Severe hypotension and coma secondary to unrecognized chronic anterior hypophysitis

Abstract We report an endocrine emergency of a 52-year-old woman with chronic anterior-pituitary failure of autoimmune origin who developed hypopituitary crisis with coma and severe hypotension provoked by an intercurrent bronchopneumonia. At admission to the ICU hypopituitarism had not been diagnosed and only Hashimoto’s thyroiditis with thyroid replacement therapy could be obtained from the patient’s history. Although the patient presented with somatic signs suggestive of hypopituitarism, other causes of coma and hypotension had first to be excluded. In the absence of specific treatment the patient died 18 h later with refractory cardiac arrest. Diagnosis of acute decompensated chronic hypophyseal failure must be considered if hypothermia, refractory hypotension and signs of infection without fever are associated with a short stature and the loss of axillary and pubic hair. Waiting for laboratory confirmation of the diagnosis must not delay immediate life-saving specific glucocorticoid treatment.

Key words Endocrine coma • Hypopituitarism • Lymphocytic hypophysitis • Hashimoto’s disease • Refractory hypotension

Introduction

Lymphocytic hypophysitis is a rare disorder characterized by interstitial infiltration of the anterior pituitary with lymphocytes and plasma cells. An autoimmuneologic cause was first suggested by Goudie and Pikerton who observed an association with Hashimoto’s disease [1]. The detection of circulating autoantibodies to cells of the human pituitary has helped to elucidate the pathogenesis of anterior hypophysitis [2–4]. Clinically the disease progresses with destruction of the parenchyma and leads to insufficiency of the anterior pituitary while the function of the posterior hypophysis remains unchanged [5]. Particularly females are affected [1, 6]. A state of crisis may progress to coma when a patient with longstanding hypopituitarism is subjected to unusual stress. The immediate threat to life results from deficiency of glucocorticoids and thyroid hormones, due to a failure in producing ACTH and TSH. Associated deficiencies of trophic hormones may cause important physical symptoms, but do not contribute directly to the acute features of the syndrome. In this report we describe the presentation of an acute hypophyseal failure and difficulties in diagnosis which prevented the institution of specific and probably curative treatment.

Case report

A 52-year-old woman was admitted to the intensive care unit (ICU) with coma (GCS 7), respiratory insufficiency and mild hypothermia (rectal temperature 35.6 °C). One hour earlier she was found lying unconscious in bed in her apartment. Evidence of previous vomiting and incontinence of urine and stool was reported by the emergency medical staff. The initial impression was acute poisoning since she had suffered from psychotic symptoms and had undergone psychiatric treatment 3 years ago. However, no tablets or empty medicine bottles were found in her environment and there were no signs of alcohol intoxication. Physical examination showed an anemic, short patient (height 143 cm, weight 50 kg) with an increased respiratory rate of 18/min. Her blood pressure was 67/42 mmHg (9/5.6 kPa), the femoral pulses were regular and equal with 115/min. Examination of the lungs revealed end-inspiratory crackles on the right side. No signs of congestive heart failure were present. The ECG showed a regular sinus rhythm with horizontal depression of the ST-segment and incomplete right bun-
dle branch block. The central venous pressure was within the normal range (+7 cmH₂O). On neurological examination neither meningism nor focal signs could be detected. The pupils were round and isocor and reacted slowly to light. A striking feature was the absence of axillary and pubic hair. The breasts were very small.

Laboratory abnormalities on admission to the ICU (normal values in brackets): Serum glucose 57 mg/dl (70–100), sodium 132 mmol/l (135–150), potassium 3.0 mmol/l (3.5–5.5), ionized calcium 1.06 mmol/l (1.12–1.32), creatinine 2.7 mg/dl (0.5–0.9), GOT 128 U/l (<18), creatinine kinase 256 U/l (10–100), LDH 761 U/l (120–240), GPT 99 U/l (<22), lactate 4.2 mmol/l (<2.5), red cell count 3.3×10¹²/l (3.8–5.0), hematocrit 30% (36–46), haemoglobin 10.2 g/dl (12.0–16.0), sodium 137 mmol/l (137–142), potassium 4.4 mmol/l (3.5–5.0), carbon dioxide 31 mmol/l (22–30), pH 7.33 and bicarbonate 15.9 mmol/l. White cell count (neutrophils 70%, lymphocytes 25%), platelets and blood urea nitrogen were within the normal range.

A chest X-ray revealed spotty white infiltrates in the right lower lobe. On transthoracic echocardiography the heart was normal except for slight diffuse hypokinesia with a reduced ejection fraction of 55%. Ultrasound examination of the upper abdomen showed slight hepatomegaly and stones in the gallbladder, but no other abnormalities. Funduscopy and cerebrospinal fluid were normal. To obtain a full patient history we contacted the family doctor who had seen the patient 3 days before admission asking for tablets for his sick mother. His information was that the patient had looked well and that she had been under thyroid replacement therapy because of Hashimoto’s thyroiditis for the last two years.

During the patient’s stay in the ICU an initial generalized seizure was successfully treated with diazepam. Together with mechanical ventilation hypotension was treated with volume replacement and dopamine (9 μg/kg/min). However, blood pressure remained at levels around 65/25 mmHg and 2 severe attacks of bradycardia had been terminated with atropine and epinephrine. The patient died 18 h after admission to the ICU with refractory cardiac arrest.

Autopsy revealed a small and firm pituitary without intracerebral haemorrhage. Also the thyroid, the adrenal glands, the uterus and the ovaries were of very small size. Suppurative confluent bronchopneumonia was visible mainly in the right lung. Microscopic examination revealed that the adenohypophysis was nearly completely destroyed with marked fibrosis, dense lympho-plasmacellular infiltrates and regressive cysts (Fig. 1A). The few residual epithelial cells showed intense immunoreactivity with antibodies to GH (Fig. 1B) and ACTH (Fig. 1C). There was no reaction with antibodies to TSH, LH, FSH and prolactin. In addition, lymphoeytic thyroiditis Hashimoto was found with marked fibrosis and atrophy of the parenchyma. The adenral cortex was reduced to one third of its normal thickness due to severe atrophy of the zona fasciculata and reticularis. The ovaries were infertile with only a few cysts lacking corpora albicantia.

In post mortem analysis of frozen plasma samples the cortisol level was 105 nmol/l (200–630), basal TSH 0.01 μU/l (0.1–5) and free T₄ 1.7 pmol/l (3–8). Free T₃ was also low (2.9 pmol/l, normal range 10–28). In search of further patient history we obtained the information that this nulliparous patient was believed to have been suffering from secondary hypothyroidism 2 years previously (basal TSH level 0.16 μU/l). Although a TRH-test was recommended by the endocrinologist, it had never been performed. A conventional X-ray of the sella turcica showed a normal anatomy. Moreover, two weeks prior to death she underwent a bone mass density evaluation of her lumbar spine with quantitative digital radiography for investigation of chronic back pain: in comparison to healthy 50-year-old females she had already lost 30% of her bone mass.

Discussion

The mortality of patients with endocrine emergencies admitted to ICU remains high [7]. Severe neurological symptoms such as coma, seizures and focal signs are often the presenting manifestations [8]. The combination of short stature, the loss of axillary and pubic hair, and hypothermia despite signs of infection suggest hypothalamic-pituitary insufficiency and can provide important clues to an early correct diagnosis. In addition, profound cardiovascular failure without hypotension and the absence of response to inotropic catecholamine therapy may suggest an endocrinological cause of the underlying disease. Features which distinguish anterior pituitary failure from Addisonian crisis are the absence of hyperpigmentation and hyperkalemia. Hypothyroidism with myxoedema coma is seen mainly in the elderly and is rare in patients aged less than 60 years. In this condition peripheral oedema is found commonly and there may be transudates into any of the serosal body cavities.

Fig. 1a–c Histological and immunohistochemical analysis of lymphoid anterior hypophysitis. a Lymphocytic hypophysitis with dense lymphoplasmacellular infiltrates, fibrosis and regressive cysts (Masson-Trichrome, ×200); b the few residual epithelial cells show intense immunoreaction with antibodies to GH (PAP, ×400) and c to ACTH (PAP, ×400)
Pituitary impairment caused by autoimmune mechanisms is a condition known as lymphocytic hypophysitis. The disease is a part of polyglandular endocrinopathy and may be associated with other autoimmune disorders such as lymphocytic thyroiditis [1], adrenal insufficiency, insulin-dependent diabetes mellitus, hypoparathyroidism and pernicious anemia. A minority of these patients have circulating autoantibodies against lactotrop or somatotrop cells [2–4]. Indeed, in this case thyroid-peroxidase autoantibodies could be measured in a concentration of 130 IU/l (<100) 2 years prior to death.

Unusual stress may provoke coma in patients with longstanding hypopituitarism and in this case the state of crisis was probably a consequence of bronchopneumonia.

Low TSH serum levels are a frequent component of multihormonal pituitary deficiency and may be the consequence of primary pituitary disease. Reduced height and loss of bone density may be a result of growth hormone deficiency in adolescence and adult life. In addition, insulin sensitivity is increased and hypoglycemia may develop in times of stress [9]. Failure in formation of corticotropin in females leads to deficiency of adrenal androgens, which causes loss of axillary and pubic hair. The lack of glucocorticoids results in asthenia, anorexia, nausea, vomiting and weight loss. Hypotension and circulatory collapse is associated with inappropriate bradycardia due to thyroid hormone deficiency. Plasma ACTH is either low or, if within the normal range, inappropriately low for the cortisol levels. Gonadotropin deficiency in women leads to amenorrhea and development of genital atrophy. In hypopituitary crisis hypotraumaemia is the rule and may be severe [10]; it is predominantly of dilutional origin, rather than being due to salt wasting because production of mineralocorticoids is largely independent of ACTH. Characteristically, plasma cortisol levels are low or low-normal.

Before commencing treatment, 20 ml of heparinized blood should be taken, centrifuged at once and the plasma frozen immediately, for analysis later (ACTH is highly labile at room temperature). Having taken the sample, treatment must be started without delay: 1) For glucocorticoid replacement give hydrocortisone 100 mg i.v. 6-hourly and it is essential that this is given before thyroid hormones to prevent a hypoadrenal collapse, which can follow acceleration of the metabolic rate. Alternatively, use dexamethasone 2 mg i.v. 12-hourly. Mineralocorticoids are not needed; 2) Restore salt and water deficiency with an infusion of 0.9% saline. A typical deficit is 2–4 l, which should be given over 24 h; 3) To treat hypoglycemia use glucose as 50% dextrose i.v. Measure the blood glucose concentrations every 2 h; 4) After clinical improvement, when the patient is able to assimilate oral medication, give oral hydrocortisone 20 mg 8-hourly. Further commence with L-thyroxine 0.05 mg on alternate days; 5) Treat the precipitating cause. Use broad-spectrum antibiotics if signs of infection are apparent, but pituitary apoplexy should also be considered (intrasellar lesion with haemorrhage, confirmed by computed tomography). In such cases, neurosurgical decompression is usually recommended; 6) Watch for the development of diabetes insipidus and treat accordingly.

In conclusion, our report of this case of fatal endocrine coma due to anterior pituitary insufficiency points to the great importance of a prompt diagnosis and specific treatment. Although hypophyseal failure is a rare cause of coma and cardiovascular collapse, it should be suspected in connection with any patient presenting hyperthermia despite signs of infection and signs of trophic hormone deficiencies.

References