A B S T R A C T

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.

K E Y W O R D S

Diabetic ketoacidosis, cerebral oedema, pyrexia

I N T R O D U C T I O N

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.

C A S E

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 (E1M1V1), 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 µmol/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), pCO2 6.7 kPa (4.5 to 6.0 kPa), pO2 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: 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.
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 M V). 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 M V. Laboratory results at that moment were sodium 169 mmol/l, potassium 3.6 mmol/l, glucose 38 mmol/l, pH 7.034, pCO₂ 8.9 kPa, and HCO₃⁻ 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.

**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**

<table>
<thead>
<tr>
<th>Time</th>
<th>Reference value</th>
<th>12:15*</th>
<th>14:03</th>
<th>15:37</th>
<th>17:23#</th>
<th>17:54</th>
<th>18:08</th>
<th>18:22</th>
<th>18:42</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea</td>
<td>3.0-7.0 mmol/l</td>
<td>33.8</td>
<td>34.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td>135-145 mmol/l</td>
<td>768</td>
<td>762</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium</td>
<td>135-145 mmol/l</td>
<td>153</td>
<td>155</td>
<td>158</td>
<td>163</td>
<td>169</td>
<td>177</td>
<td>176</td>
<td>176</td>
</tr>
<tr>
<td>Potassium</td>
<td>3.5-4.7 mmol/l</td>
<td>5.0</td>
<td>3.3</td>
<td>2.2</td>
<td>2.1</td>
<td>3.6</td>
<td>2.1</td>
<td>3.5</td>
<td>2.7</td>
</tr>
<tr>
<td>Glucose</td>
<td>4.10 mmol/l</td>
<td>84.9</td>
<td>74.2</td>
<td>59.7</td>
<td>43.2</td>
<td>38</td>
<td>38</td>
<td>33</td>
<td>39</td>
</tr>
<tr>
<td>Effective serum osmolality³</td>
<td>391</td>
<td>384</td>
<td>376</td>
<td>369</td>
<td>376</td>
<td>392</td>
<td>385</td>
<td>391</td>
<td></td>
</tr>
</tbody>
</table>

*Presentation and initiation of treatment; #clinical deterioration; `effective serum osmolality = 2 x [Sodium]ₜ₉₀₅ + 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 pCO₂ 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. After cardiac arrest and in several neurological conditions mild therapeutic hyperthermia and fever control proved to be protective. 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 conditions. 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. On the other hand, fever may have also been a symptom of neurological disease and new onset type I diabetes. Acta Paediatr. 1997;86:626-31. 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. On the other hand, fever may have also been a symptom of neurological disease and new onset type I diabetes. Acta Paediatr. 1997;86:626-31.

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**


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