Primary hypophysitis: clinical-pathological correlations

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Abstract

Objective: Primary hypophysitis comprises of three distinct histomorphological entities: lymphocytic, granulomatous and xanthomatous. Clinical features of the three subtypes for diagnostic and treatment strategies have yet not been well characterized.

Methods: Endocrine function, visual fields and acuity as well as magnetic resonance imaging characteristics were assessed before and after transphenoidal surgery in the largest series of 31 patients with primary hypophysitis (21 lymphocytic, 6 granulomatous, and 4 xanthomatous cases).

Results: Only lymphocytic hypophysitis occurred during pregnancy (30%) and was associated with other autoimmune diseases (24%). Visual fields and acuity abnormalities were not seen in xanthomatous hypophysitis. Lymphocytic and granulomatous hypophysitis most often resulted in severe dysfunction of the adrenal, gonadal and thyroidal axes as well as diabetes insipidus. For patients presenting with xanthomatous hypophysitis most often, mild anterior pituitary axis failure was documented and posterior pituitary involvement was hardly found. The outcome after transphenoidal biopsy was generally favorable. Pre- or postsurgical glucocorticoid treatment was very effective in 75% of the lymphocytic form in reducing the pituitary size. In contrast, glucocorticoid therapy was less effective in granulomatous or xanthomatous hypophysitis.

Conclusion: Diffuse destruction of the complete pituitary gland including the infundibulum has to be considered in lymphocytic and granulomatous hypophysitis, whereas in xanthomatous, a circumscribed anterior pituitary lesion leading to compression of the pituitary gland without alteration of the pituitary stalk and optic chiasm can be assumed.

European Journal of Endocrinology 155 101–107

Introduction

Primary hypophysitis is an inflammation of the pituitary gland, not secondary to infections or neighboring lesions. It is rare but increasingly recognized and has thus become an important entity in the differential diagnosis of nonsecreting, space-occupying lesions of the sella turcica. The disease has an unpredictable natural history, ranging from spontaneous recovery (1–3) to death (4). Its treatment at the moment is only symptomatic and aimed at reducing the size of the enlarged pituitary. Pituitary surgery (5, 6), lympholytic drugs such as glucocorticoids (7, 8), azathioprine (9), and methotrexate (10), or radiotherapy (11) are the current approaches.

Primary hypophysitis comprises of three distinct histopathological subtypes: lymphocytic, granulomatous and xanthomatous (12). Pathogenesis, the natural history and unique clinical features of the three histopathological subtypes are not well characterized. We present a large series of 31 histologically proven cases of primary hypophysitis having been collected in several German neuropathological departments during the last 13 years. The histomorphological changes of pituitary glands have been correlated to pretherapeutic symptoms and postoperative adjuvant therapy.

Materials and methods

Patients

The study population included 31 patients who underwent transphenoidal surgery in nine German neurosurgical departments (Aachen, Bielefeld, Erlangen, Göttingen, Lübeck, Meiningen, Münster, Recklinghausen, and Trier) from 1992 to 2005.

Clinical studies

Endocrine function, visual fields and acuity were assessed before and after surgery in all patients. Cerebrospinal fluid tapping was performed preoperatively in 10 patients. Preoperative magnetic resonance imaging (MRI) data were analyzed in 23 patients.
Histopathological appearance

Pituitary surgical specimens were fixed in 4% buffered formalin, embedded in paraffin and stained with hematoxylin and eosin. Ziehl-Neelsen and Grocott methamine silver. Hypophysitis was diagnosed (12), lymphocytic in 21 patients, granulomatous in 6 patients, and xanthomatous in 4 patients (Table 1). Both anterior and posterior pituitary tissue were involved in 13 (62%) lymphocytic cases, and three (50%) granulomatous hypophysitis cases. Only the anterior lobe was infiltrated in eight (38%) lymphocytic cases, three (50%) granulomatous cases and in all four (100%) patients with xanthomatous hypophysitis.

Statistical analysis

The outcome measures analyzed in this study were compared in the three independent histopathological groups using the Wilcoxon rank-sum test, performed after the Kruskall–Wallis test. A \( P \) value less than 0.05 was considered statistically significant.

Results

Clinical features

The mean age at presentation was similar in lymphocytic and granulomatous hypophysitis, but tended to be younger in xanthomatous (Table 1). On an average, the age was 10 years younger in females than in males.

Headache was the most common complaint at presentation, followed by decreased libido and potency.

Table 1 Presurgical clinical features of 31 patients with lymphocytic, granulomatous or xanthomatous hypophysitis.

<table>
<thead>
<tr>
<th></th>
<th>Lymphocytic (n=21)</th>
<th>Granulomatous (n=6)</th>
<th>Xanthomatous (n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at presentation (years, mean±s.d.)</td>
<td>10 females: 39.7±12.1</td>
<td>3 females: 40.0±11.3</td>
<td>3 females: 29.0±2.7</td>
</tr>
<tr>
<td></td>
<td>11 males: 46.3±15.4</td>
<td>3 males: 47.3±16.4</td>
<td>1 male: 41.0</td>
</tr>
<tr>
<td>Female-to-male ratio</td>
<td>0.91</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Headache (n and %)</td>
<td>14 (67%)</td>
<td>5 (83%)</td>
<td>3 (75%)</td>
</tr>
<tr>
<td>Decreased libido and potency, secondary amenorrhea (n and %)</td>
<td>52 (%)</td>
<td>2 (33%)</td>
<td>4 (100%)</td>
</tr>
<tr>
<td>Duration of symptoms (months, mean±s.d.)</td>
<td>12.4±16</td>
<td>11.2±11</td>
<td>82±90</td>
</tr>
<tr>
<td>Association with pregnancy (n and %)</td>
<td>3 of 10 (30%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Association with other autoimmune diseases (n and %)</td>
<td>5 of 21 (24%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Visual fields and acuity (n and % impaired)</td>
<td>9 of 21 (43%)</td>
<td>5 (83%)</td>
<td>0</td>
</tr>
<tr>
<td>Number (cells/mm³) in the CSF</td>
<td>26.7±19</td>
<td>7.3±2</td>
<td>NE</td>
</tr>
<tr>
<td>Endocrine impairment:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gonadal axis</td>
<td>16 of 20 (80%)</td>
<td>4 of 5 (80%)</td>
<td>3 of 3 (100%)</td>
</tr>
<tr>
<td>Adrenal axis</td>
<td>15 of 21 (71%)</td>
<td>6 of 6 (100%)</td>
<td>1 of 4 (25%)</td>
</tr>
<tr>
<td>Thyroidal axis</td>
<td>17 of 21 (81%)</td>
<td>5 of 6 (83%)</td>
<td>2 of 4 (50%)</td>
</tr>
<tr>
<td>Growth hormone</td>
<td>3 of 7 (43%)</td>
<td>2 of 2 (100%)</td>
<td>3 of 4 (75%)</td>
</tr>
<tr>
<td>Hyperprolactinemia</td>
<td>3 of 19 (16%)</td>
<td>2 of 6 (33%)</td>
<td>1 of 4 (25%)</td>
</tr>
<tr>
<td>Diabetes insipidus</td>
<td>10 of 21 (48%)</td>
<td>3 of 6 (50%)</td>
<td>1 of 4 (25%)</td>
</tr>
<tr>
<td>MRI imaging:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pituitary stalk thickening</td>
<td>11 of 16 (79%)</td>
<td>3 of 3 (100%)</td>
<td>1 of 3 (33%)</td>
</tr>
<tr>
<td>Suprasellar extension</td>
<td>9 of 16 (64%)</td>
<td>2 of 3 (67%)</td>
<td>0</td>
</tr>
<tr>
<td>Benefit of high-dose glucocorticoids*</td>
<td>1 of 1</td>
<td>1 of 1</td>
<td>0 of 1</td>
</tr>
</tbody>
</table>

CSF, cerebrospinal fluid; NE, not evaluated. *Transient shrinking of pituitary mass.
lymphocytic hypophysitis (5 out of 6 and 9 out of 21 respectively). Visual abnormalities were not observed in xanthomatous hypophysitis. Perimetry testing was performed in seven patients and revealed mono- or bitemporal hemianopsia. Fundoscopic examination was found within normal limits in all the patients.

**Presurgical endocrine findings**

A deficit in one or more pituitary axes was found in 29 out of 31 (94%) patients (Table 1). The endocrine deficit was complete in seven patients, and partial in the remaining 22 patients, showing similar prevalence among the histological subtypes. The most common deficits were those of the gonadal axis, followed by those of the adrenal and thyroid axes.

Impaired gonadal function was found in 23 out of 28 (82%) tested patients, with no frequency differences in the three histological subtypes. In seven patients, low levels of estradiol (<110 pmol/l during reproductive years, and <37 pmol/l after menopause) and testosterone (<10.0 nmol/ml) were revealed without any elevation of gonadotropins. Low gonadotropins (luteinising hormone <0.8 IU/l, follicle-stimulating hormone <1.2 IU/l) with normal sexual steroid levels were seen in only two patients.

Impaired adrenal function was present in 22 out of 31 (71%) patients. The adrenal deficit was more frequent in lymphocytic and granulomatous than in xanthomatous hypophysitis. Morning basal cortisol was decreased (<138 nmol/l) in 20 cases, of which 12 showed an insufficient cortisol rise (<550 nmol/l) after stimulation with supraphysiological doses of ACTH (250 µg). Three additional patients, showing otherwise normal basal cortisol levels, had an insufficient rise of serum cortisol after dynamic testing. ACTH itself was evaluated in 15 patients and found to be low (<3.3 pmol/l) in eight cases. Central hypoadrenalism was not confirmed by other tests such as low-dose ACTH test or insulin tolerance test. Preoperative, long-term replacement with physiological doses of hydrocortisone had been performed only in one patient.

Impaired thyroid function was present in 24 out of 31 (77%) patients, with no differences in the three histological subtypes. Fifteen patients had secondary hypothyroidism (thyroid-stimulating hormone <0.45 IU/l and free triiodothyronine/free thyroxine <2.0–4.2/8.0–17.0 pmol/l), five patients revealed low fT3/fT4 without lowering of TSH. In the remaining four patients, TSH was decreased but thyroid hormones were still within the normal limits. One patient suffered from hyperthyreosis during Hashimoto’s crisis. Preoperative, long-term replacement with physiological doses of thyroid hormones had been performed in six patients.

A decreased secretion of growth hormone (GH) assessed either by an insufficient rise of GH after insulin-induced hypoglycemia or by low insulin-like growth factor-1 levels (<69 ng/ml), was present in 8 out of 13 (62%) tested patients. The GH deficit was more frequent in granulomatous and xanthomatous than in lymphocytic hypophysitis.

Hyperprolactinemia (>530 µU/ml) was observed in 6 out of 29 (21%) tested patients, with no frequency differences among the three histological groups. Only one female developed hyperprolactinemia (<50 µU/ml), manifested by the inability to breastfeed her newborn.

Diabetes insipidus was preoperatively present in 14 out of 31 (45%) patients, 48% in lymphocytic, 50% in granulomatous, and 25% in xanthomatous hypophysitis. All patients received desmopressin replacement before pituitary surgery.

**Presurgical meningitis suspicion**

Meningitis was presurgically considered in 10 out of 31 (32%) patients, and led to the drawing of cerebrospinal fluid (Table 1). The lymphomonocytic pleiocytosis tended to be more severe in lymphocytic than granulomatous hypophysitis (26.7 ± 19 versus 7.3 ± 2 cells/mm³).

**Presurgical MRI**

In 19 patients (14 lymphocytic, 2 granulomatous and 2 xanthomatous hypophysitis) coronal and sagittal T1-w MR images were analyzed (Fig. 1). In four patients (two lymphocytic, one granulomatous and one xanthomatous hypophysitis) only radiological reports were available. Enlargement of the pituitary gland and fossa was seen in all but one xanthomatous hypophysitis. Lymphocytic and granulomatous subtypes were in T1-weighted images, most often isointense triangular or dumbbell shaped masses, whereas xanthomatous lesions were hypointense and round. Suprasellar extension with alteration of the optic chiasm was found in nine (64%) lymphocytic and two (67%) granulomatous hypophysitis. All lymphocytic and granulomatous lesions showed a remarkable contrast enhancement, revealing cystic lesions in three lymphocytic and one granulomatous hypophysitis. Due to pregnancy in three patients, no gadolinium was applied. Pituitary stalk thickening was observed in all (100%) granulomatous patients, in 11 (79%) lymphocytic patients and only in one (33%) xanthomatous hypophysitis patient. Pituitary stalk displacement by pituitary mass without thickening was seen in xanthomatous hypophysitis patient.

**Presurgical corticoid trial**

High-dose glucocorticoid therapy (60 mg/day methylprednisolone) was performed in three patients (Table 1). A transient shrinkage of the pituitary mass, as well as improvement of headache and vision, was achieved in two cases; one with lymphocytic hypophysitis, one with granulomatous hypophysitis, but not in the patient with xanthomatous hypophysitis.
Figure 1 Preoperative sagittal (right) and coronal (left) T1-w MR images, gadolinium-enhanced. (A) lymphocytic (B) granulomatous and (C) xanthomatous hypophysitis. (A) Homogeneously enhancing dumbbell-shaped pituitary mass with suprasellar extension and alteration of the optic chiasm. Pituitary stalk cannot be identified. Note the dural enhancement. (B) Cystic appearing triangular shaped and inhomogeneously enhancing sellar mass with suprasellar extension and thickening of the pituitary stalk. Note the dural enhancement. (C) Mild enhancing well-defined intrasellar tumor. Normal enhancing pituitary gland can be identified. Note the pituitary stalk displacement without stalk thickening.
**Postsurgical follow-up**

A postsurgical follow-up was available in all 31 patients (Table 2). The follow-up time ranged from 1 to 133 months (median: 24 months).

Headache resolved postoperatively in 18 out of 22 (82%) patients, with no differences among the three histological subtypes, and persisted in four patients. Visual fields and acuity improved shortly after surgical decompression of the optic chiasm in 11 of the 14 patients. Cranial nerve palsies fully recovered in all five patients.

Pituitary function after surgery improved in 14 out of 31 (45%) patients, remained deficient in nine (29%), and deteriorated in the remaining eight patients (26%). The improvement was mainly contributed by the recovery of gonadal function, which occurred in 13 out of 23 (57%) patients without subtype predominance. Hyperprolactinemia reversed to normal levels in all six patients, thereby presumably influencing gonadal function in four patients (three lymphocytic and one xanthomatous hypophysitis). Two patients, both preoperatively suffering from secondary amenorrhea, became pregnant about 12 months after transphenoidal biopsy of xanthomatous hypophysitis. Adrenal and thyroidal axes only occasionally improved. Hyperthyroidism in the one patient with Hashimoto’s thyroiditis returned to euthyroid levels within 12 weeks postoperatively. The deterioration of pituitary function was mainly due to the new occurrence of diabetes insipidus (5 out of 11 patients). Emerging insufficiency of adrenal axis was found in four lymphocytic cases. Additionally, the thyroidal axis deteriorated in three of them.

Postoperatively, all but three patients (one lymphocytic and two xanthomatous hypophysitis) were dependent on hormonal substitution therapy. Twelve patients received high-dose glucocorticoid therapy, starting at 60 mg of decortilen daily and tapering the dose every 5 days. This treatment was very effective in reducing the pituitary size in the lymphocytic form: six out of eight patients responded within 3 months and maintained a reduced size for up to 33 months of follow-up. Moreover, one of the two patients whose pituitary mass did not decrease during glucocorticoid treatment, showed recovery of adrenal function as well as disappearance of diabetes insipidus. In contrast, glucocorticoid therapy was less effective in granulomatous (one out of three patients responded) and no response in xanthomatous hypophysitis. Re-enlargement of the pituitary mass was observed upon glucocorticoid tapering in three lymphocytic patients and in one granulomatous without glucocorticoid tapering. Following the second transphenoidal surgery, two lymphocytic patients received low-dose (3 Gy) radiotherapy, whereas one granulomatous was treated by gamma-knife irradiation. Three patients (one lymphocytic, two granulomatous hypophysitis) died after transphenoidal surgery, one of cardiac arrhythmia after 55 months, one of fatal upper gastrointestinal bleeding after 45 months, and one of unknown cause after 25 months.

**Discussion**

The clinical symptoms of primary hypophysitis necessitating operation are mostly due to inflammatory irritation of sellar and parasellar structures as well as to the suprasellar extension of the pituitary mass lesions (6, 10, 13, 14). Here, they did not considerably differ among the histological subtypes. But interestingly, visual compromise has, to date, not been described in cases with xanthomatous hypophysitis (13, 15, 16). This is most likely due to the relatively small size of the pituitary mass in most cases without affecting the optic

| Table 2 | Postsurgical clinical features of 31 patients with lymphocytic, granulomatous or xanthomatous hypophysitis with follow-up time ranging from 1 to 133 months (median: 24 months). |
|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| **Lymphocytic (n=21)** | **Granulomatous (n=6)** | **Xanthomatous (n=4)** |
| Headache (n and % improved) | 11 of 14 (78%) | 5 of 5 (100%) | 2 of 3 (67%) |
| Visual fields and acuity (n and % improved) | 9 of 9 (100%) | 2 of 5 (40%) |
| Endocrine improvement* | | | |
| Gonadal axis | 9 of 16 (56%) | 2 of 4 (50%) | 2 of 3 (67%) |
| Adrenal axis | 2 of 15 (13%) | 0 of 6 (0%) | 1 of 2 (50%) |
| Thyroidal axis | 2 of 17 (12%) | 1 of 5 (20%) | 1 of 2 (50%) |
| Growth hormone | 2 of 3 (67%) | 1 of 2 (50%) | 2 of 4 (50%) |
| Hyperprolactinemia, resolved | 3 of 3 (100%) | 2 of 2 (100%) | 1 of 1 |
| Diabetes insipidus, resolved | 1 of 10 (10%) | 0 of 3 (0%) | 0 of 1 |
| Endocrine impairment** | | | |
| Gonadal axis | 1 of 4 (25%) | No impairment | No impairment |
| Adrenal axis | 4 of 6 (67%) | No impairment | No impairment |
| Thyroidal axis | 3 of 4 (75%) | No impairment | No impairment |
| Growth hormone | 3 of 3 (100%) | No impairment | No impairment |
| Diabetes insipidus | 5 of 11 (45%) | No impairment | No impairment |
| Benefit of high-dose glucocorticoids | 6 of 8 (75%) | 1 of 3 (33%) | 0 of 1 |

*Endocrine improvement: hormone levels returning to normal values making hormonal substitution unnecessary.

**Endocrine impairment: postoperative emerging necessity for hormonal substitution therapy in patients with preoperative normal hormone values.
A Gutenberg and others

unselective diffuse inflammatory destruction of pituitary of ACTH-, FSH/LH- or TSH-producing acinar cells.

lymphocytic subtypes. The sequence of pituitary axes

to insufficiency of somatotropic axis, which was present in pituitary impairment. The main difference was in the revealed different severity of anterior pituitary failure of the histological subtypes of primary hypophysitis cases presented with hypogonadism. Most interestingly, and occurred only in two of our patients suffering from lymphocytic hypophysitis (18). Selected studies, although the frequency of impairment was in relation of axes insufficiency corresponds to other

terized by diminished secretion of some or all of the most probably secondary to hypophysitis (6).

and fatigue, lumbar function is indispensable to exclude viral or bacterial CNS disease. Lymphomonocytotic cells (> 5 cells/mm³) were found in eight out of ten patients, but altogether white cell count was rather low, and cerebro-spinal fluid was sterile in all cases. Therefore, aseptic meningitis or cerebrospinal fluid leucocytosis is most probably secondary to hypophysitis (6).

In patients presenting with fever or even meningism and hypophysitis showed other autoimmune diseases like juvenile diabetes mellitus, Wegener’s granulomatosis, psoriasis or Hashimoto’s thyroiditis. Associated autoimmune disorders are only incidentally reported in granulomatous subtype, such as individuals suffering from Crohn’s disease (19), psoriasis (20) and Hashimoto’s thyroiditis (13) and no association in xanthomatous cases (15, 16, 21).

Hypopituitarism in primary hypophysitis is characterized by diminished secretion of some or all of the hormones of the anterior pituitary (22). The observed relation of axes insufficiency corresponds to other studies, although the frequency of impairment was twice as high in our patients than in other reports from patients with lymphocytic hypophysitis (18). Selected deficiency of a single pituitary hormone is less frequent and occurred only in two of our patients suffering from lymphocytic and xanthomatous hypophysitis. Both cases presented with hypogonadism. Most interestingly, the histological subtypes of primary hypophysitis revealed different severity of anterior pituitary failure with granulomatous showing the most profound pituitary impairment. The main difference was in the insufficiency of somatotrophic axis, which was present in 100% granulomatous patients and in only 43% in lymphocytic subtypes. The sequence of pituitary axes failure might be due to early and selective loss of ACTH-, FSH/LH- or TSH-producing acinar cells caused by a target autoantigen (18), exacerbating the unselective diffuse inflammatory destruction of pituitary acinar cells. The common presence of adrenal deficiency and hypothyroidism apparently distinguishes patients suffering from lymphocytic and granulomatous hypophysitis from patients with xanthomatous hypophysitis.

Considering posterior pituitary function, diabetes insipidus occurred in 50% of patients suffering from lymphocytic and granulomatous hypophysitis respectively and corresponded well to pituitary stalk thickening in MRI. The single occurrence of diabetes insipidus without accompanying hyperprolactinemia can be considered to be caused by the diffuse inflammatory infiltration rather than by compression of the posterior lobe and pituitary stalk. Lacking pituitary stalk infiltration (15, 16, 21), diabetes insipidus is rare in xanthomatous hypophysitis (25%) and is most likely explicable due to the more circumscribed inflammation confined to the anterior pituitary lobe.

Initial treatment with immunosuppressive drugs like glucocorticoids is generally recommended in cases suspected for lymphocytic or granulomatous hypophysitis where vision is not endangered by pituitary mass lesion (8, 10). However, endocrinological and neuroradiological improvement under pre- or postoperative high-dose corticosteroids is most often not only incomplete, but also only transient or even fails (8, 10, 14, 20, 23–29). The only prospective trial of glucocorticoid use in lymphocytic hypophysitis showed that methylprednisolone reduced MRI mass in seven out of nine patients and improved anterior pituitary function in four patients (8, 15, 16, 21). Deterioration of pituitary function most often resulted from onset of diabetes insipidus followed by emerging adrenal insufficiency. Iatrogenic injury of the pituitary and stalk rather than progression of inflammatory infiltration has to be assumed, because deterioration was associated with surgery. Glucocorticoid trial was once reported as beneficial in an xanthomatous subtype (15, 16, 21). In two of our xanthomatous patients, no apparent benefit could be shown after an either pre- or postsurgical therapeutic trial with corticosteroids. Instead, half of our patients revealed improvement of anterior pituitary dysfunction shortly after surgery and none suffered from endocrinological deterioration. Therefore, transphenoidal surgery should be recommended in xanthomatous lesion, even if no threat to vision is reported (15, 16, 21).

Our study demonstrates partial or even full recovery of pituitary function in more than half of our patients following transphenoidal surgery. Recovery mostly applied to gonadal function, presumably due to correction of hyperprolactinemia by decompression of the pituitary stalk. Convincingly, both patients with xanthomatous hypophysitis, initially presenting with secondary amenorrhea became pregnant 12 months after pituitary surgery. But strikingly, in five patients, even adrenal and thyroidal hypofunction fully recovered after surgery and intermittent hormonal substitution therapy. On the other hand, spontaneous recovery (1–3) has to be considered.

The clue to diagnosis and the approach to the management of patients with primary hypophysitis must be guided by the predominant mechanism leading

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to hypopituitarism in each case. Diffuse destruction of the complete pituitary gland including the infundibulum has to be considered in lymphocytic and granulomatous hypophysitis. In xanthomatous hypophysitis, a circumscribed anterior pituitary lesion leading to compression of the pituitary gland without alteration of the pituitary stalk and optic chiasm can be assumed. Outcome after transphenoidal biopsy is generally favorable, but if a threat to vision is absent, corticosteroid trial as an initial treatment of lymphocytic hypophysitis is recommended. Ambivalent response to glucocorticoids should be expected in granulomatous hypophysitis. In xanthomatous hypophysitis, a circumferential mass in the pituitary stalk has to be considered in lymphocytic and granulomatous hypophysitis.

Acknowledgements

We would like to thank Prof Dr W Feiden (Homburg), Dr M Hasselblatt (Münster), Prof Dr W Paulus (Münster) and Prof Dr J Weis (Aachen) at Departments for Neuropathology for providing the hypophysitis biopsy specimen. We are thankful to Prof Dr M Bettga (Trier), and Prof Dr J Weis (Aachen) at Departments for Neurosurgery and Psychiatry for providing clinical data of the patients under their care.

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Received 19 January 2006
Accepted 11 April 2006

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