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Patient report

Ayla Güven*, Suna Hancili, Elif Y. Karatoprak and Bülent Tasel

Symptomatic cerebral infarction in a child with severe diabetic ketoacidosis

Abstract

Background: Diabetic ketoacidosis (DKA) is a common initial presentation of pediatric type 1 diabetes mellitus. Intracerebral complications of DKA pose significant mortality and morbidity rates.
Objective: Our aim is to emphasize the importance of early identification, investigation, and treatment for patients who present with DKA and stroke.
Case report: Here, we report a case of a 4-year-old female patient who presented with ischemic-hemorrhagic stroke as a complication of DKA.
Conclusion: Cerebrovascular complications of DKA in children are a rare condition; however, higher risks take place in their youngest age. Clinicians should be aware of these complications so as to develop appropriate approach for its management.

Keywords: cerebral infarction; diabetic ketoacidosis (DKA); type 1 diabetes mellitus.

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Introduction

Diabetic ketoacidosis (DKA) is a common initial presentation with newly diagnosed type 1 diabetes mellitus. Intracerebral complications which occur in 0.3%–1% of patients with DKA pose significant mortality and morbidity rates (1–3). Cerebrovascular complications of DKA in children are a rare condition, based on case series, it has been presumed that approximately 10% of intracerebral complications, however, higher risks take place in their youngest age (1, 2, 4). Therefore, clinicians should be aware of these complications so as to develop appropriate approach for its management.

Here, we report a case of a 4-year-old female patient who presented with ischemic-hemorrhagic stroke as a complication of DKA. Our aim is to emphasize the importance of early identification, investigation, and treatment for patients who present with DKA and stroke.

Case report

A previously healthy 4-year-old female patient was referred to our endocrinology department with DKA for further evaluation and treatment. Before coming to our center, insulin and sodium bicarbonate bolus had been given prior to hydration.

On examination, her weight was 15.1 kg (25–50p), height was 107 cm (75–90p), respiratory rate was 37 breaths per minute, pulse was 124 per min, blood pressure was 102/64 mm Hg (<90p), and axillary temperature was 36.8°C. She appeared extremely dehydrated, had dried lips and tongue with a loss of skin turgor, and had an estimated fluid deficit of 8%–10%. She was tachypneic with Kussmaul's breathing and lethargic. The score in the Glasgow Coma Scale was determined as 10. The Babinski sign was negative bilaterally.

Laboratory investigations showed ketonuria, serious acidosis [pH: 6.88; HCO_3: 3.5 mmol/L; pCO_2: 18.8 mm Hg (2.47 kPa)], and hyperglycemia (plasma glucose: 353 mg/dL). Serum sodium concentration was found to be 132 mmol/L (corrected sodium 136 mmol/L), potassium 3.8 mmol/L, and serum osmolality 312 mmol/kg. Level of HbA1c was 14.2% (normal range 4.8%–6.0%) and urea nitrogen was 39 mg/dL (normal range 15.0–36.0 mg/dL). Immediately, maintenance and deficit replacement fluids were calculated. Administration of fluid deficit was

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planned within 36 h with the goal of 50% volume replacement within first 12 h. Rehydration with 0.9% saline was started (20 mL/kg/h over the first 2 h), followed by continuous intravenous infusion of a 5% glucose solution containing 100 mEq/L sodium chloride, 40 mEq/L 7.5% potassium chloride, and 30 mEq bicarbonate (2 mEq/kg) over 4 h. Insulin infusion was started with 0.05 U/kg/h. Capillary blood glucose was monitored hourly; electrolytes, urea, and blood gases were repeated with an interval of 2 h. After first 6 h of therapy, plasma glucose was found to be 329 mg/dL, pH 7.07, HCO_3 5.4 mmol/L, sodium 135 mmol/L, and potassium 4.1 mmol/L. Subsequently, bicarbonate treatment was stopped and fluid replacement therapy was continued with appropriate adjustments. Sodium levels remained stable during therapy and glucose levels reduced <75 mg/dL per hour. Despite her altered level of consciousness, there were no signs of cerebral edema (CE). Her DKA was resolved about 36 h after the admission, yet the fatigue continued and she did not want to be fed, resulting in keeping her blood sugar within the range between 200 and 250 mg/dL of intravenous insulin and fluid therapy was extended to 48 h. On the third day, there were no symptoms other than a slight weakness; subcutaneous insulin therapy was started with an adequate caloric diet for diabetic people. During the control visit, on the fourth day, a left-sided ptosis was observed. Neurological examination revealed positive Babinski reflex on the right side, right-sided hemiparesis, and gait disturbance. Firstly, a computed tomography scan of the brain was performed. It did not show any signs of CE but with a suspicious hypodense lesion at the level of the left thalamus and mesencephalon, magnetic resonance imaging (MRI) and MR-angiography (MRA) of the brain were recommended by the interpreting neuroradiologist. Then MRI and MRA of the brain were performed and showed an ischemic-hemorrhagic infarction of the left thalamus and mesencephalon (Figure 1).

To find the possible causes, screening for coagulation profile and prothrombotic conditions (prothrombin time, activated partial thromboplastin time, factor VIII, factor V Leiden, antithrombin III, protein C, protein S, D-dimer, fibrinogen, antiphospolipid antibodies, and anticardiolipin antibodies) showed normal values. Homocysteine level was normal as well. Echocardiography showed no specific findings. Blood culture yielded negative findings.

One week later, the control cranial MRI showed unchanged lesions without progression. Rehabilitation therapy and supportive treatment were continued. Her neurological symptoms gradually receded except for mild gait disturbance. After 20 days of hospitalization to select the right dose and timing of insulin therapy, she was discharged in good clinical and neurological recovery. A follow-up cranial MRI and MRA were performed 1 month after discharge, showing significant improvement of the previously described area (Figure 2). Today, she can walk stably with completely regained neurological function and she is in good metabolic control.

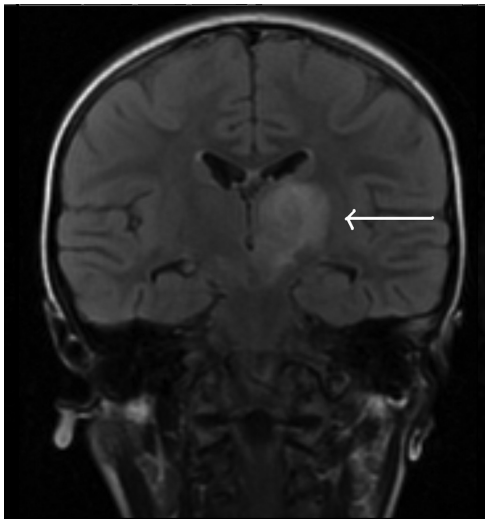

Figure 1 MRI of the patient shows an ischemic-hemorrhagic infarction of left thalamus and mesencephalon (marked by the arrow) (on coronal T2-weight image).

Discussion

Diabetic ketoacidosis is a life-threatening condition with high mortality and morbidity rates in children (1–3, 5).

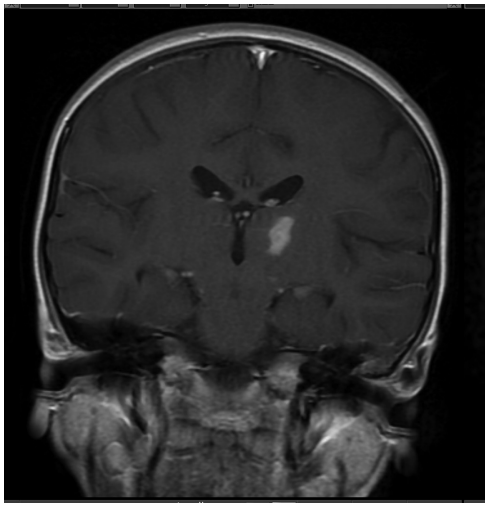

Figure 2 Follow-up MRI of the patient (1 month after the onset of symptoms) shows resolving of the previously described area (on coronal T2-weight image).

This is predominantly assignable to intracerebral complications especially to CE which is the most common and serious complication and results in the death of 21%–24% of the affected patients (1, 3, 6). Even though, several neurologic deficiencies have been associated with DKA, conversely, may be due to lack of recognition, ischemic-hemorrhagic stroke is an uncommon presentation during the DKA episodes (1, 2, 7, 8).

Diabetic ketoacidosis is a metabolic disorder characterized by hyperglycemia, ketonemia, and acidemia due to severe insulin deficiency. This potentially fatal complication of diabetes is, contrary to common belief, more than a simple defect in glucose metabolism; it is also associated with a systemic inflammatory response characterized by vascular endothelial injury and coagulopathy (1, 4, 9). It is proposed that the oxidative stress induced by hyperglycemia and ketosis contributes to this inflammatory reaction and results in increased markers of inflammation, cytokines, and complement activation (1, 4, 9). Even more, in recent studies, multiple coagulation changes have been demonstrated in children and adults with DKA, including increased platelet aggregation, elevated levels of plasma homocysteine and procoagulants, decreased activity of anticoagulants, and impaired fibrinolytic activity (1, 10–12). Dehydration, hyperglycemia, hyperosmolarity, tissue hypoxia, and acidemia-induced red blood cell rigidity which is a cause of hyperviscosity and vasoconstriction may all have an additive role regarding prothrombotic tendency (1, 12, 13). These features may also explain why children who present with DKA are at an increased risk of cerebral infarction.

There are limited reports concerning the association between DKA and stroke in children. Despite its importance, the exact mechanism by which DKA induces stroke still remains unclear. Although, some of the cases presented in the literature are not associated, it is often thought to be secondary to CE. To some researchers, the proposed underlying pathogenesis of DKA-related CE is the administration of excessive rate of intravenous fluid infusion, in combination with the rapid correction of hyperglycemia and hypernatremia (14–16). This theory was supported by a former report regarding two children with DKA who had acute cerebral infarction and extra pontine myelinolysis (5). However, recent studies do not support this theory (17–22). In a large retrospective multicenter study, Glaser et al. (17) compared 61 children with DKA-related CE to 181 randomly selected controls with uncomplicated DKA, and to 174 controls with uncomplicated DKA matched to the cases based on age and DKA severity and determined no association between fluid or sodium infusion rates and risk of CE. Also, in a latest pilot study, Glaser et al. measured brain apparent diffusion coefficient values by using magnetic resonance diffusion weighted imaging to quantify subclinical CE in children with DKA randomized to two intravenous fluid regimens and found that using different rates of fluid infusion protocols were not associated with distinct differences in MRI measures of CE (19). They suggest that DKA-related CE and cerebral injury are caused by cerebral hypoperfusion and the effects of reperfusion during DKA treatment (17–23). Furthermore, a nationwide, multicenter, randomized, prospective study (The Pediatric Emergency Care Applied Research Network Fluid Therapies Under Investigation in DKA; PECARN DKA FLUID Study Group) is currently in progress to analyze the impact of fluid rehydration regimens and fluid sodium content on neurological and neurocognitive outcomes in children with DKA (24). As stroke itself may provoke CE, it becomes difficult to understand whether stroke in DKA is the cause or due to CE (1, 2, 25). Our patient did not have CE, but so many major risk factors such as a newly diagnosed patient who was <5 years old, severe acidosis and hypocapnia, high initial serum urea nitrogen concentration, elevated serum osmolality and severe dehydration were present (6, 17, 18, 26, 27). Furthermore, sodium bicarbonate and insulin bolus had been given to our patient before coming to our hospital. In the clinical studies, it is established that rapid infusion of bicarbonate has a relative risk for the development of CE by causing paradoxical central nervous system acidosis (17, 28–30). Likewise, insulin therapy can be started immediately, but must be started after the initial rehydration bolus because rapid reduction in glucose causes rapid changes in serum osmolality which may precipitate CE (28, 29). For instance, Edge et al. (31) compared 43 children with DKA-related CE to 169 controls with uncomplicated DKA and established that insulin administration in the first hour of the treatment was associated with CE. It has also been recognized that the use of bicarbonate frequently accompanied with high-dose insulin protocols, especially the combination of both might have worsened the risk of CE; yet its role concerning stroke is unknown (28, 29, 32). Therefore, it is possible that severe metabolic derangement contributes to the development of cerebral infarction. In our patient, while coagulation profile and plasma homocysteine level was in the normal range we presumed that all the factors mentioned earlier were responsible for the stroke.

Finally although neurological deterioration in children with DKA is most likely to be as a result of CE because of the prothrombotic tendency in these children, clinicians should consider ischemic stroke in the differential diagnosis (4, 12). The initial presentation of pediatric stroke can be subtle with nonspecific changes in behavior

or altered level of consciousness; therefore, a monitoring of the neurological status is recommended for at least 48 h, even if the metabolic derangements have normalized (4, 12, 33). Furthermore, well-defined rehydration strategy in the first hours of therapy is crucial and can reduce neurological complications. For this reason, urgent critical care and diabetes consultation should be obtained. Our findings emphasize the importance of prompt evaluation and appropriate approach for the management of intracranial crises in DKA.

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