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CASE REPORT

Fatal cerebral oedema in adult diabetic ketoacidosis

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ABSTRACT

In this report, a case of adult onset fatal cerebral oedema as a rare complication of diabetic ketoacidosis (DKA) is described and confirmed at post-mortem pathological examination. The pathogenesis of cerebral oedema due to DKA is still unknown. Potential mechanisms include the administration of sodium bicarbonate leading to intracellular acidosis, excessive fluid infusion causing swelling of brain tissue, or reduction of plasma osmolarity by a rapid fall in glucose levels causing osmotic swelling.

KEYWORDS

Diabetic ketoacidosis, cerebral oedema, pyrexia

INTRODUCTION

Cerebral oedema is a rare but severe complication of diabetic ketoacidosis (DKA), mainly seen in young children and adolescents, which may result in death. In young adults cerebral oedema due to DKA has only occasionally been reported.[1-4]

We present a case of a 31-year-old male who died of cerebral herniation due to cerebral oedema caused by DKA as the initial presentation of diabetes mellitus. Potential mechanisms and pathological data are discussed.

CASE

A 31-year-old comatose male presented at the emergency department. He was born in Zambia and had lived as a student in our country for three months. He had no known relevant previous medical history. His family history was negative for diabetes mellitus. Since three weeks he had complained of fatigue. Recent symptoms were dry cough, fever and vomiting. On physical examination, the patient was comatose ($E_1M_1V_1$), had dilated pupils with a very slow reaction to light, intact cornea reflexes, and no meningeal signs. His temperature was 38.5°C, blood pressure 70/30 mmHg, with a regular and equal pulse of 132 beats/min and a respiratory rate of 30 breaths/min. Auscultation of the heart and lungs was normal. Examination of the abdomen was unremarkable. Urine output was absent, even after catheterisation.

Laboratory investigations revealed: haemoglobin 11.4 mmol/l (8.5 to 11.0 mmol/l), haematocrit 0.59 l/l (0.40 to 0.52 l/l), leucocytes 13.3 x 10^3/l (4-11 x 10^3/l), urea 33.8 mmol/l (3.0 to 7.0 mmol/l), creatinine 768 µmol/l (60 to 110 µµol/l), sodium 153 mmol/l (135 to 145 mmol/l), potassium 5.0 mmol/l (3.5 to 4.7 mmol/l), chloride 107 mmol/l (97 to 107 mmol/l), glucose 84.9 mmol/l (4 to 10 mmol/l) and C-reactive peptide of 3 mg/l (0 to 17 mg/l). Liver enzymes were normal. Arterial blood gas analysis showed metabolic acidosis: pH 7.112 (7.35 to 7.45), pCO_2 6.7 kPa (4.5 to 6.0 kPa), pO_2 40.5 kPa (9.5 to 13.0 kPa), $HCO3^-$ 15.4 mmol/l (22 to 26 mmol/l), base excess -14.0 mmol/l (-2-2 mmol/l) and oxygen saturation 99% on oxygen (15 l/min) via non-rebreathing mask. Lactate was 4.2 mmol/l (0.5 to 1.7 mmol/l). Anion gap was 30. Urine was positive for ketones and negative for nitrite. Chest X-ray was normal.

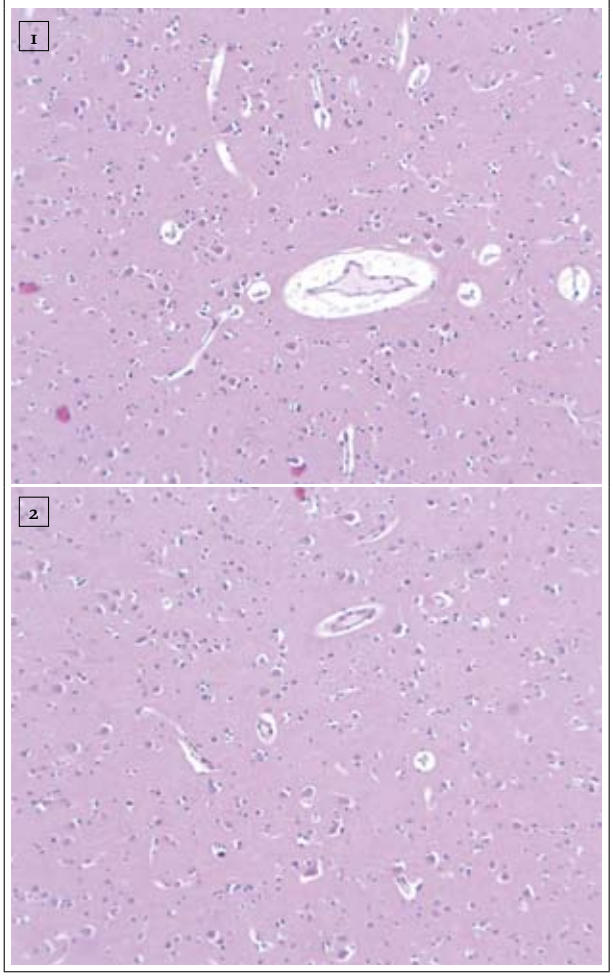
Patient was admitted to the intensive care unit (ICU) with severe hyperglycaemia with severe metabolic (lactic) acidosis and coma, diagnosed as DKA, based on a high anion gap, high glucose and ketones in urine. In addition, oliguric renal failure probably due to dehydration, electrolyte abnormalities and fever of unknown origin were noted. He was treated for DKA according to the national guidelines with fluids and insulin IV.[5] NaCl 0.9% at a rate of 0.5 l/h was infused. Insulin was administered as a bolus of 10 IUs followed by 7 IUs/h. Earlier, in the emergency

department, the patient had already received 3x 500 ml hydroxyl-ethyl starch solution infusion (Na 154 mmol/l). Cultures were taken and tests for TBC, HIV and malaria performed. The results were negative. Intravenous amoxicillin/clavulanic acid was started empirically. Serum sodium, potassium, glucose and arterial blood gasses were measured hourly (*table 1*). Norepinephrine was started because of hypotension, not responsive to fluid resuscitation.

Initially, the patient started to wake up after metabolic correction (max. $E_2M_3V_2$). Maximal urine output was 20 ml/h. Four hours after admission to the ICU he suddenly developed an acute rise in temperature up to 42°C and epileptic seizures. His coma score deteriorated again to $E_1M_1V_1$. Laboratory results at that moment were sodium 169 mmol/l, potassium 3.6 mmol/l, glucose 38 mmol/l, pH 7.034, pCO_2 8.9 kPa, and HCO_3^- 16.9 mmol/l. Neurological examination by the consulted neurologist confirmed the comatose state and an urgent CT scan of the brain was requested to rule out cerebral oedema or infection. Before CT scanning could be performed, the patient developed a sudden cardiac arrest with asystole. Cardiac resuscitation was immediately initiated. Return of spontaneous circulation was quickly established; however, the patient developed recurrent episodes of ventricular tachycardia, ventricular fibrillation and pulse-less electrical activities with asystole. External pacing was initiated with inadequate cardiac output. Cardiac resuscitation was finally discontinued 75 minutes after the start of cardiopulmonary resuscitation.

Autopsy showed extensive perivascular, pericellular and interstitial oedema of the brain (*figures 1* and *2*), and cerebral herniation was confirmed. Furthermore, pulmonary oedema was seen compatible with acute lung injury (ALI). Surprisingly, there were no signs of infection, bowel ischaemia or organ failure. All post-mortem cultures were negative.

Figures 1 and 2. *Slides of the brain showing vascular congestion, perivascular and pericellular oedema*



DISCUSSION

We have described a case of adult-onset fatal cerebral oedema as a rare complication of DKA, which could be confirmed at post-mortem pathological examination. The pathogenesis of cerebral oedema due to DKA is still unknown. Three possible mechanisms have been suggested but never proven: 1) administration of sodium bicarbonate leading to intracellular acidosis,[6,7] 2) excessive fluid infusion causing swelling of brain tissue,[8,9] and 3) reduction of plasma osmolarity by a rapid fall in glucose levels causing osmotic swelling.[6,10-12]

Two of these mechanisms could have played a role in our case. First, we noted a rapid fall in glucose levels due to

Table 1. *Laboratory test results during treatment for diabetic ketoacidosis*

Time	Reference value	12:13*	14:03	15:37	17:23#	17:54	18:08	18:22	18:42
Urea	3.0-7.0 mmol/l	33.8	34.8						
Creatinine	60-110 umol/l	768	762						
Sodium	135-145 mmol/l	153	155	158	163	169	177	176	176
Potassium	3.5-4.7 mmol/l	5.0	3.3	2.2	2.1	3.6	2.1	3.5	2.7
Glucose	4-10 mmol/l	84.9	74.2	59.7	43.2	38	38	33	39
Effective serum osmolality[1]		391	384	376	369	376	392	385	391

***Presentation and initiation of treatment; #clinical deterioration; [1]effective serum osmolality = 2 x $[Sodium]_{serum}$ + glucose.**

rehydration and insulin administration. Potentially this may have caused swelling of the brain. However, the rapid reduction in glucose levels was accompanied by a simultaneous rise in plasma sodium, resulting in a modest reduction of plasma osmolality from 391 to 369. Second, we infused large amounts of fluids according to and not more than is suggested in the practice guidelines. Third, although the metabolic acidosis slightly improved, the persistent acidosis was caused by ongoing hypercarbia and respiratory acidosis. Increased dead space ventilation due to ALI or neurogenic pulmonary oedema may have played a role in the persistent combined acidosis. Pulmonary oedema could be demonstrated post-mortem. The increase in pCO_2 levels may have caused intracellular acidosis and mimic the same situation as has been observed in mechanism 1 after sodium bicarbonate administration. However, in this patient sodium bicarbonate was not administered.

We speculate that another mechanism may have played a role. Fever could have contributed to the cerebral deterioration. We have previously demonstrated that in a patient resuscitated after cardiac arrest and showing initial improvement, pyrexia resulted in fatal cerebral oedema.[13] After cardiac arrest and in several neurological conditions mild therapeutic hypothermia and fever control proved to be protective.[14] Possibly, this observation could be translated to other clinical settings like our case.

Temperatures exceeding 40°C cause transient vasoparalysis in humans, resulting in cerebral metabolic uncoupling and loss of pressure-flow autoregulation. These findings may be related to the development of brain oedema, intracerebral haemorrhage, and intracranial hypertension observed after prolonged therapeutic hyperthermia. Furthermore, deliberate hyperthermia critically worsens the extent of histopathological damage in animal models of traumatic, ischaemic and hypoxic brain injury. However, it is unknown whether these findings translate into episodes of spontaneous fever in neurologically injured patients.[15]

On the other hand, fever may have also been a symptom of cerebral oedema and imminent cerebral herniation.

The progressive hypernatriaemia was not completely understood. Fluids infused had maximum sodium levels of 154 mmol/l and loss of water through renal elimination is not relevant at a urine output of 20 ml/h, such as may be seen in diabetes insipidus. Most likely, third-spacing of hypotonic fluids due to gastrointestinal paralysis or capillary leakage – as was seen in the lungs – may have caused a further rise in sodium levels.

CONCLUSION

In conclusion, adults presenting with DKA may develop fatal cerebral oedema, although this is rare. Rapid correction of hyperglycaemia and osmolality and persistent respiratory acidosis due to ALI or neurogenic lung oedema may have contributed to the fatal outcome.

Fever may be seen as a symptom of neurological disease or could have contributed further to the final outcome. Therefore we feel that also in DKA, fever control is of pivotal importance to prevent further damage due to fever.

REFERENCES

1. Troy PJ, Clark RP, Kakarala SG, Burns J, Silverman IE, Shore E. Cerebral oedema during treatment of diabetic ketoacidosis in an adult with new onset diabetes. Neurocrit Care. 2005;2(1):55-8.
2. Hiller KM, Wolf SJ. Cerebral edema in an adult with diabetic ketoacidosis. Am J Emerg Med. 2005;23(3):399-400.
3. Leary P, Dunbar K. Avery close call. Am J Med. 2005;118(9):968-71.
4. Dixon AN, Jude EB, Banerjee AK, Brian SC. Simultaneous pulmonary and cerebral oedema, and multiple CNS infarctions as complications of diabetic ketoacidosis: a case report. Diabet Med. 2006;23(5):571-3.
5. NIV-guidelines for the treatment of acute diabetic disregulation: diabetic ketoacidosis and hyperglycaemic hyperosmolar non-ketotic syndrome. http://www.internisten.nl/home/richtlijnen/niv2.
6. Glacer N, Barnett P, McCaslin I, et al. Risk factors for cerebral edema in children with diabetic ketoacidosis. N Engl J Med. 2001;344:264-9.
7. Hoorn EJ, Geary D, Robb M, Halperin ML, Bohn D. Acute hyponatriemia related to intravenous fluid administration in hospitalized children: an observational study. Pediatrics. 2004;113:1279-84.
8. Bureau MA, Begin R, Berthiaume Y, Shapcott D, Khoury K, Cagnon N. Cerebral hypoxia from bicarbonate infusion in diabetic ketoacidosis. J Pediatr. 1980;96:968-73.
9. Hoorn EJ, Carlotti APCP, Costa LAA, et al. Preventing a drop in effective plasma osmolarity to minimize the likelihood of cerebral edema during treatment off children with diabetic ketoacidosis. J Pediatr. 2007;150:467-73.
10. Mel J, Werther G. Incidence and outcome of diabetic cerebral oedema in childhood: are there predictors? J Paediatr Child Health. 1195;13:17-20.
11. Rosenbloom A. Intracerebral crisis during treatment of diabetic ketoacidosis. Diab Care. 1990;1322-33.
12. Hale P, Rezvani I, Braunstein A, Lipman T, Martinez N, Garibaldi L. Factors predicting cerebral edema in young children with diabetic ketoacidosis and new onset type I diabetes. Acta Paediatr. 1997;86:626-31.
13. Bergman R, Tjan DH, Adriaanse MW, van Vugt R, van Zanten AR. Unexpected fatal neurological deterioration after successful cardio-pulmonary resuscitation and therapeutic hypothermia. Resuscitation. 2008;76(1):142-5.
14. Polderman KH. Induced hypothermia and fever control for prevention and treatment of neurological injuries [review]. Lancet. 2008;371:1955-69.
15. Cremer OL, Kalkman CJ. Cerebral pathophysiology and clinical neurology of hyperthermia in humans. Prog Brain Res. 2007;162:153-69.