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N Sato, G Sze and K Endo

*AJNR Am J Neuroradiol* 1998, 19 (3) 439-444

<http://www.ajnr.org/content/19/3/439>

This information is current as  
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# Hypophysitis: Endocrinologic and Dynamic MR Findings

Noriko Sato, Gordon Sze, and Keigo Endo

**PURPOSE:** Our purpose was to assess the worth of dynamic MR imaging in the evaluation of vascular changes of the pituitary in patients with lymphocytic hypophysitis.

**METHODS:** Five patients (four males, one female; 9 to 53 years old) with lymphocytic hypophysitis or infundibuloneurohypophysitis were studied. All patients underwent endocrinologic studies and a series of two to five MR examinations performed over a period of 8 months to 5 years, including a total of nine dynamic imaging studies.

**RESULTS:** Two patients had panhypopituitarism and three had partial hypopituitarism. Diabetes insipidus was present in four patients. Among the five patients, the pituitary was enlarged in three, of whom two showed improvement on follow-up MR studies. Three patients had a thickened stalk, which improved on subsequent examinations. In all nine dynamic studies, the enhancement time of the whole pituitary was delayed to over 90 seconds, even though five of the nine conventional, simultaneously performed MR studies showed a normal pituitary. The peak time of posterior pituitary enhancement in the first dynamic study was also delayed in all patients (from 60 to 120 seconds). In two patients, normal early enhancement of the posterior pituitary was identified on initial studies but not on subsequent studies.

**CONCLUSION:** Dynamic MR imaging can display an abnormality of the hypophysial vasculature even if the pituitary disease is seen to regress on the conventional MR study. The delay or even the lack of early enhancement of the posterior pituitary in lymphocytic hypophysitis may be due to secondary inflammatory changes.

Lymphocytic hypophysitis is a rare inflammatory disease of the pituitary gland. It was originally thought to cause adenohypophysitis in young women during pregnancy or in the postpartum period (1-3). However, this disease is now known to occur in both pituitary lobes, at all ages, and in both sexes (1, 4-8). Recently, Imura et al (9) suggested that what was previously termed idiopathic diabetes insipidus was frequently due to lymphocytic infundibuloneurohypophysitis. In this entity, enlargement of the pituitary stalk or neurohypophysis is seen. This enlargement regresses spontaneously or with glucocorticoid treatment.

In 1993, we described patients with idiopathic diabetes insipidus who showed decreased posterior pituitary vasculature, manifested by the lack of normal early enhancement of the posterior pituitary (10). In

that study, we demonstrated a relationship between the posterior pituitary function and its vascularity, but our results did not reveal the cause of the absence of early enhancement of the posterior pituitary. It may be due to congenital lack, to poor development of the posterior pituitary organ or arterial supply, or to secondary changes of vascular destruction. In 1994, Maghnie et al (11) also demonstrated delayed enhancement of both the anterior and posterior lobes of the pituitary in patients with hypopituitarism.

Lymphocytic infundibuloneurohypophysitis is considered to be one of the causes of idiopathic diabetes insipidus (9). The present study was performed to observe the pituitary vascular changes in patients with lymphocytic hypophysitis on follow-up dynamic studies. We evaluated a series of magnetic resonance (MR) examinations, including dynamic imaging studies, obtained over a period of 8 months to 5 years, to observe changes in the pituitary vasculature and to correlate these findings with pituitary endocrinologic studies.

## Methods

We reviewed the findings in five patients, examined during the period 1987 to 1996, who had lymphocytic hypophysitis or infundibuloneurohypophysitis. Four patients were male and

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Received June 3, 1997; accepted after revision September 18.

From the Departments of Diagnostic Radiology (N.S.) and Nuclear Medicine (K.E.), Gunma University School of Medicine, Japan; and the Department of Diagnostic Radiology, Yale University School of Medicine, New Haven, Conn (G.S.).

Address reprint requests to Noriko Sato, MD, Department of Diagnostic Radiology, Gunma University School of Medicine, 3-39-15, Shouwa-machi, Maebashi, Gunma, 371 Japan.

TABLE 1: Clinical Characteristics and Endocrinologic Findings in Five Patients

Case	Age, y/Sex	Clinical Presentation	Endocrinologic Study		Treatment
			Anterior Lobe	Posterior Lobe	
1	31/M	Slight fever, general fatigue, arthritis, headache, polyuria, polydipsia, dry skin, decreased libido, cold intolerance	Panhypopituitarism	Diabetes insipidus (partial)	Biopsy, steroid replacement therapy (desmopressin, thyrotropin, glucocorticoid, testosterone)
2	53/M	Decreased libido	Partial hypopituitarism (LH)*	No study	Biopsy, steroid replacement therapy (testosterone)
3	48/M	Diplopia (abductor palsy), headache, vomiting, polyuria, polydipsia, arthritis, myositis	Panhypopituitarism	Diabetes insipidus (partial)	Steroid replacement therapy (desmopressin, thyrotropin, glucocorticoid)
4	14/M	Polyuria, polydipsia, short stature	Partial hypopituitarism (TSH, GH, LH, FSH)*	Diabetes insipidus (complete)	Replacement therapy (desmopressin, thyrotropin, growth hormone)
5	9/F	Polyuria, polydipsia, short stature	Partial hypopituitarism (GH)*	Diabetes insipidus (complete)	Replacement therapy (desmopressin, growth hormone)

\* Insufficient hormones.

one was female; ages ranged from 9 to 53 years (Table 1). All patients had two to five follow-up MR studies performed over a period ranging from 8 months to 5 years (Table 2). None of the patients had a family history of diabetes insipidus or any history of autoimmune diseases, such as rheumatoid arthritis, thyroid disease, or systemic lupus erythematosus.

All patients had MR imaging of the sella turcica with 1.5-T superconductive units. T1-weighted MR images were acquired in the coronal and sagittal planes with parameters of 300–400/15/3–4 (repetition time/echo time/excitations), a 192 × 256 matrix, a 20-cm field of view, a 3-mm section thickness, and a 0.0- to 0.6-mm intersection gap. In cases 1 through 3, T2-weighted sagittal or coronal MR images were obtained with parameters of 2000–3300/80–105/2, a 192 × 256 matrix, a 20-cm field of view, a 3-mm section thickness, and a 0.0- to 0.6-mm intersection gap.

Dynamic MR studies were performed in all patients. Three contiguous sagittal conventional or fast spin-echo images were obtained. For the conventional spin-echo sequences, the imaging parameters were 150/15/1, a 192 × 256 matrix, a 23-cm field of view, a 4-mm section thickness, and a 0.8-mm intersection gap. For the fast spin-echo sequences the parameters were 567/14/2, an echo train length of eight, a 192 × 256 matrix, a 20-cm field of view, a 3-mm section thickness, and a 0.3-mm intersection gap. Actual sampling time per image was 29 seconds for both dynamic sequences. Four serial sequences were repeated after rapid hand injection (2 mL/s) of gadopentetate dimeglumine (0.1 mmol/kg of body weight). The changes in enhancement seen on the dynamic studies were evaluated quantitatively. A small (1- to 2-mm<sup>2</sup>) region of interest was placed on both the anterior and posterior pituitary lobes in each dynamic phase to observe the peak time of posterior pituitary enhancement and the time to complete enhancement of the whole pituitary. The dynamic studies were performed twice in each patient, except for case 2, and the changes in the enhancement pattern were observed. The direction of the frequency-encoding gradient was anteroposterior in all sagittal images to shift the dorsum sellae marrow fat posteriorly (12).

Plasma vasopressin concentrations were determined by radioimmunoassay, and plasma and urinary osmolarities were measured before and after 4 to 8 hours of water deprivation. Plasma concentrations of growth hormone, prolactin, luteinizing hormone, follicle-stimulating hormone, thyrotropin, cortisol, free T4, and testosterone were measured. Provocative tests were performed in all patients except for case 2 as follows: for thyrotropin and prolactin, after a bolus injection of 500 µg of thyrotropin-releasing hormone; for luteinizing hormone and follicle-stimulating hormone, 100 µg of gonadotropin-releasing

hormone; for growth hormone, 100 µg of growth hormone-releasing hormone or 0.1 U of regular insulin per kilogram of body weight; and for cortisol, 100 µg of corticotropin-releasing hormone or 0.1 U of regular insulin per kilogram of body weight. Multiple blood samples were collected to measure plasma hormone concentrations before and for up to 120 minutes after the injections. In case 2, a provocative test was performed only for cortisol.

Cases 1 and 2 had histologically proved disease by transphenoidal biopsy. In case 1, biopsy specimens showed chronic inflammation with fibrous change, numerous lymphocytes, and infiltration of plasma cells. No caseous necrosis or Langerhans multinucleated giant cells were present. In case 2, biopsy specimens showed adenohypophysitis with focal lymphocytic infiltrate with lymphoid follicle formation and attached portions of dense hyalinized fibrous tissue. The remaining three patients were diagnosed on the basis of clinical and endocrinologic studies, MR imaging findings, response to steroid therapy, and natural clinical course, according to the criteria of Imura et al (9) (Table 1).

## Results

Clinical and MR findings for the five patients are summarized in Tables 1 and 2. Endocrinologic studies showed panhypopituitarism with partial diabetes insipidus in cases 1 and 3. In case 2, the serum luteinizing hormone and testosterone levels were low and the provocative test for cortisol was borderline. No hormonal examination was done for the posterior lobe. Endocrinologic studies showed complete diabetes insipidus in cases 4 and 5. In case 4, the plasma cortisol response was normal; however, all other hormonal responses were low, and the basal serum prolactin level was elevated. In case 5, the plasma growth hormone response was low, but other hormonal responses were normal.

On MR imaging, three patients (cases 1 through 3) had large pituitary masses without the posterior pituitary high intensity. The pituitary masses were isointense with slight heterogeneity on T1-weighted images. Contrast-enhanced T1-weighted images revealed heterogeneous pituitary enhancement in cases 1 and 2 (Fig 1). On follow-up MR studies, the en-

TABLE 2: Conventional and Dynamic MR Findings in Five Patients

Case	Age, y/Sex	MR Study	Interval between Studies, mo	Conventional MR Study			Enhancement Time (in seconds) on Dynamic MR Study		Cavernous Sinus
				Anterior Lobe	PPHI	Stalk	Anterior Lobe	EEPP	
1	31/M	1st	16	Enlarged +++	-	Unclear	>120*	120†	Normal
		2nd		Enlarged +	-	Normal	>120*	120†	
2	53/M	1st	8	Enlarged +++	-	Normal	90*	-	L side swollen, T2 very low, narrowed L internal carotid artery
		2nd		Enlarged +++	-	Normal			
3	48/M	1st	2	Enlarged ++	-	Thickened +	>120*	90†	Both sides swollen, T2 very low, poor enhancement
		2nd	4	Enlarged ++	-	Normal			
		3rd	3	Enlarged +	-	Normal			
4	14/M	4th	12	Normal	-	Normal	90*	-	Normal
		1st		Normal	-	Thickened +++			
		2nd		Normal	-	Thickened +			
		3rd		Normal	-	Thickened +			
5	9/F	4th	12	Normal	-	Thickened +	>120*	120†	Normal
		1st		Normal	-	Thickened +++			
		2nd		Normal	-	Thickened +			
		3rd		Normal	-	Normal			
		4th		Normal	-	Normal			
	5th	Normal	-	Normal	>120*	-	30		
Control (see [10])							60	30	

Note.—PPHI indicates posterior pituitary high intensity; EEPP, early enhanced posterior pituitary; -, not identified; +, mild; ++, moderate; +++, prominent. \* completely enhanced time (sec) of the whole pituitary after the injection.

† peak time (sec) of posterior pituitary enhancement after the injection.

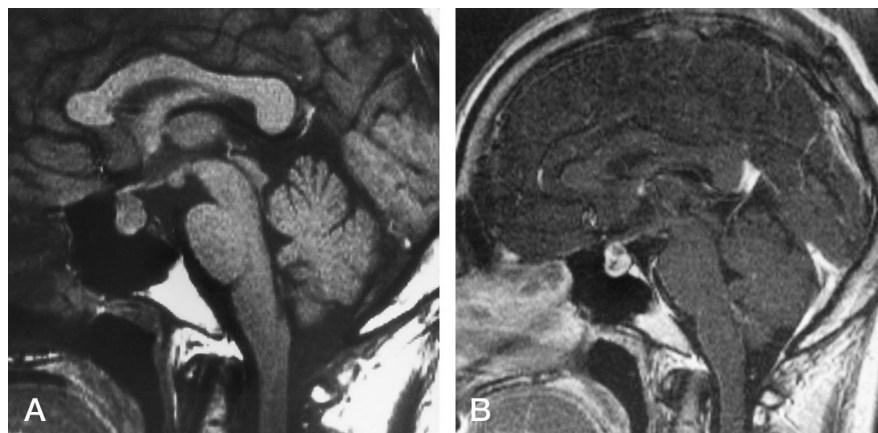


FIG 1. Case 1: MR images and pathologic findings in the pituitary.

A, Sagittal T1-weighted image (400/15/4) shows an isointense, large pituitary mass without posterior pituitary high signal.

B, Sagittal contrast-enhanced T1-weighted image (400/15/3) shows heterogeneous enhancement.



FIG 2. Case 3: A series of conventional and dynamic MR studies.

A, First study, January 1994. Sagittal contrast-enhanced T1-weighted image (400/15/4) shows the pituitary is enlarged and the stalk is thickened. Dural enhancement is noted adjacent to the pituitary fossa (arrow).

B, Fourth study, October 1994. Sagittal contrast-enhanced T1-weighted image (400/15/4) shows the enlarged pituitary and the abnormally thickened stalk have improved and are nearly normal in appearance.

C, Coronal contrast-enhanced T1-weighted image (400/15/4) obtained at the same time as B shows the bilateral cavernous sinuses are enlarged and heterogeneously and poorly enhanced. Most of the cavernous sinuses remain isointense (arrows) and can be distinguished from the enhanced pituitary.

D, Dynamic study (150/15/1) performed in March 1994. The first image, 30 seconds after injection, shows the early enhanced posterior pituitary. The stalk is enhanced simultaneously.

E, Dynamic study (150/15/1) performed in October 1994. The first image within 30 seconds after injection shows the lack of early enhanced posterior pituitary (although the stalk is enhanced), suggesting the result of inflammation.

larged pituitaries improved in cases 1 and 3 over a period of 1 year 4 months, and over 8 months, respectively (Figs 1 and 2). In case 3, the stalk was thickened and also improved within 2 months (Fig 2). However, in case 2, the enlarged pituitary did not improve, although steroid therapy was given. Cases 4 and 5 had thickened stalks, which improved over 1 to 4 years without treatment. The anterior pituitary was normal on conventional MR images. Posterior pituitary high intensity was absent in both patients. In case 2, the left internal carotid artery became narrow after 8 months. In case 3, both cavernous sinuses were swollen with heterogeneous enhancement and low signal intensity on T2-weighted images. Dural enhancement was noted adjacent to the pituitary fossa in case 3 (Fig 2).

Two dynamic studies were performed in each patient over a period of 7 months to 2 years, except case 2, who had only one dynamic study. Complete enhancement time of the whole pituitary was delayed to more than 90 seconds after the injection in all patients (Table 2). In control subjects, complete enhancement time of the whole pituitary has been shown to be 60 seconds after the injection (10). Only a part of the pituitary was enhanced even at 120 seconds after the injection in our cases 1, 3, 4, and 5

(Fig 3). The complete enhancement time of the whole pituitary in case 3 improved from over 120 seconds to 90 seconds after injection on follow-up (Fig 2). On the first study of all patients, early enhancement of the posterior pituitary was observed within 30 seconds after injection (Fig 2), except for case 2, in whom early enhancement was not seen. The finding of early enhancement within 30 seconds is normal. However, the peak time to posterior pituitary enhancement was delayed to over 60 seconds after injection in all patients (Table 2) (normal peak time of the posterior pituitary enhancement is 30 seconds after injection) (10). On the second studies in cases 3 and 5, the normal early enhancement of the posterior pituitary within 30 seconds was not observed (Figs 2 and 3), indicating progressively decreased vascularity.

## Discussion

Lymphocytic hypophysitis is a rare inflammatory disease of the pituitary gland. It has a female predilection and frequently affects young women during late pregnancy or in the postpartum period (1-3). In recent years, however, many cases have been reported that were not related to pregnancy (1, 6, 8) and that occurred in men (1, 6, 7).

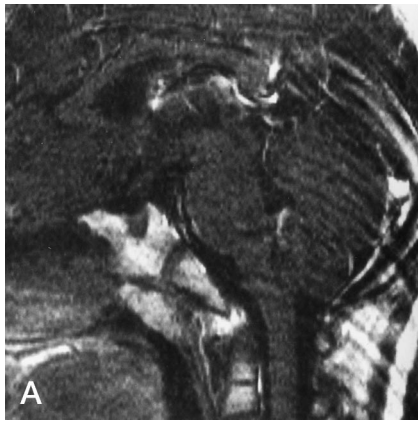
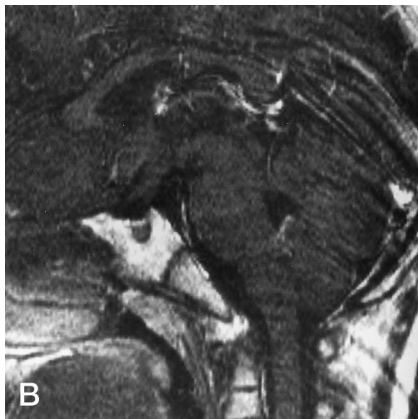


FIG 3. Case 5: Delayed pituitary enhancement in the second dynamic study.

A, The first dynamic image (150/15/1), 30 seconds after injection, shows faint enhancement only on the superior surface of the pituitary. No early enhanced posterior pituitary is shown, although cerebral veins are well enhanced.

B-D, On the second, third, and fourth dynamic images, 60, 90, and 120 seconds, respectively, after injection, the pituitary is gradually enhanced from its superior aspect. The pituitary has not completely enhanced even on the fourth dynamic study, indicating delayed pituitary enhancement.



Lymphocytic infundibuloneurohypophysitis is a newly described pituitary disorder in which lymphocytic inflammation confined to the hypothalamic-neurohypophysial system causes diabetic insipidus. In 1970, Saito et al (13) reported a case of diabetes insipidus caused by chronic lymphocytic inflammation in the neurohypophysis revealed at autopsy. Kojima et al (14) presented a similar case in 1989. In 1993, Imura et al (9) reported thickening of the pituitary stalk or enlargement of the neurohypophysis on MR images in patients with idiopathic diabetes insipidus. These abnormalities disappeared during follow-up. Biopsy samples revealed chronic inflammation, with infiltration of lymphocytes and plasma cells. Diabetes insipidus was thought to be caused by lymphocytic infundibuloneurohypophysitis, as detected on MR images. Lymphocytic infundibuloneurohypophysitis was thought to be a common cause of what was previously considered to be idiopathic diabetes insipidus (9). Lymphocytic infundibuloneurohypophysitis was differentiated from lymphocytic adenohypophysitis by the involvement of different areas. However, in 1996, Nishioka et al (15) reported two cases as a variant of lymphocytic infundibuloneurohypophysitis. In these cases, masses were not localized in the neurohypophysial system but involved the adenohypophysitis. Previously, lymphocytic hypophysitis was considered to affect the anterior lobe only. However, neurohypophysial dysfunction presenting as diabetes insipidus can be attributed either to direct inflammatory invasion or to destruction in lymphocytic hy-

pophysitis (1, 5, 16). Most case reports have described a homogeneously enhanced mass in pituitary hypophysitis. However, Ahmadi et al (17) reported the findings at contrast-enhanced MR imaging in five patients with lymphocytic hypophysitis, describing heterogeneous enhancement in three of the five. In our study, two patients had similar heterogeneous enhancement. Cavernous sinus involvement also occurs in this disease (18, 19), as seen in our cases 2 and 3. T2-weighted images depict this abnormality well, which appears as a region of low signal intensity. Our study also suggests that there are variations of localization in lymphocytic hypophysitis.

In 1993, we reported decreased vascularity of the posterior pituitary lobe in patients with idiopathic diabetes insipidus at dynamic MR imaging and demonstrated a relationship between the posterior pituitary function and its vascularity (10). However, the etiology of the decreased vascularity could not be determined. It was suggested that it could be due to congenital lack, to poor development of the posterior pituitary organ or arterial supply, or to secondary changes of vascular destruction. This study demonstrates progressively decreasing pituitary vasculature in patients with lymphocytic hypophysitis or infundibuloneurohypophysitis on follow-up dynamic MR studies, suggesting that decreased pituitary vasculature or lack of early enhancement of the posterior pituitary is due to secondary inflammatory change. The arteries may be destroyed first, followed by scarring, which contributes to both the delay and the

decrease in enhancement. Progression of the inflammatory changes leads to the destruction of the normal arterial supply of the posterior pituitary. In one case, the anterior pituitary showed vascular improvement while the posterior pituitary did not. The reason for the discrepancy may be that the posterior pituitary has a direct arterial supply, whereas the main blood supply to the anterior pituitary is via the portal system, flowing down from the stalk.

It has been reported that the endocrinologic abnormality in patients with lymphocytic infundibuloneurohypophysitis is limited to the posterior pituitary, except for growth hormone (9). However, in our cases, all anterior pituitary hormonal functions were insufficient except for adrenocorticotrophic hormone in case 4, which suggests that the inflammatory changes can affect the adenohypophysis also. This abnormality was detected only by the dynamic study. During the acute stage of inflammation, the conventional MR images showed the anatomic abnormality, such as pituitary enlargement or thickening of the stalk, but after regression of the disease, the abnormality was detectable only by the dynamic study.

### Conclusion

Recent advances in MR imaging techniques have provided new insights into the pathogenesis of pituitary disease, especially lymphocytic hypophysitis. In this study, we showed that follow-up dynamic MR studies can detect a destructive process of the hypophyseal vasculature even when conventional MR studies have shown a regression of the pituitary disease.

### Acknowledgments

We thank Satoko Kano and Kazumichi Onigata for assistance with data collection.

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