SHORT REPORT

Lymphocytic and granulocytic hypophysitis: a single centre experience

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Abstract
Lymphocytic and granulocytic hypophysitis are rare pituitary masses. A series of five dealt with at a single centre is presented and discussed. Retrospective analysis of pathology records revealed the cases. Of pituitary mass lesions dealt with in this centre, 0.8% have the diagnosis. Five females presented, one pregnant at the time of presentation, three presenting with signs and symptoms of panhypopituitarism, and two with visual problems. All were treated by surgical means. All had good postoperative visual function, but all were panhypopituitar. Follow-up was for a mean of 4 years and 1 month. This rare condition should be treated by surgical means to obtain a diagnosis. Further treatment of residual tumour can be with corticosteroids. Good visual function should be expected, but so should permanent loss of pituitary function.

Keywords: Granulocytic hypophysitis, lymphocytic hypophysitis, pituitary tumours

Introduction
Granulocytic hypophysitis (GrHy) was first described in 1917,1 lymphocytic hypophysitis (LyHy) in 1962,2 and the first operation for granulocytic hypophysitis was reported in 1980.3 They are rare in published series of pituitary tumours with reports of LyHy occurring in 0.38–1.1% of all sellar pathology requiring surgery.4,5 It is suggested that they are the same condition, but at different stages with similar causation.4,6–10

This paper discusses five (0.8%) consecutive cases out of 619 who had had pituitary surgery during the last 15 years in this single centre.

Methods
A retrospective analysis of cases with a histological diagnosis of LyHy or GrHy, obtained using the comprehensive database of the neuropathology department in this hospital.

Case histories

Case 1
A 26-year-old female presented in her 38th week of pregnancy with a 2-week history of headaches and reduced vision. She was found to have bitemporal hemianopia. Computed tomography (CT) showed an enhancing pituitary mass. She underwent emergency caesarean section. Magnetic resonance imaging (MRI) 2 days later showed a decrease in tumour size with a return to normal vision. Ten days later her vision had deteriorated, without sign of pituitary haemorrhage and she underwent emergency trans-sphenoidal surgery. Histology revealed lymphocytic hypophysitis. Postoperatively she developed headache, sinusitis, postnatal depression and a cerebrospinal fluid (CSF) leak. Seventeen days after surgery there was still a leak and elective repacking was undertaken trans-sphenoidally. Twelve days later the leak had recurred and craniotomy successfully closed the leak. One week later she was discharged with no CSF leak. Postoperatively she had panhypopituitary malfunction and normal vision. She has been followed for 10 years.

Case 2
A 32-year-old female presented with amenorrhoea for 10 months, headache for 1 month and 3 weeks history of impaired visual fields. MRI showed a pituitary tumour thought to be an adenoma. Endocrine investigation found her to be panhypopituitary. She underwent transnasal trans-sphenoidal hypophysectomy. Histology showed granulomatous...
hypophysitis. She was well postoperatively and after 10 months follow-up she remains panhypopituitary with normal vision.

**Case 3**
A 38-year-old female had a 3-year history of panhypopituitarism and diabetes insipidus (DI) with a known enhancing mass, on CT, in her pituitary fossa. She then developed visual acuity and field loss over 2 months. Cerebral angiography was negative for aneurysm. A diagnosis of pituitary tumour was made. She underwent transnasal trans-sphenoidal hypophysectomy. Histology revealed granulomatous hypophysitis. After 7 years follow up she remains panhypopituitary with normal vision.

**Case 4**
A 45-year-old female developed diplopia with bilateral sixth and seventh nerve palsies, and unexpectedly MRI demonstrated a pituitary tumour. Five months later she was diagnosed as having panhypopituitarism. She had normal vision. She declined surgery. Thirteen months later her vision deteriorated to counting fingers in her right eye over 1 week. She underwent transnasal trans-sphenoidal hypophysectomy. Histology showed granulomatous and lymphocytic hypophysitis. After 2 years follow-up she remains panhypopituitary with normal vision.

**Case 5**
A 46-year-old female presented with secondary amenorrhoea and headache. She was found to be panhypopituitary and had a mass in the pituitary fossa causing chiasmal compression on MRI. She had normal vision. She underwent transnasal trans-sphenoidal hypophysectomy. Histology showed granulomatous and lymphocytic hypophysitis. After 6 months follow-up she remains panhypopituitary.

**Results**
Six-hundred-and-nineteen pituitary tumours have been operated upon in this centre in the last 15 years of which five (0.8%) have a histological diagnosis of LyHy or GrHy.

In summary:
- all are female;
- mean age 37.4 years (range 26–46);
- follow-up for a mean of 4 years 1 month (range 6 months – 10 years).

Three patients presented initially with signs of reduced pituitary function and two presented initially with visual problems. Time from first presentation to histological diagnosis varied from 3 weeks to 3 years (mean 1.5 years). The one patient who was pregnant at presentation had the shortest time to diagnosis.

All were treated by trans-sphenoidal hypophysectomy. All were panhypopituitary with normal vision postoperatively. There was one surgical complication of posttrans-sphenoidal hypophysectomy CSF leak which eventually required craniotomy for repair.

**Discussion**
This study of a single centre's experience with the unusual condition of granulocytic and lymphocytic hypophysitis confirms the rarity of it with 0.8% being found. This compares with other series of 0.38% and 1.1% of all sellar pathology requiring surgery. This unit's catchment population is approximately 3 million and all surgery for pituitary masses is dealt with at this single unit, therefore this low number is felt to be a true reflection of the local incidence.

The majority occur in females (M:F = 1:7), it is mainly associated with pregnancy and is rare in children.

Presentation, as in the cases described herein, is usually with chiasmal compression problems or panhypopituitarism. Sixty per cent will present with mass effect causing headache, nausea and vomiting, and chiasmal compression; 70% will present with endocrine abnormalities, with many presenting with both. Certain hallmarks of this condition are that 79–98% are female, 47–62% will have onset in the peripartum period, and 31% will have a sudden onset of DI suggesting GrHy/LyHy, rather than a more common pituitary tumour. Idiopathic DI may be due to GrHy/LyHy and is due to inflammatory changes in the vessels of the posterior pituitary gland. Endocrine abnormalities are thought to develop earlier with GrHy/LyHy than other pituitary mass lesions affecting corticotrophin (56%) and thyrotrophin (40%) more often than in pituitary adenoma.

GrHy/LyHy is associated with systemic autoimmune disease. There is a 30% coexistence of LyHy and other autoimmune disorders. Autoimmune diseases known to be associated with GrHy/LyHy include Hashimoto's thyroiditis, Graves disease, retroperitoneal fibrosis, dacr- ooadenitis, systemic lupus erythematosus (SLE), parathyroiditis, pernicious anaemia, pancreatitis and idiopathic adrenalitis. A diagnosis of GrHy must prompt a search for systemic granulomatous disease. It has been suggested that partly because of these known associations that GrHy and LyHy are the same condition at different stages. It has also been suggested that it has a viral aetiology.

It has recently been suggested that the rare association of aseptic meningitis with a pituitary mass is
diagnostic of GrHy/LyHy and that appropriate antiinflammatory medication is indicated; the first case was described in 1992, the second in 1997 and the third in 1999.24

Histologically, an acute inflammatory response is seen causing glandular enlargement with an extensive infiltration of lymphocytes and plasma cells, usually in the anterior pituitary with rare involvement of the posterior pituitary. Normal endocrine cells are consistently present, but are reduced in number, with electron microscopy revealing a reduction in secretory granules. Although minor inflammatory reactions are found in the normal pituitary they are clearly not as florid.

Imaging characteristics are generally indistinguishable from any other pituitary tumour, being hypointense or isointense to brain on T1-weighted MRI and hyperintense on T2 with uniform enhancement. Recently, a tongue like extension along the basal hypothalamus, diaphragm sellae enhancement and adjacent dural enhancement have been proposed as diagnostic of GrHy/LyHy on imaging; Kristoff et al.5 found that symmetrical sellar enlargement is seen in 66% on MRI with pituitary stalk thickening in 56%.

In general, surgery is recommended for this condition to decompress the mass effect and to obtain a histological diagnosis. However, Kristoff et al.5 Gagné et al.30 and Ishihara et al.31 have all recommended primary therapy with corticosteroids where mass effect is not present. Despite their recommendation, Kristoff et al.5 having obtained histological confirmation in only three of their nine patients, declared that ‘some uncertainty will always persist without histological confirmation of the diagnosis’. Histological diagnosis remains important whilst there remain no truly definitive non-histological features. Therapy with corticosteroids alone has some success in up to 62%, but relapse is almost certain upon cessation of the drug. Immunosuppression has also been considered.

Surgical treatment is generally possible by standard trans-sphenoidal approaches with suggestions that encountering inflamed sphenoid sinus mucosa is indicative of GrHy/LyHy and a recommendation to commence pituitary resection laterally at first to preserve as much normal pituitary as possible. In the long-term panhypopituitarism, if already present, can be expected including long-term DI, but with good return of visual function if previously compromised. Hyperprolactinaemia from stalk compression usually resolves. Recurrence can occur. Empty sella syndrome and persistent glandular enlargement are possible long-term sequelae.

Conclusions

Lymphocytic and granulocytic hypophysitis are considered by many authors to be the same condition presenting with signs and symptoms of pituitary insufficiency or mass effect. The extent of pituitary dysfunction is disproportionate to the findings of compression on the images when compared to a standard adenoma. To resolve the mass effect requires surgery and anti-inflammatory therapy if residual tumour is present; blind therapy with corticosteroids alone, although advocated by some is not recommended in this unit. Recurrence may occur despite this as it may be an autoimmune disorder. Long-term follow-up is required because of this and because of its devastating effect on pituitary function.

References

14 Cemeroğlu AP, Blaives M, Muraszko KM, Vazquez DM. Lymphocytic hypophysitis presenting with


**Comments**

This rare condition has been sporadically reported over the last two decades. Nottingham reports its series here. The report describes in detail their five cases, at least those which were referred for surgery. The individual cases are well described and, fortunately, all did well, for of course, it is a benign disease, whose progression is unknown. The authors go on to discuss the indications for surgery, arguing strongly in favour of decompression biopsy. This is the core argument for publishing the paper, I feel. The authors comment briefly regarding the age of their patients which included women in the perimenopausal age. This is of greater interest, but not touched on enough in my view. They comment on the place of steroids in treatment, but argue against their use because of the problems of necessitating long-term therapy. There are no hormone details which is a major fault of the paper.

This is a big rush series and reasonably argued. Furthermore, our Journal has not got 'its' series, I find to my surprise. There is a report of a Rathke’s cyst in association, but nothing else.

At the recent European workshop in pituitary adenomas there was a half-day session devoted to hypophysitis. It is clear that no one really is comfortable with management. My own experience confirms this. One can get very rapid results in treating with steroids in a classic case, such as a young woman presenting perinatally, and steroids can be reduced quite quickly to a low level. Does this treatment allow some retention of pituitary function which is almost inevitably lost with surgery? On the other hand, a man presenting with a cavernous sinus syndrome who was thought to have sarcoid, but whose biopsy showed hypophysitis (confirmed by Asa) remains on relatively high doses of prednisolone over a year following surgery. Or again, what does one do on finding a tough mass in a post menopausal women presenting with intractable headaches and panhypopituitarism? The smear biopsy confirms the disease — should one go on to clear the fossa? Will the residual continue to swell with the inflammation? Lots of unanswered questions.

So, in conclusion, this paper is not really novel and does not quite address all the dilemmas facing decisions in this difficult disease. I would argue that it is time for the UK to have a hypophysitis register. If it were to be in Nottingham, I would have no problem with that.

M. Powell

This manuscript describes a series of five cases of lymphocytic or granulocytic hypophysitis from a single Neurosurgical Centre. Following a description of each, this entity and the approach to its diagnosis and management are reviewed briefly.
Throughout the Discussion, the authors emphasize the role of surgical decompression and negate the use of corticosteroids. This is despite the fact that there are many reports of successful shrinkage of gland enlargement with steroid therapy. I do think the Abstract and Discussion should be modified to indicate that medical therapy may play a role. Finally, the authors do not mention the measurement of anti-pituitary antibodies in this context. Whilst this test is not very sensitive, it can be of some diagnostic utility.

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