Nephroquiz
(Section Editor: M. G. Zeier)

An old patient with end stage renal disease and sudden onset of confusion and lethargy

Case

The patient, a 97-year-old Caucasian male, was found in a lethargic and confused condition in his apartment. He was admitted to the emergency room of our hospital. Past medical history included end stage renal disease secondary to hypertension – treated by haemodialysis for the last 5 years, symptomatic bradycardia – treated with a permanent cardiac pacemaker and hypothyroidism. Prescribed medication included levothyroxin, calcitriol, furosemide, captopril, erythropoetin, calciumacetate and iron. According to the patient’s nephrologist, the patient had been well. He did not use alcohol or tobacco. There had been no problems during haemodialysis so far.

On physical examination the patient was indeed lethargic and confused. His blood pressure was 150/80 mmHg; heart rate was 68 bpm, body temperature 36.5°C and respiratory rate 16 breaths per minute. The patient was diaphoretic, the skin turgor was normal and there was no oedema. He had neither neck stiffness nor any paralysis. The cardiac auscultation was unremarkable and breathing sounded normal. There were a few crackles over the base of the left lung. The remainder of the examination was unremarkable.

The results of the laboratory evaluation are given in Table 1.

Table 1. Selected laboratory values at admission

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haematocrit (%)</td>
<td>39</td>
</tr>
<tr>
<td>White-cell count (per mm³)</td>
<td>8 000</td>
</tr>
<tr>
<td>Platelet count (per mm³)</td>
<td>249 000</td>
</tr>
<tr>
<td>Glucose (mmol/l)</td>
<td>1.9</td>
</tr>
<tr>
<td>Sodium (mmol/l)</td>
<td>135</td>
</tr>
<tr>
<td>Potassium (mmol/l)</td>
<td>5.19</td>
</tr>
<tr>
<td>Calcium (mmol/l)</td>
<td>2.13</td>
</tr>
<tr>
<td>Phosphate (mmol/l)</td>
<td>1.7</td>
</tr>
<tr>
<td>Alanine aminotransferase (mmol/l)</td>
<td>0.12</td>
</tr>
<tr>
<td>Aspartate aminotransferase (mmol/l)</td>
<td>0.30</td>
</tr>
<tr>
<td>Creatinine (µmol/l)</td>
<td>685</td>
</tr>
<tr>
<td>Urea (mmol/l)</td>
<td>18.2</td>
</tr>
<tr>
<td>Lactate dehydrogenase (µmol/l)</td>
<td>3.34</td>
</tr>
<tr>
<td>Total protein (g/l)</td>
<td>59.7</td>
</tr>
<tr>
<td>Albumin (g/l)</td>
<td>33.0</td>
</tr>
<tr>
<td>C-reactive protein (mg/l)</td>
<td>13.4</td>
</tr>
<tr>
<td>Thyroid stimulating hormone (mU/l)</td>
<td>0.71</td>
</tr>
</tbody>
</table>

Questions

What was the patient’s major laboratory abnormality and what would you do next?
What differential diagnoses would you consider to explain the abnormality?
What further diagnostic procedures and what therapy would you recommend?
Answers to the quiz on the preceding page

The patient had symptomatic hypoglycaemia. He received 50 ml of a 40% glucose solution intravenous (IV) and responded immediately. He became fully oriented and reported increasing fatigue over the last few weeks. Within the next 4 h the patient's blood glucose level decreased again and a continuous IV infusion with a 10% glucose solution was started after a further bolus of 40% glucose. Under this regimen there were stable blood glucose levels between 4.8 and 7.7 mmol/l.

Blood samples drawn, before glucose supplementation was first started, demonstrated markedly increased levels of insulin (2.86 nmol/l, normal range 0.02–0.16) and C-peptide (32.5 nmol/l, normal range 0.26–1.39). Serum cortisol was normal (447 nmol/l) and a toxicological screening for sulfonylurea and repaglinide was negative.

This clinical presentation is consistent with Whipples’ triad: presence of symptoms indicative of hypoglycaemia, low plasma glucose (<2.2 mmol/l) and relief of symptoms after plasma glucose is raised. Symptoms of hypoglycaemia include neuroglycopenic (behavioural changes, lethargy, confusion, fatigue, blurred vision, seizures, coma) and autonomic (sweating, palpitation, tremor, hunger, nausea) changes [1]. Repeated hypoglycaemic events lower the threshold for these responses: this is particularly true for the autonomic ones. The present patient predominantly demonstrated a neuroglycopenic response. This is indicative of repeated hypoglycaemic episodes in the past.

Hypoglycaemia in patients with end stage renal disease is usually caused by concomitant medication. Since the kidney accounts for about 50% of systemic insulin clearance, diabetic patients with stable insulin – or sulfonylurea – treatment and renal insufficiency are at an increased risk of hypoglycaemia [2–4]. Additional drugs with hypoglycaemic potential are salicylates and cotrimoxazol [5,6]. Mildly elevated levels of insulin and C-peptide are often observed in chronic renal failure, however, they usually do not cause hypoglycaemia [3]. In the present case there were markedly elevated C-peptide and insulin – much beyond the levels found in renal insufficiency per se. On the other hand, renal insufficiency is also associated with peripheral insulin resistance – and this might protect patients from hypoglycaemia to some extent [7]. There are also studies indicating starvation in uraemic patients as a potential risk factor for spontaneous hypoglycaemia. Substrate limitation in such patients might impair hepatic and kidney gluconeogenesis [8,9].

The cause of hypoglycaemia in the present case most likely was an insulinoma. Other differential diagnoses such as hypothyroidism, Addison’s disease or factitious hypoglycaemia were excluded by laboratory examinations. The manifestation of hypoglycaemia in this patient might have been facilitated by some degree of malnutrition (the serum albumin level was 33 g/l).

Insulinomas are the most common functioning pancreatic endocrine tumours with an incidence of 4 per one million [1,10]. They are usually small, unifocal and almost all (97%) are located in the pancreas. The malignancy rate is about 10% [10]. The definitive treatment for insulinoma is surgical removal. However, about 40% of them remain undetectable by current imaging procedures before surgery. Intra-operative localisation of the tumour either by palpation or by intra-operative ultrasound is the gold standard [11,12]. Preoperative localization procedures, such as abdominal CT or ultrasound, have sensitivity below 60%; sensitivity of magnetic resonance imaging is between 50 and 90%. Endoscopic ultrasound performed by an experienced investigator seems to be the most sensitive (up to 94% reported) non-invasive technique for localization of insulinoma [11–13]. A further localizing procedure is scanning using 111In-pentetreotide, a tracer which binds to the somatostatin type 2 or type 5 receptors. These are expressed in only 46% of insulinomas. In the presence of a positive scan there is a possibility of successful medical treatment with long acting octreotide [10,14,15].

Medical treatment with diazoxide is usually recommended for patients with negative scintigraphy who cannot be treated surgically [16]. Diazoxide was previously used as an IV antihypertensive agent. Its major side-effect was hyperglycaemia. It acts directly on beta cells and reduces insulin secretion [17,18]. Blood glucose levels begin to rise 1 h after intake of the tablet and last about 8 h. Duration of effect might be prolonged in patients with renal failure. Diazoxide also stimulates catecholamine release, which in turn activates adenylate cyclase and increases cyclic AMP (cAMP). cAMP inhibits glycogen synthesis and enhances glycogenolysis [17]. Response rates to diazoxide in insulinoma are between 60 and 80%. The most common side effects are nausea, fluid and sodium retention, hypotension and hirsutism [16].

In our patient the efforts to locate a suspected insulinoma included ultrasound, computed tomography and an 111In-pentetreotide scintigraphy of the whole body. All were unsuccessful. The patient refused endoscopic ultrasound as well as surgical exploration.

Further clinical course

Diazoxide was started at 100 mg every 8 h on hospital day 4 and captopril was stopped. Blood glucose increased to 9 mmol/l and glucose infusion was terminated at hospital day 6. An attempt to lower the diazoxide dose to 75 mg every 8 h was unsuccessful
because of a symptomatic blood glucose decrease. There was a slight increase of inter-dialytic weight gain within the next days. Blood glucose remained stable between 4.5 and 6.7 mmol/l throughout the remainder of the hospital course. The patient was transferred to his apartment on day 22, where he was cared for by ambulatory nursing assistance. Diazoxide was continued after discharge.

Conflict of interest statement. None declared.

References


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