Clinical Features, Magnetic Resonance Imaging, and Treatment Experience of 20 Patients with Lymphocytic Hypophysitis in a Single Center

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■ OBJECTIVE: **Lymphocytic hypophysitis (LYH) is a rare autoimmune inflammatory disease of the pituitary gland. In this study, we aim to characterize LYH at presentation and focus on the management and prognosis of LYH.**

■ METHODS: **A retrospective study of patients with LYH was conducted between 2011 and 2018 at a single institute. The patients were included by pathologic conformation and strict exclusion criteria. Clinical profile, imaging, and management data were collected.**

■ RESULTS: **Twenty patients with LYH (16 women and 4 men) were included. Ten patients were diagnosed histologically and the remaining 10 patients were confirmed clinically of exclusion criteria. The median age at diagnosis was 37 years (range, 16–58 years). Presenting symptoms were followed by polyuria/polydipsia (11, 55%), vision changes (10, 50%), headache (8, 40%), menstrual irregularities and amenorrhea (4, 20%), diplopia (1, 5%), or sexual dysfunction (1, 5%). Eight patients had partial anterior pituitary hormone dysfunction. The thyroid-stimulating hormone axis was most involved. Ten patients received transsphenoidal surgery, 5 patients experienced steroid pulse therapy, and observation was performed on 5 patients. Only 5 patients (25%) showed improvement of anterior pituitary dysfunction after initial management. Recovery of diabetes insipidus occurred in 2 patients (18%). The overall recurrence rate was 22.2%.**

■ CONCLUSIONS: **Nonoperative treatment is a better option for most patients with LYH because it is effective and noninvasive. Surgery is recommended for definitive diagnosis, severe or rapid progression of neurologic impairment, and glucocorticoid insensitivity. Periodic follow-up is mandatory in a patient's long-term management.**

INTRODUCTION

Lymphocytic hypophysitis (LYH) is an infrequent primary disorder, associated with an inflammatory process. Histologically, LYH is characterized by diffuse infiltration of the pituitary gland with lymphocytes, plasma cells, and fibrosis change.[1] Anatomically, LYH can be further classified into adenohypophysitis or infundibuloneurohypophysitis according to the involvement of inflammation. The presenting symptoms correspond to the location of the lesion (e.g., neurohypophysitis usually appears as polydipsia and polyuria secondary to the lack of antidiuretic hormone).

LYH appears predominantly in young women, especially in the later pregnancy and early postpartum periods, which is considered to be related to the autoimmunity of LYH.[1] According to recent data, the estimated incidence of LYH is 1 case in 9 million persons/year, although the incidence may be underestimated.[2,3]

Because of the autoimmune aspect of LYH, there are several articles describing antigens and antibodies in the disease. Rupp and Paschkis[4] first described panhypopituitarism caused by

Key words
- Diabetes insipidus
- Lymphocytic hypophysitis
- Stalk thickening
- Steroid pulse therapy

Abbreviations and Acronyms
ACTH: Adrenocorticotropic hormone
APA: Antipituitary antibody
DI: Diabetes insipidus
FSH: Follicle-stimulating hormone
GH: Growth hormone
IGF: Insulinlike growth factor
LH: Luteinizing hormone
LYH: Lymphocytic hypophysitis
MRI: Magnetic resonance imaging
PA: Pituitary adenoma
TSH: Thyroid-stimulating hormone
TSS: Transsphenoidal surgery

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lymphoplasmacytic pituitary infiltration in 1953. Several years later, an autoimmune pathogenesis for LYH was introduced for the first time by Gaudie and Pinkerton.[5] With the increased understanding of autoimmune diseases and evolution of laboratory assays, some autoantigens involved in LYH have been identified, and antipituitary antibodies (APAs) have also been detected in patients with LYH. However, conflicting results in detecting APAs by different methods have impaired the clinical relevance of those antibodies. In addition, those antibodies can disappear over time, as shown by longitudinal research.[4] Caturegli et al.[1] reported that an immunoblotting method is more sensitive (64% vs. 57%) and specific (86% vs. 76%) than an immunofluorescence method. These issues limit the clinical application of APAs, and therefore, pathogenetic autoantigens should be further studied.

With the increased understanding of LYH, the treatment is mainly focused on alleviating the inflammation process, symptomatic control, and replacement of hormone deficiency. Steroid pulse therapy is usually useful to ameliorate the inflammation process and also relieves the compression of surrounding structures and symptomatic presentations.[6,7] For glucocorticoid-resistant cases, immunosuppressive agents, such as methotrexate, azathioprine, and experimental rituximab and infliximab, have also been applied.[8,9] Transsphenoidal surgery (TSS) still plays an important role in patients with severe or rapid progression of neurologic dysfunction and glucocorticoid insensitivity. Overall, the prognosis of LYH is comparatively good. However, the natural course, pathogenesis, and treatment options still need to be further researched. The aim of this report is to summarize the clinical presentation, endocrine status, magnetic resonance imaging (MRI), and management and prognosis of LYH.

METHODS

A retrospective study of patients with LYH was conducted from 2011 to 2018. The diagnosis of LYH was based on histopathologic conformation from a surgical specimen, or on the clinical presentation associated with characteristic features of MRI. The follow-up period lasted $\geq$6 months.

Exclusion criteria were as follows:

1) All secondary LYH were excluded. Patients who had also had systemic inflammatory conditions such as Langerhans cell histiocytosis, Wegener granulomatosis, sarcoidosis, drug-induced hypophysitis, and other infectious lesions were excluded.
2). Patients with granulomatous or xanthomatous or other mixed forms of primary hypophysitis in histology were excluded.

The differential diagnoses of pituitary adenoma (PA) in the sellar region, craniopharyngioma, or intracranial germinoma were excluded by laboratory assays (e.g., hormones or tumor markers in serum and cerebrospinal fluid) and clinical features.

Clinical performance, imaging, treatment, and outcome data were collected. All vision changes were detected by ophthalmologic examinations. The pretreatment and posttreatment endocrine examinations were collected.

Relevant endocrine tests included thyroid-stimulating hormone (TSH) and thyroid hormone levels (thyroid axis), growth hormone (GH) and insulinlike growth factor (IGF: GH axis), luteinizing hormone (LH), follicle-stimulating hormone (FSH), and testosterone (gonadotropin axis), and a random cortisol or adrenocorticotropic hormone (ACTH) stimulation test (adrenal axis). Diabetes insipidus (DI) was diagnosed when serum osmolality was >295 mOsm/kg, whereas a corresponding urine osmolality was <300 mOsm/kg in fluid deprivation tests in the case of polyuria and polydipsia and a subsequent response to arginine vasopressin was observed. In the case of prolactin, the level of deficiency or excess was defined on the basis of the assay-specific reference range. For imaging, an experienced radiologist reviewed all the images in this study in a predefined format based on the published standard, including symmetric enlargement, uniform contrast enhancement, thickened pituitary stalk and loss of the hypophysis bright spot on T1 imaging, a cystic appearance with ring enhancement, and central necrosis.[10-12] Furthermore, Gutenberg et al. reported a diagnostic scoring system to distinguish LH from PA based on imaging performance. Scoring rules are as follows (negative values favor LYH, positive favor PA): age $\leq$30 years (score = −1); related to pregnancy (−4); the volume of the pituitary 6 cm^3 (+2); high or medium gadolinium enhancement (−1); heterogeneous enhancement on MRI (+1); asymmetric sellar mass (+3); disappearance of the posterior pituitary bright spot (−2); thickened pituitary stalk (−5); and sphenoid mucosal thickening (+2). All patients were calculated respectively.

The follow-up period lasted for $\geq$6 months. The outcome was judged by endocrine assessment, imaging results, and follow-up data. Posttreatment endocrinologic changes were defined as follows: improved implied partial or complete recovery of hyperpituitarism, and a reduced dosage or discontinuation of hormone replacement. Stable indicated that the pretreatment condition remained unchanged. Worse signified worsened endocrine function compared with pretreatment, or a newly emerging pituitary deficiency. Recurrence was defined when the pituitary mass enlarged again in the follow-up period.

Because of the small sample size, nonparametric statistics were chosen. Qualitative data were represented in the form of frequency and percentage as well as median and mean values (with standard deviation). The association between qualitative variables was assessed by the Fisher exact test for all 2 × 2 tables where the χ^2 test was not valid because of small sample size. A P value <0.05 was considered to be statistically significant. The results were graphically represented where deemed necessary. SPSS version 20 (IBM Corp., Armonk, New York, USA) was used for analysis.

RESULTS

Patient Demographics

Twenty patients with LYH (16 women and 4 men) were analyzed from 2011 to 2018 at our institute. Ten patients were diagnosed by histopathology through TSS and the remaining 10 patients were diagnosed by clinical presentation and characteristic imaging. The median duration from onset of symptom to diagnosis of LYH was 5 months (range, 1–60 months). The median age at diagnosis was 37 years (range, 16–58 years). Female patients were mainly in their 20s or 30s. Of 16 female patients, 3 were in an early postpartum

Table 1. Clinical Profile with Lymphocytic Hypophysitis at Presentation in 20 Patients

Case Number	Gender/ Age (years)	Associated with Pregnancy?	Symptomatic Presentation	Pretreatment Anterior Pituitarism	Radiologic Score of Gutenberg	Duration of Symptoms (Months)	Management Type	Follow-Up (Months)
1	F/30	Y	Visual changes	TSH	−4	3	TSS	11
2	F/28	Y	Visual changes	TSH	−4	4	TSS	37
3	M/26	NA	Headache, visual changes, decreased libido	Hyperprolactinemia	−1	1	TSS	87
4	F/58	N	Visual changes, polyuria, and polydipsia	TSH + hyperprolactinemia	−5	36	TSS	15
5	F/30	N	Headache, visual changes	Hyperprolactinemia	−4	3	TSS	72
6	F/18	N	Headache, amenorrhea	Hyperprolactinemia	−2	6	TSS	49
7	F/53	N	Visual changes	N	−1	36	TSS	59
8	F/34	N	Headache, amenorrhea, and galactorrhea, visual changes	Hyperprolactinemia	−1	6	TSS	53
9	F/43	N	Headache, visual changes	N	−5	1	TSS	29
10	F/30	N	Headache, visual changes,	N	−6	2	TSS	—
11	M/56	NA	Polyuria and polydipsia	N	−8	6	SPT	15
12	F/30	Y	Headache, visual changes, polyuria, and polydipsia	ACTH + TSH + hyperprolactinemia	−13	4	SPT	19
13	F/42	N	Polyuria and polydipsia, fever, amenorrhea, and galactorrhea	ACTH + TSH + FSH/ LH + hyperprolactinemia	−8	9	SPT	10
14	F/47	N	Polyuria and polydipsia, headache	Growth hormone/ insulinlike growth factor	−8	2	SPT	15
15	F/16	N	Polyuria and polydipsia, diplopia	Hyperprolactinemia	−9	3	SPT	54
16	F/52	N	Polyuria and polydipsia, fatigue	ACTH + FSH/LH + hyperprolactinemia	−7	12	SPT	17
17	M/40	N	Polyuria and polydipsia	N	−8	6	WO	11
18	F/25	Y	Polyuria and polydipsia	N	−3	12	WO	—
19	F/40	N	Amenorrhea, polyuria, and polydipsia	ACTH	−5	60	WO	87
20	M/43	NA	Polyuria and polydipsia, headache	N	−1	4	WO	44

—, patient lost to follow-up.
F, female; Y, yes; TSH, thyroid-stimulating hormone; TSS, transsphenoidal surgery; M, male; NA, not applied; N, no; SPT, steroid pulse therapy; ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone; WO, watchful observation.

period and 1 was in late pregnancy. The median follow-up was 49 months (range, 11–87 months).

Clinical Presentation and Laboratory Examination

The common symptoms of LYH at presentation are shown in Table 1. Eight patients presented with a headache. Decreased vision was observed in 10 patients, 3 of whom had bitemporal hemianopsia. One patient had only diplopia. Two patients had a mass effect–like headache and vision changes without any hormone dysfunction. They acquired postoperative thyrotrophin and cortisol deficiency after TSS and recovered early in the follow-up.

For the endocrine data, 9 patients had mild hyperprolactinemia. The level of prolactin had not exceeded 3 times the upper limit. In one of the patients, this effect was attributed to pregnancy. Four patients had only hyperprolactinemia in an endocrine aspect and they all recovered after TSS. Of 16 female patients (excluding 4 postmenopausal patients and 1 early postpartum patient), amenorrhea was seen in 4. Of the 4 patients with amenorrhea, only 1 patient had galactorrhea. Patients who needed hormone replacement were considered to be pituitary hormone deficient. Before treatment, anterior pituitary deficiency, DI, and prolactin were evaluated (Tables 1 and 2). Partial anterior pituitary hormone deficiency was seen in 8 patients, with thyrotrophin 5/20 (25%),

Table 2. Comparison of the Three Groups in Terms of Endocrine and Radiologic Data

Clinical Data	Group 1*	Group 2	Group 3	Total
Total numbers	10	6	4	20
Clinical presentation				
Headache	5	2	1	8
Visual changes	9	1	0	10
Anterior pituitary dysfunction	3	4	1	8
Thyroidal axis	3	2	0	5
Adrenal axis	0	3	1	4
Gonadal axis	1	1	0	2
Growth hormone/insulinlike growth factor axis	0	1	0	1
Hyperprolactinemia	5	4	0	9
Diabetes insipidus	1	6	4	11
Radiology (magnetic resonance imaging)				
Symmetric enlargement	8	2	1	11
Homogeneous contrast enhancement	5	2	2	9
Thickened pituitary stalk	1	6	2	9
Loss of posterior pituitary hyperintensity	1	6	2	9
Suprasellar extension	9	1	0	10
Cystic appearance	3	2	1	6
Endocrine assessment				
Improved	2	3	0	5
Stable	6	3	2	11
Worse	1	0	1	2
Regression on magnetic resonance imaging	10	5	1	16
Recurrence	2	2	1	5

*Group 1, treated by transsphenoidal surgery; group 2, treated by steroid pulse therapy; group 3, treated by watchful observation.

corticotrophin 4/20 (20%), gonadotrophin 3/20 (15%), and GH/IGF 1/20 (5%). Eleven patients presented with DI, 3 of whom had isolated DI at presentation. Four patients experienced DI along with partial anterior pituitary deficiency. There was a significantly different proportion of DI between the surgical group (1 patient) and nonsurgical group (10 patients), which was consistent with imaging results such as a thickened pituitary stalk and loss of posterior pituitary hyperintensity. There were also some other nonspecific symptoms such as fatigue, dizziness, and nausea. Case 13 presented with a low fever that continued for 9 months.

In the nonsurgical group, tumor marker tests from serum were all normal. No positive results were observed for autoantibodies (antineutrophil cytoplasmic antibodies, or autoantibodies associated with Sjögren syndrome [SSA-Ab, SSB-Ab], antinuclear antibodies, or antithyroid antibodies [TPOAb, TRAb, and TGAb]). The surgical group did not perform an autoantibodies examination when they denied the history of systemic diseases.

Neurologic Findings

All patients had pretreatment imaging available with a broad variety of MRI results. Table 2 summarizes the pretreatment MRI features. The space-occupying lesions were intrasellar in 10 patients and showed suprasellar extension in 10 patients, 3 of whom had parasellar extensions. Nine patients had a thickened pituitary stalk. Eleven patients seemed to have diffuse pituitary expansion. In addition, 9 patients showed homogenous enhancement. Moreover, 9 patients had loss of the neurohypophysis bright spot on T1 imaging and abnormal enhancement of the infundibulum. The radiologic score of Gutenberg is shown in Table 1. According to the scoring system of Gutenberg et al.,[10] the median score was −5 (range, −1 to −13). Central hypointensity on T1-weighted images after contrast was seen in 6 patients, suggesting central necrosis or cyst formation. The classic central hypointensity is shown in Figure 1. Because of the absence of T2-weighted coronal images of our MRI, we did not assess the parasellar T2 dark sign.

Treatment of Disease

Hormone replacement was administered as initial management if necessary. Ten patients had undergone TSS. The volume of pituitary mass in the surgery group (group 1) was significantly larger than in the nonoperative group (group 2 + group 3; $P < 0.05$). The operations were all performed by senior neurosurgeons. The indications of surgery were the different degree of vision changes and persistent severe headache. Moreover, the group of operative patients had fewer preoperative endocrine dysfunction than did the nonoperative patients, because only 3 patients had mild TSH axis deficiency. At surgery, 8 of these patients were observed to have a sallow and grayish mass, with tough texture and little blood supply, and with significant adhesion to surrounding tissue, which was notably different from classic PA. Two patients with a cystic lesion had viscous ivory-white fluid and a sallow and grayish cystic wall. No cystic fluid was retained for the other examination.

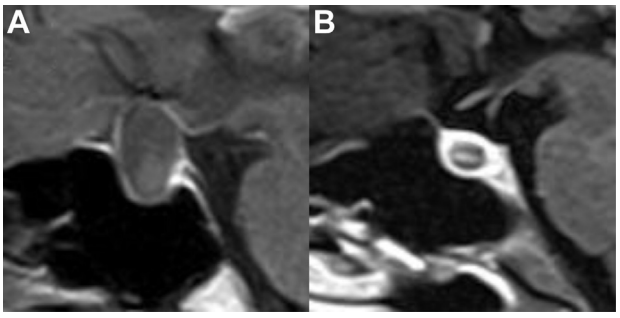

Figure 1. Contrast-T1 images (**A**, **B**) showing a central hypointensity of sellar mass, with an enhanced rim. They were both diagnosed using surgical specimens.

No complications such as cerebrospinal rhinorrhea, infection, or hemorrhage occurred.

Steroid pulse treatment was administered to 5 patients without severe complications. Only the first glucocorticoid pulse treatment was included in the analysis from 1 patient who received the therapy once more. Three patients received intravenous injection of methylprednisolone and the initial dose ranged from 500 mg to 1000 mg and continued for 3–5 days. The 5 patients who accepted steroid pulse treatment received a dose ranging from 48 mg to 60 mg daily (median, 60 mg). The duration of steroid pulse therapy varied greatly and ranged from 6 weeks to 14 weeks. The withdrawal was tapered and the reduction regime was similar. One patient took 5 mg daily permanently. All 5 patients had mild weight gain without Cushing syndrome, and 1 had slight osteoporosis and hyperglycemia. Those side effects resolved when the dose of glucocorticoid was reduced or withdrawn.

Five patients chose watchful observation because of mild established hypopituitarism and possible complications of corticosteroid. Hormone replacement at a physiologic dose was performed as necessary.

Outcomes and Follow-Up

The outcomes were observed after initial treatment for a median follow-up of 49 months. Two patients failed to follow up. For the surgical cohort, the nonendocrine symptoms, such as headache and vision changes, improved markedly. Postoperative new-onset anterior pituitary dysfunction was seen in 6 patients, including case 3 and case 6 of the TSH axis, case 7 of the ACTH axis, case 8 of the FSH/LH axis, case 9 of the TSH/ACTH axis, and case 2 of the GH/IGF axis. The newly emerging anterior pituitary dysfunction had recovered in the follow-up period (range, 3 months–2 years). Three patients with temporary DI improved within 6 months. Two patients experienced recurrence in the follow-up period (case 7, 1 year; case 10, 5 years), because the pituitary was enlarged compared with baseline MRI. Steroid pulse treatment was then conducted for these patients, with a positive response.

In the medical therapy group, MRI regressions were observed in 4 patients (80%). As shown in Figure 2, glucocorticoid treatment was useful in alleviating the occupying effect significantly even if the volume of pituitary was sufficiently large to compress adjacent tissue. Patient 11 showed little reaction to medical therapy because the only symptom of DI stayed the same. Therefore, we could only perform hormone replacement to control polyuria and polydipsia. Patient 14 experienced recurrence because of the discontinuation of steroid on her own, and this female patient retook steroid pulse treatment, which remained effective. Patient 15 developed new LH/FSH axis and GH/IGF axis deficiencies 1 year after initial treatment, but the pituitary mass stayed unchanged. Menstruation went back to normal after the patient received hormone replacement. Recovery of the ACTH axis deficiency was seen in 2 patients.

For the patients of the watchful observation group (group 3), patient 20 had persistent headache and progressed as the pituitary mass enlarged 1 year later. This patient chose radiotherapy in the local hospital. The mass shrunk but panhypopituitarism developed, and his headache stayed the same. He finally received hormone replacement. Patient 18 failed to complete long-term follow-up. The remaining 3 patients had a regression of a thick pituitary stalk. However, DI had not improved.

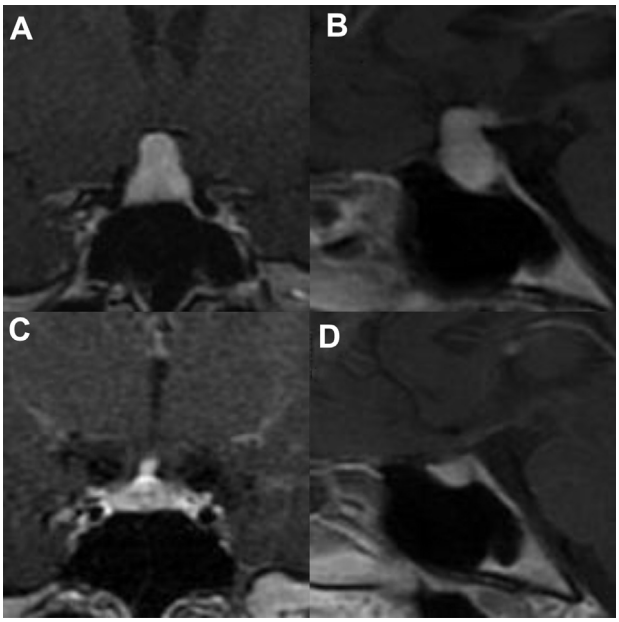

Figure 2. (**A**-**D**) Example of case 12 in Table 1. This female patient presented with a headache, vision changes, and diabetes insipidus in the 2 months post partum. Magnetic resonance imaging showing the marked changes after initial steroid pulse therapy. At baseline, the coronal (**A**) and sagittal (**B**) T1-weighted magnetic resonance imaging showed homogenously enhanced pituitary mass, thickened pituitary stalk, and compressed optic chiasm. The contrast-enhanced coronal (**C**) and sagittal (**D**) showed significant shrinkage in sellar mass and suprasellar extension after receiving steroid pulse therapy for 4 months. The patient's symptoms resolved almost completely except for mild diabetes insipidus, and she showed partial recovery of anterior pituitary dysfunction.

DISCUSSION

LYH is a rare inflammatory disorder that is characterized by diffuse infiltration of the pituitary gland by lymphocytes and plasma cells and fibrosis changes. The natural history of LYH has a wide spectrum, ranging from coexistent with clinical presentation, endocrine symptoms, and imaging hallmarks or a compression effect in the absence of radiologic features. LYH predominantly occurs in women, especially in young women.[2,7,12,13] Caturegli et al.[1] reviewed 492 patients with LYH reported from 1962 to 2008. The female/male ratios were approximately 4:1. Moreover, the casers showed a striking temporal association with pregnancy.[1,2] Our study has a similar gender ratio of female/male, but 4 female patients (25%) who were in the last month of pregnancy or early postpartum is less than the 57% reported by Caturegli et al.[2] This finding is probably an indication of the autoimmune cause of LYH, but further research is essential.

The most common symptoms in our populations were DI (n = 11, 55%), vision changes (n = 10, 50%), headache (n = 8, 40%), and

anterior pituitary deficiency (n = 8, 40%). The incidence of DI was similar in the studies of Wang et al.[13] and Honegger et al.,[12] in which it was also the most common pituitary dysfunction. Therefore, DI may be a useful factor in diagnosing LYH and could aid in differentiation from PA, because DI was seldom seen in PA.[14] Moreover, DI seems to be insensitive to all kinds of treatment. Wang et al.[13] reported that only 10% of DI had improved after treatment. Khare et al.[7] reported complete recovery of anterior pituitary in 33%, but no improvement of DI. In Chiloiro's[15] study, DI was considered to be a negative indicator concerning the response to the glucocorticoids in LYH because glucocorticoid therapy had no effect on restoring posterior pituitary function. Similar to a previous study, permanent hormone replacement was selected for DI in our study because no obvious improvement was obtained with any other treatment.[15]

Vision changes were the most common nonendocrine symptoms, which is in accordance with previous reports.[7,12] In this study, patients in the operative group rarely presented with preoperative pituitary hormone deficiency but rather with occupying-effect symptoms. Nine patients with vision changes received TSS, and all showed obvious improvement. Headache was another common symptom in LYH, which also responded well to both surgery and medical treatment. Patients with LYH usually experience headache in a model of incremental onset, which often happens in a few hours or days.[12] In this study, headache was relieved in all except patient 20. However, patient 20 would probably have had a primary headache rather than a headache association with LYH, because the patient showed no response to the treatment and the headache persisted in the long-term follow-up. Persistent fever was a rare condition that happened in patient 13, which was considered to be a result of damage to the thermoregulatory function of the hypothalamus.

For the pretreatment endocrine assessment, the pattern of ACTH>TSH>LH/FSH>GH axis deficiency and specific vulnerability of ACTH secretion to LYH have been proposed in several reports.[2,7,16,17] However, in 2 recent studies with a large sample size, Wang et al.[13] and Honegger et al.[12] both found that hypogonadism was the most common symptom of anterior pituitary dysfunction. In the present study, the frequency was as follows: TSH axis (n = 5, 25%), ACTH axis (n = 4, 20%), FSH/LH axis (n = 2, 10%), and GH/IGF axis (n = 1, 5%), which is inconsistent with some previous studies. However, this conclusion still needs to be tested in large-scale cohorts and by the further study of whether there is a significant difference in selective attacking in any kinds of pituitary cells. Therefore, the frequency of anterior pituitary hormone deficiency has little clinical value in the diagnosis of hypophysis retrospectively, but it is helpful that the marked hyperpituitarism incompatible with the small pituitary mass was more linked with the diagnosis of LYH. Hyperprolactinemia was seen in 9 patients, likely associated with stalk effect of the pituitary mass or pregnancy in women. Both surgery and medical therapy were effective in hyperprolactinemia, with only 1 patient still having mildly high hyperprolactinemia after medical therapy.

With the development of imaging techniques and the increased understanding of imaging features in LYH, more patients could be diagnosed by clinical features and MRI. MRI could diagnose typical LYH even without pathologic confirmation. LYH is characterized by a symmetric intensively and homogenously enhancing mass, with thickened pituitary stalk, loss of posterior pituitary hyperintensity, and intact sellar floor. Gutenberg et al.[10] have developed an algorithm to distinguish PA from LYH, with a sensitivity of 92% and a specificity of 99%, thereby determining prospective treatment. However, a central cyst was found in 6 patients (30%) in this study, suggesting necrosis or cyst formation, which was consistent with results from Germany.[12] In this study, Honegger et al. reported that 32% of patients (21/65) had a central necrosis on MRI. Pérez-Núñez et al.[11] also reported the finding of a cystic MRI appearance in LYH. We assumed that cystic development would be the manifestation of different stages of disease development. We did not submit the cyst to any other forms of examination, such as microbiological tests to explore the development of LYH. The diagnosis of LYH should be taken into account in cystic MRI appearance with suspicious clinical presentation. Overall, imaging diagnosis had a great impact on treatment choice and influenced outcomes directly.

With the pathogenesis of LYH being explored deeply, the preferred management modalities have gradually changed. Medical therapy has been widely accepted as the first-line treatment. Caturegli et al.[2] reported that 64% of 379 patients were operated on between 1964 and 2004. However, the proportion of patients who have received surgery has decreased gradually. The German study reported that approximately 30% of patients received TSS compared with 40% receiving watchful observation and 30% receiving medical treatment.[18] Another study in China with a larger sample also reported that only 30% of patients underwent surgery.[13] However, few guidelines for LYH have reached consensus.

In this study, 10 patients (50%) had undergone TSS because of vision changes and severe headache, with all being almost completely relieved. On the other hand, newly postoperative anterior pituitary hormone deficiency and DI was found in 7 patients, compared with only 3 patients with preoperative TSH axis dysfunction. These postoperative pituitary dysfunctions had almost recovered after a short duration of hormone replacement. Pretreatment anterior pituitary dysfunction was seen in 3 patients in the operative cohort, and TSS showed no positive effect on recovering anterior pituitary dysfunction. Recurrence occurred in 2 patients after 1 year and 4 years and was detected by enlargement of the pituitary mass on MRI. The patients took medical therapy subsequently, and the effect was satisfactory. Honegger et al.[18] reported improvement of anterior pituitary function in only 2/25 patients, and recovery from DI rarely occurred after surgery. Nevertheless, deterioration of original pituitary function and newly occurred pituitary dysfunction did occur. Several other studies[19-21] have also reported that surgery played little role in improving pituitary function. This is the main limitation of surgery compared with medical therapy, because medical therapy can improve pituitary function without introducing new pituitary dysfunction.

At operation, 8 patients presented with sallow and grayish mass, tough in texture and with little blood supply, and with significant adhesion to the surrounding tissue, which was similar to a previous report.[13] Fibrotic changes are a reasonable

explanation. For the patients misdiagnosed as having PA, this characteristic of LYH was helpful in differentiating from PA at surgery. The intraoperative frozen section and simple decompression could be better implemented to prevent iatrogenic hyperpituitarism at that time. However, it was difficult to distinguish LYH from other types of primary hypophysitis.

Steroid pulse therapy was administered to 5 patients. Four (80%) presented with regression of the pituitary mass on MRI similar to the findings in the report by Honegger et al.[18] Partial anterior pituitary dysfunction recovery occurred in 3 patients (60%), which showed a clear advantage to operation. Patient 15 developed new FSH/LH and GH/IGF axis deficiency without MRI, which progressed 1 year later, and she received hormone replacement because of insensitivity to steroid therapy. We inferred that the inflammation had destroyed pituitary cells as a result of the final stage of LYH. Patient 14 experienced a recurrence because of the discontinuation of steroid without permission and then retook steroid pulse treatment, which still remained effective. Because of the small number of cases, the association of duration and dose of treatment with the outcome was not calculated. In Honegger et al.'s study,[18] 32 patients received glucocorticoid therapy with highly variable doses and durations. The glucocorticoid dose was calculated as prednisolone equivalent. The dose ranged from 20 to 500 mg daily (median, 65 mg). The duration varied from 4 days to 1 year (median of 2 months). The investigators found that the duration of high-dose glucocorticoid therapy was unrelated to the relapse rate.[18] However, Wang et al.[13] reported that a lower recurrence rate was associated with a low taper rating and a long duration of steroid administration and that there was a significant difference in recurrence between administration durations of a pharmacologic dose of steroids of $\geq$6 and <6 months. The recurrence rate was approximately 40% in the medical group in both studies, but steroid therapy could still be effective.[13,18] In this study, no serious side effects were observed, and these symptoms were almost relieved after steroid therapy stopped, which was similar to Wang et al.'s study. However, Honegger et al. had reported a high rate of side effects, which may be attributed to the relatively high dose of glucocorticoids (Honegger et al.,[18] 60 mg vs. Wang et al.,[13] 30 mg)'. A large prospective study with a long follow-up period should be conducted to analyze the suitable dose and duration of steroid pulse therapy.

In this study, watchful observation was performed in 5 patients with only mild DI. One patient progressed 1 year later and subsequently accepted radiotherapy at a local hospital. The patient seemed to have permanent panhypopituitarism. For LYH, radiotherapy cannot remove compression as quickly as surgery or alleviate the inflammation process like medical therapy. Khare et al.[7] reported that all 15 patients experienced regression under observation. Similarly, Honegger et al.[18] also found that the watchful observation group had better recovery of endocrinologic deficits than did the medical therapy group, with a lower relapse rate. However, for the 2 reports discussed earlier, the bias of the severity of the condition should not be ignored. Patients with surgical or medical treatment may have a worse condition than the observation group. Generally, because DI is insensitive to surgery and medical therapy, observation may be the better choice for infundibuloneurohypophysitis with only DI.

For LYH, it is important to make an accurate diagnosis before treatment based on the clinical features and characteristic MRI results. Medical treatment is noninvasive and economical and offers a potential improvement in endocrine function compared with surgery. However, there are still many problems to be studied, such as the dose of glucocorticoid and the duration of administration. Watchful observation also results in a satisfactory outcome but more cases are needed to prove this. Nonoperative treatment should gradually become the primary choice, and surgery is mainly suitable for the rapid progression of neurologic dysfunction or obvious local mass effect that is insensitive to steroid pulse therapy.

In the present study, immunosuppressive treatment was not applied. It was reported that patients with no reaction to steroid pulse therapy responded well to the immunosuppressive drug.[8,9] However, because of the small number of patients treated, the role of immunosuppressive treatment still needs to be studied further.

Our study has the limitation of being retrospective, from a single center, and with relatively few patients. Moreover, APAs are not available in China. A larger prospective multicenter controlled study should be conducted to further elucidate the pathogenesis and natural history of LYH and to formulate the guidelines of treatment.

CONCLUSIONS

Nonoperative treatment is the better choice for most patients with LYH, because it is effective and noninvasive. Surgery is recommended for definitive diagnosis, severe or rapid progression of neurologic impairment, and glucocorticoid insensitivity. Periodic follow-up is mandatory in the patient's long-term management.

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