Cerebral complications in diabetic ketoacidosis

Şükrü Hatun, Filiz Çizmecioğlu, Demet Toprak

Department of Pediatrics, Kocaeli University Faculty of Medicine, Kocaeli, Turkey

SUMMARY: Hatun Ş, Çizmecioğlu F, Toprak D. Cerebral complications in diabetic ketoacidosis. Turk J Pediatr 2005; 47: 170-172.

Although much is known about diabetic ketoacidosis (DKA) and its treatment, the pathology of cerebral complications in patients who develop ketoacidosis is not yet well understood. In this article, we discuss the cerebral complications due to DKA by presenting two cases who were admitted with severe DKA and who both developed early and severe neurological complications.

Key words: diabetic ketoacidosis, cerebral edema.

Despite recent progress in the diagnosis and long-term treatment of type 1 diabetes, diabetic ketoacidosis (DKA) continues to be the most significant cause of death in childhood diabetes. According to the studies reported from the United States, mortality due to DKA is between 0.21 and 0.25%[1]. Late referrals to hospitals and/or insufficient treatment regimens are responsible for even higher mortality rates in some countries and regions[2]. The mortality of DKA is mostly due to cerebral complications, of which the most is frequently seen cerebral edema. Although DKA can be seen in all ages, cerebral edema usually occurs in childhood. Glaser et al. reported 6,977 DKA case from the United States, of whom 61 (0.8%) presented with cerebral edema; 13 (21%) of those died and 13 (21%) recovered with severe neurologic deficits[3]. It is not clear if cerebral complications are related to the treatment or if they develop in an idiosyncratic manner. However, it is worthwhile to estimate the risk of complications and to carry out the treatment regimen according to the severity of the risk. In this report, cerebral complications due to DKA are discussed by presenting two cases of severe DKA with an emphasis on their treatments.

Case Reports

Case 1

A 13-year-old boy with a weight of 25 kg was presented with anisocoria, a Galsgow coma score (GCS) of 5, profound metabolic acidosis and severe dehydration. His vital findings at admission were as follows: fever 36°C (axillary), blood pressure 97/62 mmHg, breathing rate 40/min/acidotic and heart rate 140/min/rhythmic. His history revealed that he had been treated at another hospital while still conscious. His serum glucose level was 600 mg/dl at admission and 2000 ml isotonic saline + 20 units regular insulin were infused over a four-hour period. Afterwards, his blood glucose level declined rapidly and 2000 ml 5% dextrose 0.45% NaCI + 20 units regular insulin were given intravenously for four hours. When he was referred to our hospital, the laboratory studies were as follows. Serum glucose 402 mg/dl, blood ketones 5.5, venous blood pH 6.93, partial pressures of arterial carbon dioxide 9.4 mmHg, HCO_3 3 mmol/L, serum osmolality, 328 mOsm/L and corrected serum Na 145 mEq/L, K 2.76 mEq/L, CI 115.2 mEq/L, urea 36 mg/dl and creatinine 0.7 mg/dl. Anion gap was calculated as -27. Initial hydrating fluid (isotonic saline, 500 ml) was given within an hour, followed by 5% dextrose in 0.2 N saline. The rate of fluid replacement was adjusted to provide only 60% of the calculated deficit within the initial 12 hours; the remaining 40% was administered during the next 24 hours. Although ketosis and hyperglycemia were corrected by rehydration and insulin infusion (0.1 U/kg), metabolic acidosis worsened. Intravenous sodium bicarbonate ($NaHCO_3$) (1 mEq/L, within 4 hours) and mannitol (0.5 g/kg/dose) were given along with mechanical ventilation. After 12 hours of treatment, his cerebral computerized

tomography (CT) showed infarction in the basal ganglia. Although Na content of intravenous fluid was 40 mEq/L, his corrected Na level reached 180 mEq/L and serum osmolality reached 406 mOsm/L. Peritoneal dialysis was done to correct severe hypernatemia, hyperosmolality and sustained metabolic acidosis. Although his metabolic and hemodynamic parameters improved with therapy, the patient died due to continued neurological deterioration.

Case 2

A 23-month-old boy weighing 14 kg had newly diagnosed diabetes. He was presented unconscious and with a GCS of 6, ketotic breath and a five-day history of lethargy. His vital findings at admission included fever 36.1°C (axillary), blood pressure 100/77 mmHg, breathing rate 32/min-acidotic and heart rate 126/min/rhythmic. His laboratory results were as follows. Serum glucose 370 mg/dl, blood ketones 4.7, venous blood pH 7.1, partial pressures of arterial carbon dioxide 11.2 mmHg, HCO_3 3 mmol/L, corrected serum Na 124.3 mEq/L, K 4 mEq/L, urea 33 mg/dl and serum osmolality 262.2 mOsm/L. Fluid resuscitation with an isotonic saline infusion (20 ml/kg/h, 280 ml) was commenced within an hour, then insulin infusion (0.07 U/kg/h) was started. Deficit and maintanence fluid (2320 ml) were administered at identical speed within the next 23 hours. The maintenance fluid of the patient, whose corrected Na was calculated as 130.6, was continued with isotonic for the first five hours. However, after five hours, $NaHCO_3$ was infused slowly (1 mEq/L, within 4 hours) due to continuing hyperglycemia, ketones and a serum pH of 7.0. At the eighth hour, the acidosis and GCS (GCS: 10) began to improve. But at the fourteenth hour relative bradycardia (82 beats/min down from 120 beats/min) without hypertension developed and at the sixteenth hour the boy became unconscious, with decerebration posturing, mydriatic pupils unresponsive to light and papilledema on fundoscopic examination. He was resuscitated with mannitol and intubated, and then hyperventilated by mechanical ventilation, but failed to respond to the treatment.

Discussion

Cases of DKA are treated according to accepted regimens, but fatal cerebral complications may occur occasionally. It is clear that most cases have minimal cerebral edema at diagnosis[4]; however, fatal cerebral complications occur during treatment. For this reason, cerebral edema diabetes continue the part of the treatment regimens of DKA[5-7]. Recent studies have shown that cerebral edema due to fluid therapy is not the only issue; the pathophysiological mechanisms of DKA cause cerebral ischemia and infarcts. These problems are seen more frequently in patients who have complications in the earlier periods of treatment[8-10]. Studies have shown that cerebral complications have a positive correlation with initial low partial pressures of arterial carbon dioxide, higher initial serum urea nitrogen concentrations and bicarbonate therapy[2]. Besides these, young age (<5 years), newly diagnosed patients, coma at referral and high corrected serum sodium levels at the beginning of therapy are also risk factors for cerebral complications[8]. Some patients may have more than one risk factor at the beginning of therapy, and minor factors associated with treatment may cause these patients to deteriorate. The first patient was treated with rapid fluid infusion and high doses of insulin at the first hospital and unfortunately was referred to us with cerebral complications. The patient had low partial CO_2 pressure usually seen in brain edema at admission. The basal ganglion infarcts found in brain edema at the 12th hour of treatment reinforces the role of not only inappropriate fluid therapy but also of brain hypoxia as theorized in the evaluation of brain edema. However, the second case had a high risk for cerebral edema because he was under five years of age and had sustained acidosis prior to admission and diagnosis. His initial pressures of arterial carbon dioxide were significantly low, and despite low serum glucose levels the blood sodium levels failed to increase. Although he was treated appropriately according to DKA protocols, cerebral complications developed during his progress. Also, in spite of the presence of indications, the effect of isotonic saline and bicarbonate infusion on the outcome is open to discussion. It is reported that rapid infusion of isotonic saline at the beginning of the treatment causes a rapid incline in capillary hydrostatic pressure and facilitates cerebral edema[11]. The most frequently overlooked sign in Dr. Muir's study[12] was heart rate deceleration. It is important to

note that the slowing did not necessarily fall to the level of true bradycardia, i.e. 60 beats per minute. More typical is the young patient with a baseline of 120 beats/min who suddenly drops to 80 or 90 beats/in and stays there. In Case 2 the bradycardia found two hours prior to signs and symptoms of cerebral edema supports Dr. Muir's observation. Poor prognostic factors associated with adverse outcomes in cerebral edema are level of neurologic depression at the time of cerebral edema, high serum urea levels and need of mechanical ventilation because of pressures of arterial carbon dioxide, levels lower than 22 mmHg[13]. Both of our patients died because of poor prognostic factors. In our clinic, approximately 10 DKA case are seen per year. For the first time this year, two severe DKA cases resulted in mortality; therefore, we aimed to share our experience. In view of these two patients, we would like to call attention to the topics below about the treatment and follow-up of diabetic ketoacidosis.

1. Children presenting with diabetic ketoacidosis, even if adolescents, should be handled differently from adults.
2. Children with severe encephalopathy at admittance should be accepted as patients at high risk for cerebral ischemia, cerebral edema and other cerebral complications.
3. Every child with diabetic ketoacidosis should be evaluated for cerebral complications. Children who are at a high risk should not receive rapid infusion of isotonic saline if there is no hypotension on admission. Bicarbonate therapy should be avoided if there is not an absolute indication, such as severe circulatory failure and a high risk of cardiac decompensation due to profound acidosis.
4. Patients who are at high risk and are presented with relative bradycardia (68-104 beats per minute), hypotension and irregular respiration should be handled and treated for cerebral edema.
5. Exceptional instructions for the treatment and follow-up of patients at high risk should be prepared and implemented in pediatric clinics.

REFERENCES

1. Daneman D. Diabetes related mortality. Diabetes Care 2001; 24: 801-802.
2. Glaser N, Barnett P, McCaslin I, et al. Risk factors for cerebral edema in children with diabetic ketoacidosis. N Engl J Med 2001; 344: 264-269.
3. Matsushima M, LaPorte RE, Maruyama M, Shimuzu K, Nishimura R, Taima N. Geographic variation in mortality among individuals with youth-onset diabetes mellitus across the world. DERI Mortality Study Group. Diabetologia 1997; 40: 212-216.
4. Kran EJ, Rockoff MA, Wallman JK, Wolfsdorf JI. Subcilinical brain swelling in children during treatment of diabetic ketoacidosis. N Engl J Med 1985; 312: 1147-1151.
5. Harris GA, Fiordalisi I, Harris WL, Mosovich LL, Finberg L. Minimizing the risk of brain herniation during treatment of ketoacidermia: a retrospective and prospective study. J Pediatr 1990; 117: 22-31.
6. Edge JA. Cerebral oedema during treatment of diabetic ketoacidosis: are we any nearer finding a causes? Diabetes Metab Res Rev 2000; 16: 316-324.
7. Felner EI, White PC. Improving management of diabetic ketoacidosis in children. Pediatrics 2001; 108: 735-740.
8. Dunger DB, Edge JA. Predicting cerebral edema during diabetic ketoacidosis. N Engl J Med 2001; 344: 302-303.
9. Muir A. Cerebarl edema in diabetic ketoacidosis: a look beyond rehydration. JCEM 2000; 85: 2509-2513.
10. Rosenbloom AL. Cerebral edema in diabetic ketoacidosis. JCEM 2000; 85: 2507-2508.
11. Carlotti AP, Bohn D, Halperin ML. Importance of timing of risk factors for cerebral oedema during therapy for diabetic ketoacidosis. Arch Dis Child 2003; 88. 170-173.
12. Muir A. Causes of cerebral edema 62nd Annual Meeting & Scientific Sessions ADA. June 14-18, 2002. Available at. http://diabeteshighlights.org/summary/index.asp?sid=1.
13. Marcin JP, Glaser N, Barnett P, et al. American Academy of Pediatrics. The Pediatric Emergency Medicine Collaborative Research Committee. Factors associated with adverse outcomes in children with diabetic ketoacidosis-related cerebral edema. J Pediatr 20002; 141. 793-797.