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BRIEF COMMUNICATION

Lymphocytic hypophysitis: a rare cause of hypoglycaemia in a man with type 2 diabetes mellitus

P. LEE,1 A. CHRYSOSTOMOU,4 B. TRESS3 and P. R. EBELING1,2,4

Departments of 1Diabetes and Endocrinology, 2Medicine, 3Radiology and 4Division of General Medicine, The University of Melbourne, The Royal Melbourne Hospital, Melbourne, Victoria, Australia

Abstract

Lymphocytic hypophysitis is a primary inflammatory disorder of the pituitary gland, which may cause panhypopituitarism. The majority of cases occur in women during the peripartum period and it is rare in men. We present a case, initially presenting with recurrent hypoglycaemic episodes, in a man with previously well-controlled type 2 diabetes mellitus. (Intern Med J 2005; 35: 254–257)

Key words: lymphocytic hypophysitis, panhypopituitarism, hypoglycaemia.

A 68-year-old Greek man, with previously well-controlled type 2 diabetes mellitus of 18 years’ duration, hypertension, atrial fibrillation and dyslipidaemia, presented with a 3-week history of lethargy, cold intolerance, decreased exercise tolerance, generalized weakness and recurrent hypoglycaemia.

His type 2 diabetes mellitus was complicated only by mild non-proliferative retinopathy. He was treated with 160 mg of oral gliclazide twice a day, and 16 U of subcutaneous intermediate-acting human insulin at night. However, during the preceding 3 weeks he developed multiple episodes of hypoglycaemia without obvious precipitants. As a result, his sulphonylurea was stopped and his insulin dose was reduced. The patient did not report symptoms of polydypsia, polyuria or nocturia.

On examination, the patient was alert, but slow to respond. There was generalized oedema and hypotension with a systolic blood pressure of 95 mmHg without any postural drop. He was afebrile and not clinically anaemic. Examinations of the cardiovascular and respiratory systems were unremarkable with no signs of left or right ventricular failure. The patient was clinically euthyroid and eugonadal. There was no gynaecomastia.

Initial investigations revealed a mild leucocytosis of $11.2 \times 10^9/L$, mild renal impairment, a serum creatinine of 0.13 mmol/L with no evidence of proteinuria. The cause of the generalized oedema was revealed when thyroid function tests demonstrated secondary hypothyroidism with a low serum thyroid stimulating hormone level of 0.02 mIU/L, low serum-free triiodothyronine of 2.1 pmol/L and low serum-free thyroxine of $<5.2 \text{ pmol/L}$. Panhypopituitarism was confirmed on a subsequent testing of pituitary hormone levels (Table 1). A short synacthen test was abnormal, with a low baseline cortisol concentration of 41.3 nmol/L and a sub optimal response to...
250 µg of synacthen with a level of 345 nmol/L after 30 min and 436 nmol/L after 60 min. A normal response is shown if the cortisol level in either post stimulation sample exceeds the basal level by at least 200 nmol/L, and either post stimulation cortisol level exceeds 550 nmol/L. The serum sodium and osmolality was normal, therefore a water deprivation test for diabetes insipidus was not performed. A lumbar puncture was not performed.

A pituitary magnetic resonance imaging (MRI) scan was then performed. The sella turcica was filled with homogeneously enhancing soft tissue material, with overall dimensions of 2 cm × 1 cm × 1 cm. The pituitary mass did not contact the optic chiasm. Closer inspection of the pituitary MRI scan showed evidence of pituitary stalk enhancement and also uniform enhancement of the pituitary mass on the dynamic study, both of which were suggestive of lymphocytic hypophysitis (Fig. 1).

A trans-sphenoidal excision of the mass was performed because of its size and the diagnostic uncertainty, and an intraoperative frozen section of the mass demonstrated inflammation. Formal histology showed a dense lymphocytic infiltrate consisting predominantly of T-lymphocytes, mixed with B-lymphocytes and monocyte-derived macrophages (Fig. 2). The appearances were entirely consistent with lymphocytic hypophysitis.

The patient made an excellent postoperative recovery and was discharged 2 days later with long-term hormone replacement therapy, including 25 mg of cortisone acetate twice a day and 100 µg of thyroxine once a day. At a review 3 months later, the oedema had resolved and his diabetes was well controlled with a haemoglobin A1c of 6.8% on gliclazide.

Lymphocytic hypophysitis is a rare cause of hypopituitarism, and characterized by destruction of normal pituitary architecture by lymphocytic infiltration. Over 100 cases have been previously reported, and a well-documented case series revealed 98% to be women with predominance during pregnancy or within 14 months postpartum.1,2 There are only approximately 10 confirmed male cases reported in the literature, with the present case being the second to be reported in Australia.3 Due to its rarity, it may often be overlooked in the differential diagnosis for pituitary mass lesions in males.

Hypoglycaemia is a well recognized complication of hypopituitarism, more commonly seen in infants and children with secondary adrenal insufficiency caused by adrenocorticotropic hormone deficiency.4,5 Although the patient reported here had previously well controlled type 2 diabetes mellitus treated with a sulphonylurea and insulin, with a HbA1c of 7.2%, the repeated hypoglycaemic

<table>
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<th>Serum</th>
<th>Level</th>
<th>Range</th>
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<td>Thyroid stimulating hormone</td>
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<tr>
<td>Free tri-iodothyronine</td>
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<td>Free thyroxine</td>
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<td>9.0–24.0</td>
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<td>Luteinizing hormone</td>
<td>&lt;0.1</td>
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<td>Follicle stimulating hormone</td>
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<td>Testosterone</td>
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<tr>
<td>Prolactin</td>
<td>&lt;14</td>
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<tr>
<td>Insulin-like growth factor-1</td>
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<td>Adrenocorticotropic hormone</td>
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<tr>
<td>Cortisol</td>
<td>64</td>
<td>120–650</td>
<td>nmol/L</td>
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Figure 1 (a) Sagittal section of the pituitary fossa showing the homogeneously enhanced and thickened pituitary stalk arising from the slightly enlarged pituitary gland; (b) coronal section of the pituitary fossa. Uniform enhancement of the pituitary lesion on consecutive images 30 s apart on dynamic study is shown.
It is well documented that spontaneous recovery with physiological hydrocortisone replacement can happen.\textsuperscript{1,2,9} Given the morbidity associated with pituitary surgery, the greatest challenge in the management of this condition lies in the establishment of a diagnosis by minimally invasive methods.

Importantly, an atypical pattern of deficiency, such as early impairment of the thyrotrophic and corticotrophic axes, uncommonly seen with pituitary adenoma, should alert the clinician to this unusual diagnosis.\textsuperscript{10–12} A wide range of auto-antibodies may be present, including anti-adrenal, pancreatic and thyroid auto-antibodies. In particular, recently discovered auto-antibodies against pituitary cytosolic proteins,\textsuperscript{13} including alpha-enolase, may be present in up to 70\% of patients with biopsy-proven lymphocytic hypophysitis,\textsuperscript{14} however, none is a specific or sensitive diagnostic test for lymphocytic hypophysitis. A significantly higher lymphocytic pleocytosis is sometimes evident in the cerebrospinal fluid compared with histologically confirmed pituitary adenoma, representing an aseptic meningeal reaction to pituitary inflammation.\textsuperscript{15}

With good characterization of soft tissues, MRI is an ideal test to diagnose inflammation of the pituitary gland. Pituitary adenomas typically appear as hypointense, late enhancing tissue masses contiguous to or compressing the adjacent normal gland, while the whole gland is enlarged and shows a homogeneous or diffusely heterogeneous early vivid enhancement pattern in lymphocytic hypophysitis (Fig. 1b).\textsuperscript{15–17} The enhancement may also involve parasellar structures, such as dura mater, sphenoid and cavernous sinuses.\textsuperscript{18} While it may also be seen in other inflammatory pituitary conditions, such as sarcoidosis, tuberculosis and histiocytosis X, a thickened and contrast-enhancing infundibular stalk is highly suggestive of the condition (Fig. 1a).\textsuperscript{19}

However, none of these non-invasive investigations is diagnostic. Indeed, it is impossible to distinguish lymphocytic hypophysitis from the other inflammatory pituitary lesions mentioned above. Commonly, the diagnosis is made after surgical resection of the abnormal pituitary tissue, as in the present case.

Although trans-sphenoidal surgery is often well tolerated, it may still be associated with significant morbidity. When one or more of the atypical features are present, a biopsy of the pituitary gland is justified to confirm the diagnosis, which may then allow a conservative approach to the management of the condition. There is limited evidence that high dose methylprednisolone pulse therapy achieves an improvement of adrenopituitary function and shrinkage of the sellar mass.\textsuperscript{14,20}

This present case illustrates a rare cause of recurrent hypoglycaemia in a man with type 2 diabetes mellitus. Hypopituitarism should be considered in this setting, particularly when the pituitary MRI features are highly suggestive of lymphocytic hypophysitis, even though it is less commonly seen in men than in women. Despite the suggestive MRI appearance, a pituitary biopsy may still be required to exclude other causes of pituitary inflammation and to plan rational therapy. In some cases sellar decompression may still be required.
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