketoacidosis. *Pediatrics* 2007;120:e1540-6.
10. Atluru VL. Spontaneous intracerebral hematomas in juvenile diabetic ketoacidosis. *Pediatr Neurol* 1986;2:167-9.
11. Rogers B, Sills I, Cohen M, Seidel FG. Diabetic ketoacidosis: neurologic collapse during treatment followed by severe developmental morbidity. *Clin Pediatr (Phila)* 1990;29:451-6.
12. Atkin SL, Coady AM, Horton D, Sutaria N, Sellars L, Walton C. Multiple cerebral haematomata and peripheral nerve palsies associated with a case of juvenile diabetic ketoacidosis. *Diabet Med* 1995;12:267-70.
13. Lin JJ, Lin KL, Wang HS, Wong AM, Hsia SH. Occult infarct with acute hemorrhagic stroke in juvenile diabetic ketoacidosis. *Brain Dev* 2008;30:91-3.
14. Azad C, Kaur R, Singh DK, Arya A. Stroke in pediatric diabetic ketoacidosis: case series. *J Trop Pediatr* 2017;63:324-7.
15. Baszynska-Wilk M, Wysocka-Mincewicz M, Swiercz A, Swiderska J, Marszał M, Szalecki M. Peripheral neuropathy as a complication of diabetic ketoacidosis in a child with newly diagnosed diabetes type 1: a case report. *J Clin Res Pediatr Endocrinol* 2018;10:289-93.
16. Tracy JA, Dyck PJ. The spectrum of diabetic neuropathies. *Phys Med Rehabil Clin N Am* 2008;19:1-26.
17. Hursh BE, Ronsley R, Islam N, Mammen C, Panagiotopoulos C. Acute kidney injury in children with type 1 diabetes hospitalized for diabetic ketoacidosis. *JAMA Pediatr* 2017;171:e170020.
18. Murdoch IA, Pryor D, Haycock GB, Cameron SJ. Acute renal failure complicating diabetic ketoacidosis. *Acta Paediatr* 1993;82:498-500.
19. Al-Matrafi J, Vethamuthu J, Feber J. Severe acute renal failure in a patient with diabetic ketoacidosis. *Saudi J Kidney Dis Transpl* 2009;20:831-4.