Abstract

Lymphocytic hypophysitis is an inflammatory, probably autoimmune-mediated disorder of the pituitary gland. The condition usually presents as a mass lesion with local pressure effects. There may be associated features of hypopituitarism and occasionally, diabetes insipidus. A definitive diagnosis can only be made by biopsy. It most frequently occurs in women in the peripartum period. Spontaneous resolution occurs in a proportion of cases. In the absence of local pressure effects, a conservative approach may be adopted in such patients.

Key words:

Lymphocytic hypophysitis, hypopituitarism, diabetes insipidus

Introduction

Lymphocytic hypophysitis is being recognized with increasing frequency. Goudi and Pinkerton first described it in 1962 on postmortem examination in a 22-year-old woman who died from adenocortical insufficiency shortly after an uncomplicated appendectomy. The majority of early cases were diagnosed at autopsy in 1980 and in 1980 the first ante-mortem diagnosis was made.

Definition

Lymphocytic hypophysitis is an inflammatory disorder, occurring predominantly in females in late pregnancy and the postpartum period. It is characterized by destruction and lymphocytic infiltration of the pituitary gland, most probably by an autoimmune process, leading to a pituitary mass lesion and/or various degrees of hypopituitarism. The lesion is usually confined to the adenohypophysis. Posterior pituitary gland or stalk involvement is less common, although patients presenting with diabetes insipidus are being increasingly reported.

Pathogenesis

It is thought to have an autoimmune basis, possibly involving both humoral and cell-mediated mechanisms. It is also known to coexist with other autoimmune conditions in up to 30% of cases, with similar histological features and organ-specific autoantibodies, particularly thyroiditis, adrenitis, and atriope gastritis. Some authors therefore consider it part of the autoimmune polyendocrine syndrome. There have been various case reports of association with other conditions such as sarcoidosis, dacrocyoadenitis, Graves’ disease and diabetes mellitus, parathyroiditis and idiopathic retroperitoneal fibrosis. Anti-pituitary antibodies have been sought using immunofluorescence on a variety of substrates including adult monkey pituitary, human fetal pituitary and rat and mouse preparations. Normal human pituitary is not easily used for immunofluorescence as corticotrophs have Fc receptors, which cause non-specific binding of immunoglobulins. Anti-pituitary antibodies are not constantly found and one explanation is that their level decreases during the third trimester of pregnancy, in line with thyroid autoantibodies, and related to the immune suppressive effects of pregnancy. They are also non-specific, having been found in the serum of normal unaffected individuals. In addition, the various methods used in their detection as outlined above may affect their reliability. On the other hand, lymphocytic hypophysitis maybe a cell-mediated immune process, with no humoral immunity involved.

To date the precise pathogenesis of lymphocytic hypophysitis remains uncertain.

Clinical features

Lymphocytic hypophysitis has a striking female predominance of approximately 8.5:1. It most commonly occurs in women in late pregnancy or in the postpartum period, regardless of race or parity. In one study, in 10 of the 14 females involved (71%), the presentation was associated with pregnancy. It occurs occasionally in males (10% of cases) who on average tend to be older than their female counterparts. It has also been reported in postmenopausal women with patients as old as 78 years and also in pediatric patients.

The clinical presentation is variable. It may be of acute onset and can occasionally lead to a fatal outcome, although with the increasing knowledge of the disease it is becoming more readily diagnosed and promptly treated. In general, the pituitary expansion and hypopituitarism caused by lymphocytic hypophysitis closely mimic that of a pituitary adenoma. In most cases reported during pregnancy, the presenting features are those of an enlarging pituitary mass with headaches and visual impairment, often bitemporal hemianopia, which may progress rapidly over a period of days. Hypopituitarism in such cases may be non-existent or only become apparent on investigation. Hormonal deficiency symptoms predominate outside of pregnancy, in those presenting in the puerperium, and are usually of insidious onset. The degree of hypopituitarism varies, and is independent of the size of the pituitary lesion. Corticotrophic and thyrotrophic function tend to be affected mostly (in 80% of cases) whilst somatotrophic and gonadotrophic function tend to be preserved. This is in contrast to the findings in hypopituitarism due to a pituitary adenoma. Mild hyperprolactinaemia is common as a result of disturbance of the hypothalamic-pituitary axis but this is usually much lower than would be expected with a prolactinoma. Diabetes insipidus is not unusual and this differentiates the condition from a pituitary adenoma.
We reviewed 66 cases reported in literature of whom 18 had diabetes insipidus (27% of cases).

The long-term clinical course of the disease is unknown. Spontaneous resolution has been reported in a large number of cases particularly in pregnancy\(^2\). There has also been one case report of complete recovery from panhypopituitarism in a 50 year old woman\(^4\). On the other hand, it can progress to severe hypopituitarism with a detrimental outcome. It has been reported that antipituitary antibodies can be found in the serum of 75% of women with the empty sella syndrome and therefore it is possible that in some cases the empty sella syndrome may represent a final stage of lymphocytic hypophysitis\(^6\). In males, the disease tends to follow a more aggressive course with cavernous sinus extension and ophthalmoplegia as well as a greater degree of hypopituitarism and less spontaneous recovery\(^2\). To our knowledge, there has been only one case of recurrence after a long interval reported in literature\(^6\).

**Differential diagnosis.**

During pregnancy and the puerperium lymphocytic hypophysitis needs to be considered in the differential diagnosis of a pituitary mass.

Sheehan’s syndrome is a major differential diagnosis of hypopituitarism presenting in the post-partum period. This is uncommon nowadays with the major advances in obstetric care.

Other important differential diagnoses include craniopharyngiomas, granulomatous diseases such as sarcoidosis, tuberculosis and histiocytosis, and metastatic disease (Table 1).

**Imaging**

On CT imaging, lymphocytic hypophysitis usually presents with a mass lesion and suprasellar extension mimicking an adenoma usually with homogenous contrast enhancement. There are characteristic features on MR imaging, mainly thickening of the sphenoid sinus, pituitary stalk enlargement and tongue-shaped extension of the lesion along the basal hypothalamus (Figures 1a, b). Dynamic MR imaging has also been utilised in the evaluation of vascular changes of the pituitary of patients with lymphocytic hypophysitis as it can display an abnormality of the hypophyseal vasculature even if the pituitary disease is seen to regress on the conventional MR study on follow up scans\(^2\).

There have also been some case reports advocating the use of gallium-67 scintigraphy as a radiological tool in the diagnosis of hypophysitis. Gallium-67 scintigraphy showed abnormal uptake in the pituitary lesion in some case reports (lymphocytic and granulomatous hypophysitis patients) and in the absence of reports concerning gallium-67 scintigraphy in other pituitary lesions, this technique may be of diagnostic value in this condition\(^4,13\).

**Histology**

This is the only method for obtaining a definitive diagnosis of lymphocytic hypophysitis. All other alternative methods provide a presumptive diagnosis. The general picture is of a chronic inflammatory process resulting in focal or diffuse adenohypophysial destruction, set in a background of fibrosis with some viable groups of pituitary cells within this. The inflammatory infiltrate is mixed but consists predominantly of lymphocytes, which are immunohistochemically positive for a lymphocyte marker (Figures 2a, b).

**Treatment**

This is very controversial at the present time. There have been reports of spontaneous resolution without any form of treatment\(^6\). On the other hand some cases have progressed to panhypopituitar...
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Conclusion

In summary, this is a rare condition that is becoming more frequently recognized.

The diagnosis should be particularly considered in women presenting with a pituitary mass in the peripartum period and in patients with a pituitary mass and associated diabetes insipidus. A conservative approach may be adopted in the first instance, in patients who do not have local pressure effects. The diagnosis can, however, only be definitively made by biopsy. This should be carried out in patients with a pituitary mass that is increasing in size. Surgical intervention is mandatory in patients with visual involvement. Treatment is controversial, but in view of its insidious clinical course, early surgical exploration is justified.

References: