Lymphocytic hypophysitis: unusual features of a rare disorder

P. J. Jenkins, S. L. Chew, D. G. Lowe*, F. Alshar†, M. Charlesworth‡, G. M. Besser and J. A. H. Wass
Departments of Endocrinology, *Histopathology, †Neurosurgery and ‡Radiology, St Bartholomew’s Hospital, London, UK
(Received 10 June 1994; returned for revision 2 August 1994; finally revised 26 October 1994; accepted 25 November 1994)

Summary

OBJECTIVE Lymphocytic hypophysitis is a rare disorder which usually affects women and is often associated with pregnancy. We reviewed our experience of this disorder in order to see whether these features were universal amongst our patients.

DESIGN A retrospective review of case notes.

PATIENTS Four patients with histologically proven lymphocytic hypophysitis.

MEASUREMENTS Each patient had undergone full radiological and biochemical assessment of anterior and posterior pituitary function.

RESULTS Only one woman presented during pregnancy, one patient was a man with coexistent active acromegaly, and one progressed over 5 years to panhypopituitarism. In one further patient, histological analysis revealed normal anterior pituitary tissue adjacent to lymphocytic follicles.

CONCLUSIONS Lymphocytic hypophysitis should be considered in the differential diagnosis of any patient with a pituitary mass. We suggest that the entire removal of such a mass is warranted both for accurate diagnosis and definitive treatment.

Lymphocytic hypophysitis is a rare disorder with less than 50 cases reported worldwide (Hayashi et al., 1991; Pestell et al., 1990). Most cases occur in women, usually in relation to pregnancy; this, together with the frequent occurrence of circulating autoantibodies, has suggested an autoimmune aetiology. Commonly, lymphocytic hypophysitis presents with features of a mass lesion, with variable loss of anterior pituitary function; posterior pituitary involvement is extremely rare. Spontaneous resolution has occurred and some authors recommend conservative treatment with or without a trial of steroids (Bevan et al., 1992; Feigenbaum et al., 1991).

We report the findings in four patients with lymphocytic hypophysitis. They demonstrate some unusual or unique features of the disease, and lead us to suggest that total hypophysectomy is warranted for accurate diagnosis and definitive treatment.

Case reports

This series represents the histologically confirmed cases of lymphocytic hypophysitis seen by the Department of Endocrinology since 1966. Endocrine and immunological data are summarized in Table 1.

Case 1

A 63-year-old woman with two children presented with a 3-year history of frontal headaches unaccompanied by any visual disturbance. For the previous two months she had been unsteady on her feet and had noticed a deepening of her voice and increasing cold intolerance; otherwise her past medical history was unremarkable and she had undergone the menopause at the age of 50 years. Physical examination revealed pallor, a small firm goitre, delayed tendon reflexes and cerebellar ataxia. Her investigations (Table 1) revealed hypothyroidism, ACTH and growth hormone deficiency, and evidence of mild cranial diabetes insipidus. Thyroid autoantibodies were positive, but the serum concentration of TSH was low (8.8 mU/l) in relation to the reduced serum T4 (20 nmol/l), suggesting both primary autoimmune disease and TSH deficiency.

CT imaging demonstrated a pituitary mass with suprasellar extension. Transsphenoidal hypophysectomy was performed which revealed a tough, grey-white, relatively avascular pituitary mass. Histology showed a relatively localized collection of lymphocytes around collections of mixed anterior pituitary cells. Occasional histiocytes were also present but there were no plasma cells and no lymphoid follicle formation (Fig. 1). Post-operatively, she remains well on thyroxine and hydrocortisone replacement. A repeat CT scan 5 years after the hypophysectomy demonstrated only a small amount of residual pituitary tissue in a largely empty fossa.

Case 2

A 23-year-old woman presented in the 38th week of her first pregnancy with severe frontal headaches. She was otherwise...
Table 1 Biochemical and immunological investigations of 4 patients with lymphocytic hypophysitis

<table>
<thead>
<tr>
<th>Serum:</th>
<th>LH/FSH (U/l)</th>
<th>Oestradiol (pmol/l)</th>
<th>T4 (nmol/l)</th>
<th>TSH (mU/l)</th>
<th>Cortisol (nmol/l)</th>
<th>GH (mU/l)</th>
<th>PRL (mU/l)</th>
<th>Autoantibodies</th>
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<tr>
<td>Case 1</td>
<td>NR</td>
<td>NR</td>
<td>20</td>
<td>8.8</td>
<td>120*</td>
<td>&lt;1</td>
<td>844</td>
<td>P: 297 → 304†</td>
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<td></td>
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<td>Case 2</td>
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<td>632</td>
<td>84</td>
<td>0.7</td>
<td>243</td>
<td>NR</td>
<td>1016</td>
<td>P: 284</td>
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<td>18</td>
<td>0.4</td>
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<td>NR</td>
<td>&lt;40</td>
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<tr>
<td>Case 3</td>
<td>6.7/6.5</td>
<td>87</td>
<td>86</td>
<td>1.0</td>
<td>859</td>
<td>2.6</td>
<td>212</td>
<td>P: 288</td>
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<tr>
<td>Case 4</td>
<td>&lt;1.0/1.0</td>
<td>–</td>
<td>95</td>
<td>0.7</td>
<td>643</td>
<td>&gt;80</td>
<td>236</td>
<td>U: 840</td>
</tr>
</tbody>
</table>

*Maximum value after glucagon 1 mg s.c.
†After a water deprivation test.
NR, Not recorded.
ANA, Anti-nuclear antibodies.
Rhf, Rheumatoid factor.

Normal ranges are: LH/FSH < 10 U/l and oestradiol 200–400 pmol/l in follicular phase of cycle; T4 58–174 nmol/l; TSH 0.4–5.0 mU/l; 0.900 cortisol 200–700 nmol/l, after glucagon or insulin tests > 550 nmol/l; GH < 5 mU/l on mean of 5 values; PRL < 360 mU/l; plasma (P) osmolality 285–295 mosmol/l with urine (U): P ratio > 2:1, after a water deprivation test P < 295 mosmol/l and U: P ratio > 2:1; in cranial diabetes insipidus, the dilute urine should concentrate after vasopressin analogue (DDAVP).

asymptomatic and physical examination was unremarkable.

After full-term spontaneous delivery of a healthy infant, a pituitary CT scan revealed a mass in the pituitary fossa with a suprasellar extension. Endocrinological investigations were normal (Table 1). Transsphenoidal hypophysectomy was recommended but the patient declined and was lost to follow-up for a period of 5 years, after which she represented with symptoms of hypothyroidism and hypoadrenalism. Investigation at this time revealed her to have panhypopituitarism (Table 1) with a pituitary mass on CT imaging, which was unchanged in size compared to 5 years previously. After replacement therapy, she agreed to surgery. Histology showed anterior pituitary cells separated by oedema fluid and an infiltrate of numerous lymphocytes and occasional plasma cells. In several areas these surrounded degenerating anterior pituitary cells. There was no evidence of a histiocytic infiltrate or granuloma formation and no lymphoid follicles were present.

Case 3

A 24-year-old nulliparous woman presented with secondary amenorrhoea. She had been an insulin dependent diabetic since the age of 7 years, but had an otherwise unremarkable past medical history apart from an episode of ketoacidosis 3 years previously. Physical examination was normal. Investigations indicated diagnoses of hypogonadotrophic hypogonadism and mild hyperprolactinaemia (Table 1). CT imaging demonstrated a mass arising out of the pituitary fossa with a suprasellar extension. Transsphenoidal hypophysectomy was performed and histology showed diffuse infiltration of the anterior pituitary by numerous lymphocytes and occasional plasma cells (Fig. 2). No lymphoid follicles were apparent but degeneration of anterior pituitary cells was present in many areas. A CT scan three years later showed no evidence of recurrence and she remains well, receiving oestrogen supplements. She does not require thyroxine or glucocorticoid replacement.

Case 4

A 47-year-old man was noticed by his new general practitioner to look acromegalic and, on further direct questioning, gave a 20-year history of easy sweating and thick skin. Over the previous year he had suffered gradual loss of libido and impotence. Physical examination revealed
classic features of long-standing acromegaly, but with normal visual fields. Investigations confirmed the diagnosis (Table 1) and revealed gonadotrophin deficiency. CT imaging showed a large pituitary mass with marked suprasellar extension. Transsphenoidal hypophysectomy was performed followed by pituitary radiotherapy, as the post-operative GH levels remained elevated. Histology revealed the presence of a chromophobe adenoma with smaller amounts of compressed non-tumorous anterior pituitary gland. Fibrous bodies were common in the tumour cells and these cells were found to be positive for growth hormone. Stains for ACTH, PRL and α-subunit were negative. In one area the tumour had an infiltrate of lymphocytes with lymphoid follicle formation; the features were of chronic follicular lymphocytic hypophysitis in a somatotroph adenoma (Fig. 3). Post-operative CT imaging revealed an empty pituitary fossa. He remains well on androgen replacement.

Discussion

Our four patients demonstrate several unusual and previously unreported features of lymphocytic hypophysitis. It is characteristically reported to be a disease of women, occurring particularly in relation to pregnancy (Hayashi et al., 1991; Pestell et al., 1990). However, only one of our three affected women was pregnant, and the fourth case was a man. Only two men with this condition have been previously reported (Pestell et al., 1990; Guay et al., 1987).

As in each of our patients, lymphocytic hypophysitis usually presents with a mass lesion with suprasellar extension visible on CT imaging. Mild hyperprolactinaemia is common, as a result of disturbance of the hypothalamo-pituitary axis, but PRL concentrations are usually much lower than those caused by a prolactinoma. Other differential diagnoses to be considered in a patient presenting with such a pituitary mass include non-functioning tumours and
granulomatous diseases such as sarcoidosis. Although variable deficiency of anterior pituitary hormones occurs in all of these conditions, posterior pituitary involvement is extremely uncommon in expanding adenomas. On the basis of her urine and plasma osmolalities after water deprivation and subsequent response to DDAVP, the patient described as Case 1 had evidence of mild cranial diabetes insipidus, which is only rarely associated with lymphocytic hypophysitis (McDermott et al., 1988). Lymphocytic infiltration of the pituitary stalk resulting in idiopathic diabetes insipidus appears to be a separate disease which tends not to involve the anterior pituitary gland (Imura et al., 1993).

A firm diagnosis of lymphocytic hypophysitis can be made only histologically. Our cases illustrate the importance of removing all of a pituitary mass if a diagnostic procedure is performed, rather than attempting to obtain a biopsy specimen, as some authors have advocated (Prasad et al., 1991). If this latter course is followed, the small amount of tissue obtained may be histologically normal and areas of chronic inflammation may be missed. In Case 1, lymphocytic hypophysitis occurred in conjunction with normal pituitary tissue. Further support for total removal of a pituitary mass is provided by Case 4, in which lymphocytic hypophysitis occurred in conjunction with a functioning pituitary adenoma. This is the first report of hypophysitis occurring with a functioning tumour. Coexistence has been previously demonstrated but the GH levels were normal (McConnon et al., 1991). The possibility of such an occurrence is of particular importance as the management of the two conditions varies. Whereas medical therapy is of proven benefit in a number of functioning pituitary adenomas, its role in lymphocytic hypophysitis remains unproven. Some authors have recommended conservative treatment or a trial of glucocorticoids (Bevan et al., 1992; Feigenbaum et al., 1991) but no trials have been performed and several patients have shown spontaneous endocrinological and radiological improvement (Bitton et al., 1991; Castle et al., 1988). Case 2 provides an illustration of an alternative course of lymphocytic hypophysitis with pro-

Fig. 2 Diffuse lymphocytic hypophysitis. H & E. x 450.
gression to severe and life threatening panhypopituitarism over a period of 5 years, suggesting that the natural history of this disease is variable and unpredictable. The pathogenesis of lymphocytic hypophysitis has been thought to have an autoimmune basis and two of our patients had a coexistent autoimmune disease; patient 1 had primary hypothyroidism, most probably Hashimoto's disease, and patient 3 had insulin dependent diabetes mellitus.

In conclusion, lymphocytic hypophysitis is a rare disorder but should be considered in the differential diagnosis of any pituitary mass. It may coexist with normal pituitary tissue and with functioning pituitary adenomas and, left untreated, can progress to severe panhypopituitarism. There are no methods of making the clinical diagnosis or predicting the outcome of untreated lymphocytic hypophysitis. For this reason, complete removal of a pituitary mass is needed to make an accurate tissue diagnosis and to decide on the correct definitive treatment.

References


