

## CASE REPORT

### OPEN ACCESS

Full open access to this and thousands of other papers at <http://www.la-press.com>.

## Lymphocytic Panhypophysitis: its Clinical Features in Japanese Cases

Yoshiharu Wada<sup>1</sup>, Yoshiyuki Hamamoto<sup>1</sup>, Yoshio Nakamura<sup>4</sup>, Sachiko Honjo<sup>1</sup>, Yukiko Kawasaki<sup>1</sup>, Hiroki Ikeda<sup>1,5</sup>, Jun Takahashi<sup>2</sup>, Yoshiaki Yuba<sup>3</sup>, Akira Shimatsu<sup>6</sup> and Hiroyuki Koshiyama<sup>1,7</sup>

<sup>1</sup>Center for Diabetes and Endocrinology, <sup>2</sup>Department of Neurosurgery, <sup>3</sup>Department of Pathology, The Tazuke Kofukai Foundation Medical Institute Kitano Hospital, Osaka, Japan. <sup>4</sup>Hyogo Prefectural Amagasaki Hospital, Amagasaki, Japan. <sup>5</sup>Ikeda Hospital, Amagasaki, Japan. <sup>6</sup>National Hospital Organization Kyoto Medical Center, Kyoto, Japan. <sup>7</sup>Kyoto University Graduate School of Medicine, Kyoto, Japan. Corresponding author email: [hamamoto@kitano-hp.or.jp](mailto:hamamoto@kitano-hp.or.jp)

**Abstract:** Lymphocytic hypophysitis is divided into three forms according to the involved tissues, lymphocytic adenohypophysitis, lymphocytic infundibulo-neurohypophysitis, and lymphocytic panhypophysitis (LPH). The term LPH was first proposed by us in 1995, although its entity and pathogenesis still remain controversial. Here we report five cases of LPH, who visited our clinics during 1994 to 2009. All cases were female of 20 to 77 years of age, and one case was associated with pregnancy. They presented with polyuria (n = 4), headache (n = 3), general malaise, polydipsia (n = 2), blunted vision, diplopia, amenorrhea or appetite loss (n = 1). Magnetic resonance imaging showed the pituitary swelling, the thickened stalk, the loss of the T1 hyperintense neurohypophysis (n = 4), or the atrophic pituitary (n = 1). Endocrinological examinations revealed deficiencies of TSH, ADH in all cases, GH, ACTH in three cases, LH, PRL in two cases, and FSH in one case, respectively. The severity of ADH deficiency varied among the cases. Anti-pituitary antibody was not detected in the cases examined. The biopsy of the pituitary lesions was performed except for one case, all of which revealed the diffuse lymphocytic infiltration. These results suggest that LPH is characterized by the female predominance, the atypical patterns of anterior pituitary hormone deficiencies and the variable degrees of diabetes insipidus in Japanese.

**Keywords:** lymphocytic panhypophysitis, hypopituitarism, diabetes insipidus

*Japanese Clinical Medicine* 2011;2 15–20

doi: [10.4137/JCM.S6254](https://doi.org/10.4137/JCM.S6254)

This article is available from <http://www.la-press.com>.

© the author(s), publisher and licensee Libertas Academica Ltd.

This is an open access article. Unrestricted non-commercial use is permitted provided the original work is properly cited.

## Introduction

Lymphocytic hypophysitis (LH) was first described in 1962, by Goudie in a case of a 22-year-old woman about one year after delivery.<sup>1</sup> In 1967, Levine reported the first successful model of experimental LH, induced by immunizing rats with a single intracutaneous injection of rat pituitary tissue emulsified in complete Freund's adjuvant.

Clinically, as shown in Figure 1, LH in humans is divided into three forms according to the involved tissues; lymphocytic adenohypophysitis (LAH), lymphocytic infundibulo-neurohypophysitis (LINH), and lymphocytic panhypophysitis (LPH).<sup>2</sup> Originally, LH was considered to be confined only to the LAH.<sup>3</sup> In 1993, Imura et al reported LINH,<sup>4</sup> and the next year, we reported a case of LH affecting both the adenohypophysis and neurohypophysis,<sup>5</sup> and first proposed the entity of LPH, which was defined as the case of LH involving both the anterior and posterior lobes.<sup>6</sup>

Recently, an association between LH and IgG4-related systemic disease<sup>7</sup> and the possibility of two different pathogenesis of LH according to the presence of T regulatory cell has been proposed.<sup>8</sup> However, the entity and pathogenesis of LPH still remain controversial. Here, in order to clarify the characteristics of LPH in Japanese, we report five cases of LPH, who

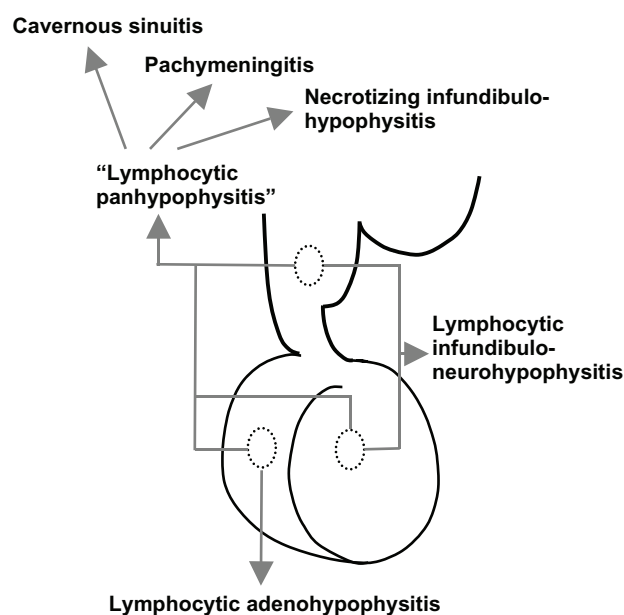
visited our clinics during 1994 to 2009, including three cases previously reported by us.<sup>5,9,10</sup>

## Subjects and Methods

The clinical characteristics of subjects are shown in Table 1, which include three cases previously reported by us; case 1,<sup>5</sup> case 2,<sup>9</sup> and case 3.<sup>10</sup> All of these five cases were female, aged 20 to 77 years. Polyuria and headache were commonly observed. Hashimoto's thyroiditis was associated in case 2. Only case 3 was associated with pregnancy. She developed LPH in the 10th week of pregnancy. Neither infection nor trauma history was associated among these cases.

Provocative tests were performed with intravenously administered 500 µg of thyrotropin releasing hormone (TRH), 100 µg of luteinizing hormone-releasing hormone (LHRH), 100 µg of corticotropin releasing hormone (CRH) and 100 µg of growth hormone releasing hormone (GRH) in all cases. Water deprivation test and pitressin test were performed only in case 1, and hypertonic (5%) saline infusion test was performed only in case 2.

Plasma levels of thyroid stimulating hormone (TSH), prolactin (PRL), luteinizing hormone, follicle stimulating hormone (FSH), adrenocorticotrophic hormone (ACTH), cortisol, growth hormone (GH) and antidiuretic hormone (ADH) were measured by specific assays. TSH, PRL, luteinizing hormone, FSH and ACTH were measured by immunoradiometric assay, and cortisol and GH were measured by radioimmunoassay in cases 1 and 2. TSH, ACTH and cortisol were measured by chemi-luminescent immunoassay, and PRL, luteinizing hormone, FSH and GH were measured by chemi-luminescent enzyme immunoassay in cases 3, 4 and 5. ADH was measured by radioimmunoassay in all cases. Anti-nuclear antigen (ANA) was measured by immunofluorescence assay (TFB<sup>®</sup>) in all cases except for case 4. Anti-centromere antibody (ACA) was measured by enzyme-linked immunosorbent assay (MBL<sup>®</sup>) in case 5. Anti-thyroglobulin antibody (anti-Tg) in cases 1, 2 and 5 and anti-thyroperoxidase antibody (anti-TPO) in cases 2 and 5 were measured by electrochemiluminescence immunoassay (Roche<sup>®</sup>). Anti-thyroid microsomal antibody (AMA) was measured by particle agglutination test (FUJIREBIO INC.<sup>®</sup>) in case 1. Rheumatoid factor (RF) was measured by turbidmetric immunoassay (SIEMENS<sup>®</sup>) in case 1. Anti-pituitary antibody (APA) was measured with



**Figure 1.** A hypothetical schema presenting three types of lymphocytic hypophysitis; lymphocytic adenohypophysitis (LAH), lymphocytic infundibulo-neurohypophysitis (LINH), and lymphocytic panhypophysitis (LPH), and their related disorder; necrotizing infundibulo-hypophysitis.

**Table 1.** Characteristics of subjects.

	Case 1	Case 2	Case 3	Case 4	Case 5
Age (years)	50	77	37	20	65
Presented symptoms					
Polyuria	+		+	+	+
Headache	+	+	+		
General malaise		+	+		
Polydipsia	+			+	
Blurred vision			+		
Diplopia		+			
Amenorrhea			+		
Appetite loss		+			

indirect immunofluorescent antibody technique using rat pituitary cells as antigen (SRL®) in cases 1, 2 and 3.

The biopsy of the resected pituitary specimen was performed in all cases. Paraffin-embedded sections were prepared from the biopsy samples fixed previously in buffered formalin. Hematoxylin and eosin staining was used for basic histology in all cases. Immunohistopathological staining with CD3 (Leica®), CD4, CD8 (Novocastra®), FoxP3 (Abcam®), and IgG4 (AbD Serotec®) was performed in two cases.

## Results

### Magnetic resonance imaging

Summary of Magnetic Resonance Imaging studies are shown in Table 2. Four cases showed diffuse enlargement of the pituitary, and one case showed pituitary atrophy. Four cases exhibited an absence of T1 hyperintense of the posterior lobe, which is considered to be a sign of diabetes insipidus.

### Histology

The biopsy of the pituitary lesions was performed in all cases. The pathological examinations showed a diffuse lymphocytic infiltration of mainly mature lymphocytes in the anterior pituitary of all cases.

In addition, the destruction of adenohypophysis was observed. No direct evidence for inflammation of neurohypophysis could be obtained, since the posterior lobe could not be obtained.

### Immunohistopathological analysis

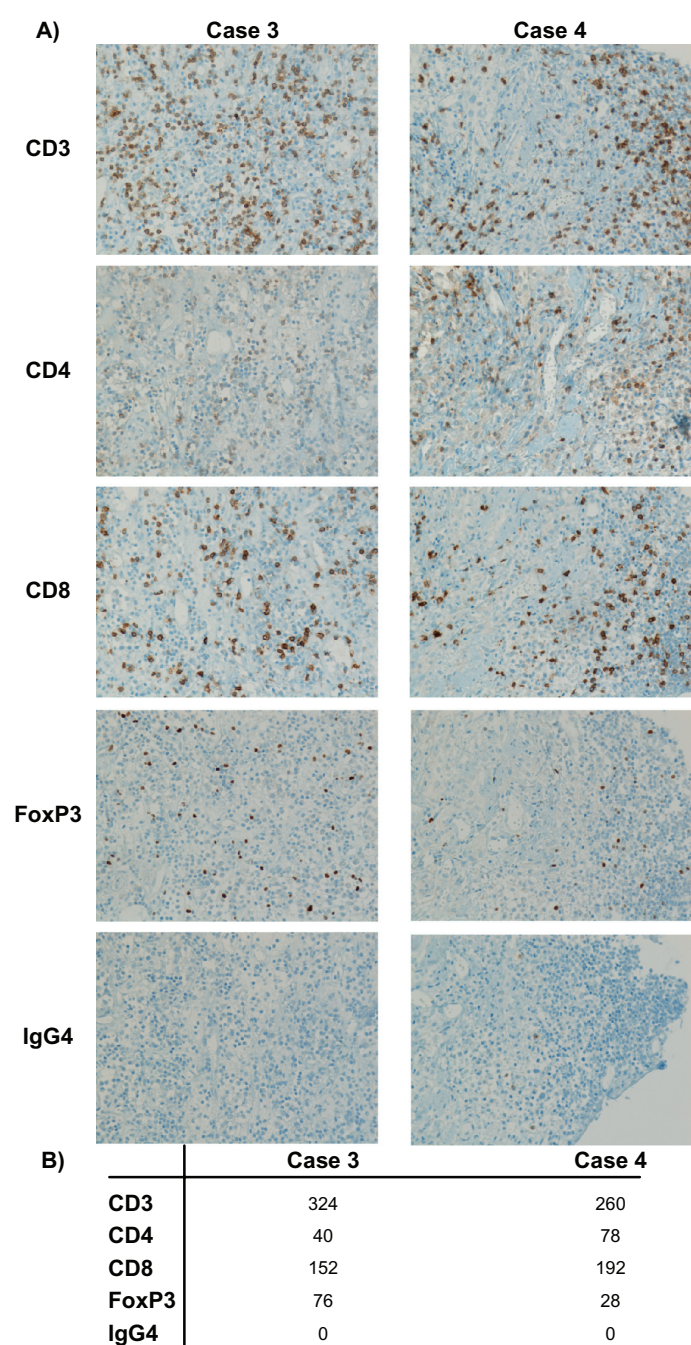
In cases 3 and 4, immunohistopathological analysis was performed. Infiltration of different numbers of CD4 and FoxP3 positive cells were observed in both cases (Fig. 2). FoxP3 positive cells were 2.7 times more abundant in case 3, while the number of CD4 positive cells in case 4 were two times more abundant than that in case 3. There was no IgG4 positive cell observed in either case.

### Provocative tests of anterior pituitary functions

Provocative tests showed various patterns. Deficiency of TSH response was observed in all cases, GH and PRL in three cases, luteinizing hormone, FSH, and ACTH in two cases, respectively. In case 1, there was a blunted GH response to hypoglycemia, whereas GH responded normally to GRH stimulation. In case 3, polyuria was developed after the replacement therapy of hydrocortisone.

**Table 2.** Magnetic resonance imaging.

	Case 1	Case 2	Case 3	Case 4	Case 5
Whole pituitary gland swelling	+	+	+	+	
Compression of the sellar floor		+	+		
Pituitary stalk thickening	+		+	+	
Absence of a high intensity signal of the posterior lobe	+		+	+	+
Pituitary atrophy					+



**Figure 2.** Immunohistopathological analysis. **A)** Samples were stained with antibody for CD3, CD4, CD8, FoxP3 and IgG4. Case 3 and case 4 were examined. High magnification are shown (20 $\times$ ). **B)** Numbers of the immuno-positive cells per field.

## ADH secretion

ADH secretion was impaired in all cases. The polyuria was observed in various severity among the cases (Table 3).

In case 1 which showed severe polyuria, urinary osmolality after water deprivation test was 173 mOsm/kg

and showed a further increase (522 mOsm/kg) after subcutaneous injection of pitressin.

All cases except for case 2 required DDAVP replacement therapy. In case 2, although DDAVP replacement therapy was not required, the hypertonic (5%) saline infusion test revealed poor response of serum ADH.

## Autoantibodies

In case 1, RF was positive although ANA, anti-Tg and AMA were negative. In case 2, ANA and anti-Tg were positive although anti-TPO was negative. In case 3, ANA was negative. In case 5, ANA, ACA, anti-Tg and anti-TPO were positive. APA was measured in cases 1, 2 and 3, although it was negative.

## Replacement therapy

In cases 2, 3 and 5, hydrocortisone and levothyroxine replacement therapies were required. In cases 1 and 4, only DDAVP replacement therapy was required due to anterior pituitary function was not greatly impaired.

## Discussion

LH is divided into three forms; LAH, LINH, and LPH. Although the autoimmunity has been suggested in the three forms, the direct evidence for autoimmune pathogenesis is still unclear. Ahmed et al reported cases with diabetes insipidus and hypopituitarism, which revealed the necrosis of infundibulum and hypophysitis,<sup>11</sup> which were considered to represent the final stage of LPH. All of our five cases were female, although male case was not infrequently reported in Caucasians.<sup>12</sup>

In the first experimental model of LH by Levine,<sup>13</sup> the adenohypophysis showed focal and diffuse infiltration with mononuclear cells, while a few posterior and intermediate lobes had minimal inflammation. The autoantigen of lymphocytic hypophysitis has not yet been identified, and it remains to be elucidated whether three forms of lymphocytic hypophysitis are based on the same pathological mechanism through autoimmunity. Especially, in LPH, it seems paradoxical to postulate that the immune system attacks two self-structures, adenohypophysitis and neurohypophysitis, which are both structurally and embryologically very different. Alternatively, it is possible that the autoimmune process targets simultaneously distinct antigens



**Table 3.** ADH secretion.

	Case 1	Case 2	Case 3	Case 4	Case 5
Urinary volume (mL)	6000	2000	6000	3980	2100
ADH (0.3–3.5 pg/mL)	0.15	0.7	0.7	0.6	0.7
Plasma osmolarity (275–290 mOsm/kg)	285	283	278	281	282
Urinary osmolarity (50–1300 mOsm/kg)	101	417	79	207	783

in the two pituitary lobes, or perhaps the process is initially confined only to the anterior lobe or the posterior lobe and then simply extend to adjacent structures, including the dura mater causing pachymeningitis and cavernous sinus.<sup>2</sup> It is intriguing that the inflammation frequently prevails from the anterior pituitary to posterior pituitary, but rarely in the reverse direction, ie, from the posterior pituitary to anterior pituitary.

It has been reported that anti-pituitary antibody is frequently observed among the patients with LH,<sup>14</sup> although our 3 cases showed negative for anti-pituitary antibody. In the literature review, the sensitivity of APA measured with immunofluorescent technique is lower than that measured with immunoblotting technique among the LPH cases.<sup>2</sup> There might be attributable to the limitation of the assay.

Several researchers have tried to identify the autoantibodies of LH. Although it has been reported that some antibodies are useful for the diagnosis of LH, it remains unclear whether the antibodies are the cause or the result of LH.<sup>15</sup>

We tried the immunohistopathological study with CD4 and FoxP3 staining. CD4 is a marker for T helper cells<sup>16</sup> and FoxP3 is a marker for T regulatory cells.<sup>17</sup> Different distribution of CD4 and FoxP3 positive cells and various patterns of autoantibodies suggest that there is a different immune pathogenesis among cases. Recently, it has been reported that an association between LH and IgG4-related systemic disease suggesting an involvement of IgG4 in the pathogenesis of LH.<sup>7</sup> However, in all of our cases there was no IgG4 positive cells observed suggesting that IgG4 is unlikely to be involved in the pathogenesis of LPH or the pathogenesis may vary among the cases as shown in different distribution of CD4 and FoxP3 positive cells in our cases.

There was a relationship between the start of replacement therapy of hydrocortisone and polyuria development in case 3. It is considered to be a central

diabetes insipidus, which was masked with secondary adrenal cortical insufficiency, since the ADH secretion is under an influence of glucocorticoid negative feedback.<sup>3</sup>

Provocative tests revealed impaired secretions of ADH and TSH in all cases, but panhypopituitarism only in one case. The pathogenesis of LPH is still unclear and various pathogenesis may be considered. The pathogenesis of LPH with diabetes insipidus and partial hypopituitarism, may be considered that the inflammation in the neurohypophysis affected partially the anterior pituitary lobe. The pathogenesis of the LPH with diabetes insipidus and panhypopituitarism, may be considered that the extension of inflammation in the anterior pituitary lobe interfered with transposition of ADH. And also, there are the cases of LPH with panhypopituitarism that cannot be confirmed whether the origin of the pituitary inflammation is adenohypophysis or infundibulo-neurohypophysis.<sup>18</sup> On the other hand, there was a discrepancy between the GH response to hypoglycemia and to GRH stimulation in case 1. This result suggests that the lesion lay in the hypothalamus including the pituitary stalk. There might be different pathogenesis of LPH among these cases.

In summary, LPH of Japanese subjects is likely to be characterized by the female predominance, the atypical patterns of anterior pituitary hormone deficiencies and the variable degrees of diabetes insipidus. The exact pathogenic mechanism of LPH still remains to be elucidated.

## Disclosure

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.



## References

1. Goudie RB, Pinkerton PH. *J Pathol Bacteriol.* 1962;83:584–5.
2. Caturegli P, Newschaffer C, Olivi A, Pomper MG, Burger PC, Rose NR. *Endocr Rev.* 2005;26:599–614.
3. Mayfield RK, Levine JH, Gordon L, Powers J, Galbraith RM, Rawe SE. *Am J Med.* 1980;69:619–23.
4. Imura H, Nakao K, Shimatsu A, et al. *N Engl J Med.* 1993;329:683–9.
5. Koshiyama H, Sato H, Yorita S, et al. *Endocrine J.* 1994;41:93–7.
6. Koshiyama H, Koh T, Shimatsu A, Nakao K. 77th annual meeting of the endocrine society (USA). 1995;6:14–7. Washington, DC.
7. Shimatsu A, Oki Y, Fujisawa I, Sano T. *Endocr J.* 2009;56:1033–41.
8. Mirocha S, Elagin RB, Salamat S, Jaume JC. *Clin Exp Immunol.* 2009;155:403–11.
9. Nakamura Y, Okada H, Wada Y, Kajiyama K, Koshiyama H. *J Endocrinol Invest.* 2001;24:262–7.
10. Arai K, Nabe K, Ikeda H, et al. *Endocrine.* 2007;32:117–21.
11. Ahmed SR, Aiello DP, Page R, Hopper K, Towfighi J, Santen RJ. *J Clin Endocrinol Metab.* 1993;76:1499–504.
12. Hamnvik OP, Laury AR, Laws ER Jr, Kaiser UB. *Nat Rev Endocrinol.* 2010;6:464–70.
13. Levine S. *Science.* 1967;158:1190–1.
14. De Bellis A, Ruocco G, Battaglia M, et al. *Clinical Science.* 2008;114:413–12.
15. Tanaka S, Tatsumi K, Kimura M, et al. *Eur J Endocrinol.* 2002;417:767–75.
16. Shimono T, Yamaoka T, Nishimura K, et al. *Eur Radiol.* 1999;9:1397–400.
17. Reiherz EL, Schlossman SF. *Cell.* 1980;19:821–7.
18. Tang Q, Bluestone JA. *Nat Immunol.* 2008;9:239–44.

**Publish with Libertas Academica and every scientist working in your field can read your article**

*“I would like to say that this is the most author-friendly editing process I have experienced in over 150 publications. Thank you most sincerely.”*

*“The communication between your staff and me has been terrific. Whenever progress is made with the manuscript, I receive notice. Quite honestly, I’ve never had such complete communication with a journal.”*

*“LA is different, and hopefully represents a kind of scientific publication machinery that removes the hurdles from free flow of scientific thought.”*

### Your paper will be:

- Available to your entire community free of charge
- Fairly and quickly peer reviewed
- Yours! You retain copyright

**<http://www.la-press.com>**