Primary hypophysitis: a single-center experience in 16 cases

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Object. The authors review their experience in the treatment of 16 patients with primary hypophysitis.

Methods. A retrospective study was undertaken to review cases of primary hypophysitis. The mean age of the patients was 47 years and there was an equal distribution of sexes. Recent pregnancy and underlying autoimmunity were noted in 50% of the patients. Two patients had undergone previous transsphenoidal operations at other centers, one for prolactinoma and another for hypophysitis. Headache, anterior pituitary deficiency, and suprasellar mass lesions were the most common presenting features. The initial presumptive diagnosis was pituitary adenoma in six patients (37.5%) and inflammatory hypophysitis in 10 (62.5%). Five patients received initial medical therapy for hypophysitis; although three (60%) responded satisfactorily, two (40%) did not and later underwent surgery.

Altogether 13 patients (81.2%) underwent transsphenoidal surgery. The histological diagnoses were lymphocytic hypophysitis in 10 (76.9%) and granulomatous hypophysitis in three (23.1%) of the surgically treated patients. A coexistent Rathke cleft cyst was noted in one patient. There was no death in this series. One patient experienced postoperative cerebrospinal fluid leakage and meningitis. One patient had bilateral internal carotid artery occlusion secondary to inflammatory involvement of the cavernous sinuses and arteritis. This patient recovered and is capable of independent functional activities.

Conclusions. All surgical patients experienced improvement in their headache and/or visual field defects and none had visual deterioration. None of the patients experienced any improvement in endocrine function and all required long-term hormone replacement. Transsphenoidal surgery was a safe and effective treatment especially for visual and pressure symptoms. A postoperative recurrence developed in two patients (15.4%) and the treatment modalities included steroid therapy, repeated surgery, and radiosurgery.

KEY WORDS • PITUITARY • HYPOPHYSITIS • TRANSSPHENOIDAL SURGERY • STERIODS • RADIOSURGERY

Inflammatory hypophysitis is a rare disorder characterized by focal or diffuse inflammatory infiltration and destruction of the pituitary gland.12,35 The precise incidence of this disorder is unknown and its early description consisted primarily of individual case reports.25,34,38,49,52 Recently, an increasing number of published clinical series have improved our understanding of this condition.8,11,15,24,32,48,55 Histologically, inflammatory hypophysitis may be classified into five types: lymphocytic hypophysitis, granulomatous hypophysitis, xanthogranulomatous hypophysitis, xanthomatosus hypophysitis, and necrotizing hypophysitis.54 Lymphocytic and granulomatous hypophysitis are more commonly encountered. The former is characterized by infiltration of the pituitary gland with lymphocytes, plasma cells, and fibrosis, and the latter by epithelioid histiocytes and multinucleated giant cells.24 It is thought that these entities share a similar origin and may represent different stages of the disease.24 The majority of cases are idiopathic, or primary, hypophysitis; secondary hypophysitis may occur in patients with systemic inflammatory disorders such as sarcoidosis, Wegener granulomatosis, Langerhans cell histiocytosis, and tuberculosis.10,12,20 Pressure symptoms and visual impairment may arise from the development of a sellar mass lesion, and mass effect, involvement of the pituitary stalk, and pituitary destruction may result in endocrine dysfunction.

The natural history of primary hypophysitis is incompletely understood and its treatment remains controversial. Conservative management with close clinical observation has been advocated based on the disease’s often benign and transient course,44 whereas medical therapy with high-dose corticosteroid agents has produced inconsistent results.23,32,33,59 Surgical intervention in the form of transsphenoidal exploration has been associated with a satisfactory outcome.11,15,24 The authors describe a single-center experience with 16 patients suffering from primary hypophysitis in which 13 of the patients were treated surgically.

CLINICAL MATERIAL AND METHODS

A retrospective review of medical records between July 1992 and January 2003 revealed 16 patients with the diagnosis of hypophysitis. The patient population was composed of eight men and eight women with a mean age of...
Primary hypophysitis

TABLE 1

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs), Sex</th>
<th>Main Symptoms</th>
<th>Pregnancy</th>
<th>Associated Conditions</th>
<th>Duration of Symptoms (mos)</th>
<th>Visual Impairment</th>
<th>MRI Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>44, M</td>
<td>headache, decreased libido, weight gain, lethargy</td>
<td>NA</td>
<td>idiopathic myopathy</td>
<td>36</td>
<td>diplopia</td>
<td>suprasellar extension, CSI</td>
</tr>
<tr>
<td>2</td>
<td>27, F</td>
<td>headache, amenorrhea, weight gain, meningism</td>
<td>no</td>
<td>none</td>
<td>36</td>
<td>none</td>
<td>suprasellar extension, thickened stalk</td>
</tr>
<tr>
<td>3</td>
<td>58, M</td>
<td>headache, decreased libido, weight loss</td>
<td>NA</td>
<td>prolactinoma resected in 1981</td>
<td>1</td>
<td>none</td>
<td>suprasellar extension</td>
</tr>
<tr>
<td>4</td>
<td>68, F</td>
<td>headache, decreased libido, weight gain, lethargy</td>
<td>no</td>
<td>none</td>
<td>3</td>
<td>none</td>
<td>suprasellar extension</td>
</tr>
<tr>
<td>5</td>
<td>45, F</td>
<td>headache, weight loss, galactorrhea</td>
<td>no</td>
<td>none</td>
<td>1</td>
<td>none</td>
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</tr>
<tr>
<td>6</td>
<td>37, F</td>
<td>headache, amenorrhea, weight gain, lethargy</td>
<td>12 mos prior</td>
<td>none</td>
<td>12</td>
<td>bitemporal hemianopia</td>
<td>suprasellar extension, thickened stalk</td>
</tr>
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<td>hypothyroidism (unknown nature)</td>
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<td>none</td>
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</tr>
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<td>8</td>
<td>40, M</td>
<td>headache, decreased libido, weight gain, lethargy</td>
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<td>none</td>
<td>60</td>
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<td>intrasellar mass</td>
</tr>
<tr>
<td>9</td>
<td>57, M</td>
<td>headache, decreased libido, lethargy</td>
<td>NA</td>
<td>none</td>
<td>18</td>
<td>none</td>
<td>suprasellar extension</td>
</tr>
<tr>
<td>10</td>
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<td>headache, diplopia, polyuria</td>
<td>NA</td>
<td>granulomatous disease (unknown nature)</td>
<td>12</td>
<td>diplopia</td>
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</tr>
<tr>
<td>11</td>
<td>37, F</td>
<td>decreased libido, amenorrhea, weight gain, polyuria, lethargy</td>
<td>no</td>
<td>orbital pseudotumor</td>
<td>1</td>
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<td>12†</td>
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<td>polyuria</td>
<td>NA</td>
<td>temporal arteritis</td>
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</tr>
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<td>13</td>
<td>38, M</td>
<td>decreased libido, weight loss, polyuria, lethargy</td>
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<td>5</td>
<td>none</td>
<td>intrasellar mass, thickened stalk</td>
</tr>
<tr>
<td>14</td>
<td>71, M</td>
<td>lethargy</td>
<td>NA</td>
<td>Grave disease</td>
<td>36</td>
<td>none</td>
<td>intrasellar mass, thickened stalk</td>
</tr>
<tr>
<td>15</td>
<td>36, F</td>
<td>headache, lethargy</td>
<td>3rd trimester</td>
<td>none</td>
<td>4</td>
<td>none</td>
<td>suprasellar extension</td>
</tr>
<tr>
<td>16</td>
<td>65, F</td>
<td>headache, lethargy, polyuria</td>
<td>no</td>
<td>none</td>
<td>12</td>
<td>none</td>
<td>suprasellar extension, thickened stalk</td>
</tr>
</tbody>
</table>

* CSI = cavernous sinus invasion; NA = not applicable.
† Recurrence after previous transsphenoidal surgery.

47.6 years (range 27–72 years). Three patients were treated nonsurgically and 13 were among the 2000 patients who underwent transsphenoidal surgery for pituitary mass lesions at our center during this time period. One patient who experienced postoperative recurrence underwent GKS. All operations were performed by the senior author (E.R.L.) and perioperative treatment was conducted jointly by the neurosurgeons and a dedicated team of neuroendocrinologists. In the 13 patients who were surgically treated, diagnoses were confirmed by a histological examination performed by the same neuropathologist (M.B.S.L.). Cases of secondary hypophysitis were excluded. The clinical presentation, ophthalmological and endocrine findings, MR imaging studies, and treatment outcomes were reviewed. The mean duration of follow up was 30 months (range 2–107 months).

**RESULTS**

Clinical Presentation

The common symptoms were headache (75%), lethargy (62.5%), and gonadal dysfunction (50%). Of the six pre-menopausal women, one was pregnant, one had undergone a previous hysterectomy, and the remaining four all presented with amenorrhea. The mean duration of symptoms was 15.8 months (range 1–60 months) (Table 1).

Three cases (18.8%) were associated with a recent pregnancy. Five patients had coexisting conditions indicative of underlying autoimmune diseases including idiopathic myopathy (Case 1), thyroid disease (Cases 7 and 14), orbital pseudotumor (Case 11), and temporal arteritis (Case 12). The last patient had previously undergone transsphenoidal surgery for lymphocytic hypophysitis at another center. Wegener granulomatosis was suspected in another patient (Case 10), but a biopsy sample of nasal mucosal lesions was not diagnostic. One man (Case 3) had a history of prolactinoma, which had been resected at another center 19 years earlier (Table 1).

Ophthalmological Assessment

Perimetry testing revealed normal visual fields in 13 patients (81.2%) and bitemporal hemianopia in three (18.8%). No optic atrophy was found on funduscopic examination.
in any patient; an impairment in extraocular muscle movement was detected in two patients (12.5%) (Table 1).

Endocrinological Assessment

In five patients, biochemical results for one or more anterior pituitary axes were unavailable because replacement therapy had been started by referring physicians and the results of the initial assessments were unavailable. Based on the available biochemical results, insufficiency of the adrenal axis was noted in 31.2% of patients. One patient (Case 2) had SIADH and presented with symptoms of meningitis (Table 2). In this patient CSF studies revealed aseptic meningitis; CSF studies were not performed in the other patients.

Findings on MR Images

All patients had a sellar mass that appeared contrast-enhanced on MR imaging. In three patients (18.8%) there were intrasellar lesions and in 13 (81.2%) suprasellar extension. Based on the available biochemical results, insufficiency of the adrenal axis was noted in 31.2% of patients. Cavernous sinus involvement was found in three patients (18.8%). Figure 1 illustrates the MR imaging features of inflammatory hypophysitis in one patient (Case 7), including a homogeneous contrast-enhancing triangular sellar mass, a thickened pituitary stalk, and cavernous sinus extension.
Primary hypophysitis

Fig. 1. Case 7. Coronal (left) and sagittal (right) Gd-enhanced MR images demonstrating features of inflammatory hypophysitis. Note the contrast-enhanced triangular sellar mass, the cavernous sinus extension, and the thickened and enhanced pituitary stalk.

Treatment of the Disease

The initial diagnosis was pituitary macroadenoma in six patients (37.5%) and hypophysitis in 10 (62.5%). All patients received pituitary hormone replacement as indicated. Thirteen patients (81.2%) underwent transsphenoidal surgery and three (18.8%) were treated nonsurgically. The surgical approaches included the sublabial transseptal technique in four patients (30.8%) and the transnasal submucosal technique in nine (69.2%).

Regarding the indications for surgery, all six patients initially believed to have pituitary macroadenoma underwent surgery. Of the remaining 10 patients with initial diagnoses of primary hypophysitis, five underwent surgery as the primary treatment and five initially received medical therapy (Table 3). In two of these last five patients, glucocorticoid therapy alone was unsuccessful and the patients (Cases 2 and 7) subsequently underwent surgery; the remaining three patients (Cases 13–15) displayed significant improvement and did not undergo surgery. The rate of good response, in terms of satisfactory relief of symptoms, to the initial “medical therapy” was 60%. One patient (Case 16) with recurrent hypophysitis after surgery also underwent GKS for a recurrence.

Operative Complications

There was no death in this series. One patient (Case 4) experienced CSF rhinorrhea and bacterial meningitis after hospital discharge and responded satisfactorily to antibiotic therapy. Another patient (Case 10), who had extensive granulomatous hypophysitis with cavernous sinus involvement, was later found to have a bilateral ICA occlusion on cerebral angiography 1 week after surgery. This resulted in bilateral ischemic cerebral infarction. After a prolonged period of rehabilitation, this patient regained normal intellectual function and relative independence in daily activities but was unable to return to work.

Pathological Examination

A histological diagnosis was obtained in all 13 patients who underwent surgery. Lymphocytic hypophysitis was diagnosed in 10 patients (76.9%) and granulomatous hypophysitis in three (23.1%). In the patient in whom a prolactinoma had previously been resected, a histological examination revealed lymphocytic infiltration and extensive fibrosis without evidence of recurrent adenoma or hyperplasia. Significant fibrosis was also noted in five other patients (Cases 5, 8, 9, and 12). One case of lymphocytic hypophysitis was associated with a Rathke cleft cyst (Case 11). The characteristic pathological features of lymphocytic and granulomatous hypophysitis are illustrated in Figs. 2 and 3, respectively.

Patient Outcomes

The 12 patients who presented with headache underwent surgery and all obtained relief immediately after the operation (100%). Normal visual fields were restored in all three patients (100%) with preoperative bitemporal hemianopia (Cases 6, 11, and 12). One of the two patients with diplopia preoperatively improved after surgery (Case 1). None of the patients experienced any visual deterioration postoperatively. One patient (Case 12) died of an unrelated cause 1 year after surgery.

No patient experienced a significant improvement in pituitary function on postoperative assessment. The three patients who had been treated nonsurgically (Cases 13–15) were asymptomatic while receiving medical treatment (Table 4). Among the 13 patients who underwent surgery, three reported a significant improvement in energy level; two of these patients were receiving GH (Cases 6 and 7) and one testosterone replacement (Case 8). Three men (Cases 1, 3, and 8) experienced improved libido and erectile function after surgery; all were receiving testosterone replacement. Long-term hormone replacement was required in all patients. Cortisol insufficiency developed in one patient (Case 9) and diabetes insipidus in another patient (Case 7) after surgery.

Recurrences of the Disorder

Two (15.4%) of 13 surgical patients with a clinical improvement postoperatively later experienced recurrent intractable headache. One (Case 2) had shown poor compliance with her steroid medication and MR imaging demonstrated a residual sellar lesion without suprasellar extension. No repeated surgery was required and this patient’s
symptoms improved with regular steroid replacement. Another patient (Case 16) experienced symptomatic recurrence 6 months after surgery. This patient initially presented with headache and MR imaging revealed a suprasellar mass lesion (Fig. 4a). Her symptoms improved after transsphenoidal surgery. Six months after surgery MR imaging revealed a residual sellar mass (Fig. 4b). Symptoms recurred in this patient and she responded well to a pharmacological dose of steroid medication (prednisone, 15 mg/day; Fig. 4c). She experienced significant steroid-induced side effects and dose reduction resulted in exacerbation of her symptoms. The patient declined further surgery and was treated with GKS (12 Gy, two isocenters). Clinical improvement occurred within a few weeks and this patient remained asymptomatic while receiving a lower dose of prednisone (5 mg/day). Follow-up MR images demonstrated the gradual shrinkage of the sellar lesion (Fig. 4d and e).

Another patient had previously undergone transsphenoidal surgery for lymphocytic hypophysitis at another center 4 months before he presented at our institution (Case 12). Visual loss developed and a recurrent sellar mass was identified 4 months after the initial surgery. The patient underwent a second operation at our center and has remained asymptomatic postoperatively.

**Discussion**

**Clinicopathological Features**

Primary hypophysitis has classically been described as affecting female patients during the early postpartum period. With improved awareness, a more diverse group of patients has been identified, including men, prepubertal girls, and nulliparous and postmenopausal women. The pathogenesis of primary hypophysitis has been attributed to autoimmunity and autoantibodies against pituitary-specific proteins have been described. Primary hypophysitis has also been associated with other autoimmune conditions such as thyroiditis, systemic lupus erythematosis, and, more rarely, primary biliary cirrhosis and polyglandular autoimmune syndrome. It is therefore interesting to observe in the present series that, although half of the patients were men, half of them also had coexistent conditions indicative of an autoimmune disorder. Recent pregnancy or a coexistent autoimmune disorder were also noted in half of the women. It appears that primary hypophysitis occurring outside the context of autoimmunity and recent pregnancy is relatively uncommon.

Of interest were two patients with other pathological conditions in the region. A coexistent Rathke cleft cyst was found in one patient (Case 11). Primary hypophysitis associated with Rathke cleft cyst has been described and has been thought to result from a granulomatous reaction to extravasated mucinous content following cyst rupture.

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Initial Diagnosis</th>
<th>Treatment</th>
<th>Pathological Diagnosis</th>
<th>Op Complication(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LyHy initial surgery</td>
<td>LyHy</td>
<td>LyHy</td>
<td>none</td>
</tr>
<tr>
<td>2</td>
<td>LyHy surgery after failed medical therapy (dexamethasone 8 mg/day)</td>
<td>LyHy</td>
<td>LyHy</td>
<td>none</td>
</tr>
<tr>
<td>3</td>
<td>PA initial surgery</td>
<td>LyHy</td>
<td>LyHy</td>
<td>none</td>
</tr>
<tr>
<td>4</td>
<td>PA initial surgery</td>
<td>LyHy</td>
<td>CSF rhinorhea, meningitis</td>
<td>LyHy</td>
</tr>
<tr>
<td>5</td>
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<td>LyHy</td>
<td>LyHy</td>
<td>none</td>
</tr>
<tr>
<td>6</td>
<td>LyHy initial surgery</td>
<td>LyHy</td>
<td>LyHy</td>
<td>none</td>
</tr>
<tr>
<td>7</td>
<td>LyHy surgery after failed medical therapy (prednisone 5 mg/day)</td>
<td>LyHy</td>
<td>LyHy</td>
<td>none</td>
</tr>
<tr>
<td>8</td>
<td>PA initial surgery</td>
<td>LyHy</td>
<td>LyHy</td>
<td>none</td>
</tr>
<tr>
<td>9</td>
<td>PA initial surgery</td>
<td>GrHy</td>
<td>ICA occlusion</td>
<td></td>
</tr>
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<td>10</td>
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<td>GrHy</td>
<td>GrHy</td>
<td>none</td>
</tr>
<tr>
<td>11</td>
<td>LyHy initial surgery</td>
<td>LyHy</td>
<td>LyHy</td>
<td>none</td>
</tr>
<tr>
<td>12</td>
<td>LyHy initial surgery</td>
<td>LyHy</td>
<td>LyHy</td>
<td>none</td>
</tr>
<tr>
<td>13</td>
<td>LyHy steroid therapy (dexamethasone 1 mg/day, methotrexate 12.5 mg/wk)</td>
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<td>NA</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>LyHy steroid therapy (hydrocortisone 40 mg AM, 20 mg PM)</td>
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<td>NA</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>LyHy steroid therapy (prednisone 5 mg AM, 2.5 mg PM)</td>
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<td>NA</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>LyHy initial surgery; GKS</td>
<td>GrHy</td>
<td>GrHy</td>
<td>none</td>
</tr>
</tbody>
</table>

* GrHy = granulomatous hypophysitis; LyHy = lymphocytic hypophysitis; PA = pituitary adenoma.

**Fig. 2.** Photomicrographs showing lymphocytic hypophysitis. The pituitary gland is diffusely infiltrated by lymphocytes and plasma cells (left), resulting in the destruction of the adenohypophysial parenchyma and clusters of residual pituitary acini (right). H & E, original magnifications × 100 (left) and × 200 (right).
our patient, however, the surgical specimen predominantly displayed a lymphocytic infiltrate and she also suffered from idiopathic orbital pseudotumor, all of which indicated that the Rathke cleft cyst may not have been causally related. Another patient had a history of prolactinoma, which had previously been resected; this man (Case 3) presented to us with a recurrent sellar mass. Surgical exploration revealed hypophysitis without any evidence of tumor recurrence. Primary hypophysitis mimicking pituitary adenomas has been widely reported.\textsuperscript{34,50} Although we were unable to verify our patient’s previous pathological diagnosis, this case further illustrates the diagnostic difficulties associated with primary hypophysitis. Inflammatory hypophysitis coexisting with pituitary adenoma is exceedingly rare.\textsuperscript{35,38} To our knowledge there has been no report of hypophysitis developing after previous pituitary tumor surgery. Whether the patient’s previous disease and operation were related to the development of hypophysitis is uncertain. The duration of his only symptom (headache) was short (1 month), which argued against long-standing disease, although the presence of extensive fibrosis revealed by this histological examination was indicative of end-stage inflammatory hypophysitis.\textsuperscript{11,40} Incidentally, fibrosis was also noted in three other patients in whom the duration of symptoms ranged from 12 to 60 months.

The clinical features of our patients resembled those described in other reported series, with headache being the most common symptom.\textsuperscript{11,15,19,24,26} Pituitary function is commonly affected in patients with inflammatory hypophysitis, with deficiencies in ACTH and TSH being the most fre-

### Table 4

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Clinical Symptom(s)</th>
<th>Endocrine Function</th>
<th>Hormone Replacement</th>
<th>Recurrence</th>
<th>Follow Up (mos)</th>
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<tbody>
<tr>
<td>1</td>
<td>no headache/diplopia, improved libido</td>
<td>no change</td>
<td>cort, T, testo</td>
<td>none</td>
<td>36</td>
</tr>
<tr>
<td>2</td>
<td>no headache</td>
<td>no change</td>
<td>cort, T, eso</td>
<td>9 mos postop</td>
<td>31</td>
</tr>
<tr>
<td>3</td>
<td>no headache, improved libido</td>
<td>no change</td>
<td>cort, testo, GH</td>
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</tr>
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<td>no change</td>
<td>cort, T</td>
<td>none</td>
<td>48</td>
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<tr>
<td>5</td>
<td>no headache</td>
<td>no change</td>
<td>cort</td>
<td>none</td>
<td>43</td>
</tr>
<tr>
<td>6</td>
<td>no headache/hemianopia, improved energy</td>
<td>no change</td>
<td>cort, T, GH, eso</td>
<td>none</td>
<td>14</td>
</tr>
<tr>
<td>7</td>
<td>no headache, improved energy</td>
<td>postop DI</td>
<td>cort, T, GH, DDAVP, eso</td>
<td>none</td>
<td>12</td>
</tr>
<tr>
<td>8</td>
<td>no headache, improved libido/energy</td>
<td>no change</td>
<td>cort, T, testo</td>
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<td>4</td>
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<td>9</td>
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<td>hypocortisolism</td>
<td>cort, T, testo</td>
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<td>107</td>
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<tr>
<td>10</td>
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<td>no change</td>
<td>DDAVP</td>
<td>none</td>
<td>2</td>
</tr>
<tr>
<td>11</td>
<td>no hemianopia</td>
<td>no change</td>
<td>cort, T, DDAVP</td>
<td>none</td>
<td>11</td>
</tr>
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<td>12</td>
<td>no hemianopia†</td>
<td>no change</td>
<td>cort, T, GH, testo, DDAVP</td>
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<td>6</td>
</tr>
<tr>
<td>13</td>
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<td>maintained on methotrexate 15 mg/wk, DDAVP</td>
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<tr>
<td>14</td>
<td>improved energy</td>
<td>no change</td>
<td>maintained on hydrocortisone 40 mg/day, T, testo</td>
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<td>51</td>
</tr>
<tr>
<td>15</td>
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<td>no change</td>
<td>maintained on prednisone 7.5 mg/day, T</td>
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<td>29</td>
</tr>
<tr>
<td>16</td>
<td>no headache</td>
<td>no change</td>
<td>cort, eso, DDAVP</td>
<td>6 mos postop</td>
<td>51</td>
</tr>
</tbody>
</table>

* Cort = corticosteroid; DDAVP = 1-deamino-8-arginine vasopressin; eso = estrogen.
† Died 1 year postoperatively of an unrelated cause.
The majority of our patients experienced lethargy and loss of libido, as well as amenorrhea in women and erectile dysfunction in men. Posterior pituitary dysfunction presenting as diabetes insipidus occurred in 31% of our patients and may result from direct inflammatory destruction and/or compression of the posterior pituitary or pituitary stalk. Neurohypophysial deficiency unassociated with adenohypophysial dysfunction, or infundibuloneurohypophysitis, is distinctly rare and was observed in one of our patients (Case 10). The condition has been described to have a self-limiting course and a good response to conservative treatment. Our patient suffered from severe headache and underwent surgery, which resulted in pain relief without improvement in his diabetes insipidus. The development of SIADH in another patient (Case 2) may be related to a coexistent aseptic meningitis. Cerebrospinal fluid leukocytosis is not uncommon in inflammatory hypophysitis, although it is uncertain whether this represents an autoimmune reaction or simply a dissemination of inflammatory cells.

Imaging studies play a crucial role in the diagnosis of inflammatory hypophysitis. Characteristic MR imaging features include a markedly contrast-enhancing sellar mass as well as thickening of the parasellar dura mater and pituitary stalk. Delayed contrast enhancement has been observed on dynamic but not conventional MR imaging stud-
Primary hypophysitis

ies in cases of hypophysitis.26 Other MR imaging findings include triangular enlargement of the sellar mass, an enlarged pituitary fossa, and thickened sphenoidal mucosa.15,24 Extraocular palsy secondary to cavernous sinus involvement has been reported in patients with inflammatory hypophysitis and was observed in two of our patients.42,52 Diplopia improved in one of our patients (Case 1) after surgery. Another patient (Case 9) experienced bilateral ICA occlusion postoperatively. We believe that this was unlikely to have been related to the surgery but was instead the result of inflammatory arteritis. Whether an alternative treatment approach might have improved the outcome is uncertain. Nonetheless, this case illustrates the potential for patients with this disease to develop serious complications.

Clinical Management

The natural history of inflammatory hypophysitis is incompletely understood and its treatment is controversial.14,40,55 Spontaneous resolution of the lesion on MR images following steroid therapy has been described, but only rarely do endocrine deficits improve.27,31 Inadequate treatment has been associated with chronic hypophysitis with granuloma formation and sudden death.24,30 Satisfactory responses to high-dose steroid therapy23,41,59 and administration of methotrexate57 have been reported. In one prospective trial of high-dose methylprednisolone pulse therapy, adenohypophysial function improved in four of nine patients and diabetes insipidus ceased or improved in all four patients with that problem. The MR imaging findings improved in seven patients; however, this has not been a consistent experience.52 Poor responses or recurrences following steroid withdrawal have been described and the significant side effects of long-term steroid therapy are also a major concern.9,33,40,45,51

When lymphocytic hypophysitis is the presumptive diagnosis (in pregnant and postpartum patients and in those with evidence of an autoimmune process), we advocate an initial trial of therapeutic corticosteroid administration, except in the face of progressive severe visual loss. Medical therapy should produce a relatively rapid reversal of symptoms related to any mass effect and a decrease in the size and extension of the lesion on follow-up MR images. Not infrequently, the need for corticosteroid therapy beyond replacement levels persists, and clinical relapse occurs when an attempt is made to reduce corticosteroid drugs to replacement levels. The preponderance of surgically treated cases in this series is related to a mistaken preoperative diagnosis in six patients, failure of medical therapy in two, and severe, intolerable symptoms in the remaining five patients. An algorithm for the treatment of patients with presumed hypophysitis is presented in Fig. 5.

In our series, five patients initially received medical therapy. Two patients (40%) who had suprasellar lesions and headache (Cases 2 and 7) did not improve and required surgery. Three patients (60%) obtained clinical improvement without surgical intervention, although one did require long-term treatment with methotrexate. Two nonsurgically treated patients (Cases 13 and 14) had intrasellar lesions and did not present with headache. One nonsurgically treated patient (Case 15) had a suprasellar lesion and headache. She was in her third trimester of pregnancy and was treated with glucocorticoid replacement. Successful treatment with ste-

roid medications in pregnant women has been reported and should be considered an important therapeutic option.30,55 Transsphenoidal surgery is a safe and effective treatment for inflammatory hypophysitis.21,24,29,34,40 Surgery provides a histological diagnosis, although its role in the definitive treatment of hypophysitis remains controversial. Some authorities consider it feasible to diagnose the condition on the basis of clinical, biochemical, and neuroimaging findings, and recommend withholding biopsy if the patient is stable and there is no threat to vision.41,49 Specific examples include postpartum women with characteristic imaging findings who also have panhypopituitarism46 and patients with lymphocytic infundibuloneurohypophysitis, which classically presents with diabetes insipidus alone.26 It can be difficult, however, to distinguish with a high degree of certainty between hypophysitis and other sellar neoplasms.13,22,29 Hypophysitis may coexist with pituitary adenomas and cases of germinoma presenting as primary hypophysitis have been reported.56 A definitive histological diagnosis may obviate the unnecessary use of high-dose steroid therapy and facilitate the treatment of other conditions such as infection or neoplasm. In our experience, 40% of cases were misdiagnosed as pituitary adenomas preoperatively, emphasizing the importance of a surgical biopsy. A histological distinction among different types of hypophysitis may carry prognostic implications, although this is still unclear. The advantages of obtaining a definitive histological diagnosis and its impact on long-term medical treatment, and the patient’s sense of well-being are considerable.

Our results also illustrate the effect of surgery in achieving rapid decompression of a mass lesion. All patients obtained resolution of their headache and visual field deficits immediately after surgery.

Our surgical strategy is one of wide decompression of the
surgical trauma and some authorities have recommended medical diagnosis and excellent relief for headache and visual symptoms without significant pressure symptoms or a threat to the optic chiasm seen on MR imaging. This patient was treated surgically and he obtained a good recovery of vision. Therefore, surgery does appear to have a role in the treatment of recurrent hypophysitis, especially when vision is threatened. In addition, surgical biopsy would appear mandatory for cases of recurrent disease in which there was no previous histological diagnosis. Our experience also indicates that radiosurgery can achieve satisfactory clinical and radiological improvement and should be considered a potential treatment modality in refractory cases.

Conclusions

Our experience in treating 16 patients with primary hypophysitis has demonstrated a variety of clinical features of this rare but intriguing condition. Most cases were associated with either recent pregnancy or autoimmune conditions and the condition was by no means uncommon in men. Its unusual associations with other pathological and variable clinical features of the sella turcica may produce significant diagnostic difficulties that illustrate the importance of detailed clinical and radiological documentation. Steroid therapy was effective in selected cases, namely those involving intrasellar lesions without significant pressure symptoms or a threat to vision. Transsphenoidal surgery is a safe and effective treatment method. It has the advantages of providing a histological diagnosis and excellent relief for headache and visual symptoms. Severe adenohypophysial dysfunction is common on presentation and rarely improves with treatment. Hormone replacement is required in most cases and long-term follow up is important. Recurrent hypophysitis may occur and treatment options include medical, surgical, and radiosurgical therapy.

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References

Primary hypophysitis


