INTERNAL MEDICINE

□ CASE REPORT □

Transient Polyuria Related to Central Diabetes Insipidus Caused by Lymphocytic Infundibulo-neurohypophysitis in a Patient Treated for Graves' Disease

Masanori Yamazaki[1], Ai Sato[1], Shin-ichi Nishio[1], Takeshi Uehara[2] and Mitsuhisa Komatsu[1]

Abstract

A 45-year-old man was hospitalized because of weight loss, finger tremor, thirst, polydipsia and increased urinary frequency. He was diagnosed with Graves' disease (GD) and central diabetes insipidus (CDI). Magnetic resonance imaging revealed the enlarged posterior pituitary with thickened stalk. Histological examination obtained from biopsy of the pituitary revealed lymphocytic infundibulo-neurohypophysitis. He received treatment with thiamazole (MMI) for GD and desmopressin acetate (DDAVP) for CDI. However, DDAVP administration could be discontinued as GD was gradually improved. This course indicates that not only the recovered renal response to arginine-vasopressin but also the immunomodulative effects of MMI might attribute to the improvement of polyuria.

Key words: central diabetes insipidus, lymphocytic infundibulo-neurohypophysitis, Graves' disease

(Inter Med 49: 1885-1890, 2010)
(DOI: 10.2169/internalmedicine.49.3381)

Introduction

Lymphocytic hypophysitis (LYH), a rare chronic inflammatory disorder of the pituitary gland developed mainly by autoimmune processes, causes pituicyte destruction and hypopituitarism (1). LYH is usually classified in lymphocytic adenohypophysitis, which is characterized by lymphocytic infiltration limited to the anterior lobe of pituitary, and lymphocytic infundibulo-neurohypophysitis (LINH), which involves the infundibulum, stalk and neurohypophysis. LINH is much less common and causes central diabetes insipidus (CDI) manifested as thirst, polydipsia and polyuria (2). Here we describe an interesting case in which polyuria caused by LINH was improved and desmopressin acetate (DDAVP) administration was discontinued during the treatment of Graves' disease (GD).

Case Report

A 45-year-old man presented with weight loss (10 kg/1.5 months), finger tremor, thirst, polydipsia and increased urinary frequency. He was 164 cm tall and weighed 52 kg. His body temperature was 36.5℃; pulse rate, 96 beats a minute, regular; and blood pressure, 106/91 mmHg. He had diffuse goitor. General laboratory data revealed low-grade hyperbilirubinemia, elevated liver transaminases, and hyperuricemia (Table 1). Rheumatoid factor and anti-nuclear antibody were positive, but there were no physical findings suggestive of rheumatoid arthritis or collagen diseases. The specific gravity of urine in early morning was low. Endocrinological examination showed increased levels of thyroid hormones and completely suppressive secretion of TSH, indicating primary hyperthyroidism. Serum levels of TSH receptor antibody (TRAb) and thyroid stimulating antibody (TSAb) were elevated (Table 2). Ultrasonographic study revealed diffuse swollen thyroid with hypervascularity. These findings were compatible with GD. Measurement of serum or urine osmolarity by cryoscopic method and arginine-vasopressin (AVP) by AVP RIA kit (Mitsubishi Chemical Medience Co., Tokyo) also revealed impaired secretion of AVP and lower urine osmolarity than serum in the early morning, thus sus-

[1]Department of Aging Medicine and Geriatrics, Division of Medicine, Institute on Aging and Adaptation, Shinshu University Graduate School, Matsumoto and [2]Department of Laboratory Medicine, Shinshu University School of Medicine, Matsumoto
Received for publication January 13, 2010; Accepted for publication April 26, 2010
Correspondence to Dr. Masanori Yamazaki, macha@shinshu-u.ac.jp

Table 1. Laboratory Data on Admission

Complete blood count			Chloride	106	mmol/L
White blood cells	6190	/μL	Calcium	9.8	mg/dL
Neutrophils	65	%	Phosphorus	3.6	mg/dL
Monocytes	11	%	Total cholesterol	216	mg/dL
Eosinophils	8	%	HDL-cholesterol	53	mg/dL
Basophils	1	%	Triglycerides	117	mg/dL
Lymphocytes	15	%	FBG	88	mg/dL
Red blood cells	5.22	$\times 10^6$/μL	HbA1c	5.0	%
Hb	16.1	g/dL	ACE	15.7	U/L
Hematocrit	47.8	%	***Serology***		
Platelets	21.0	$\times 10^4$/μL	ESR	1	mm/hr
Urinalysis			IgG	890	mg/dL
Specific gravity	1.005		IgM	29	mg/dL
glucose	−		CRP	0.03	mg/dL
protein	−		RF	2+	
occult blood	−		ANA	×40	
Blood chemistry			***Tumor markers***		
Total bilirubin	1.38	mg/dL	AFP	5.7	ng/mL
Direct	0.23	mg/dL	HCG-β	< 0.2	ng/mL
ALT	8	U/L	***Cerebrospinal fluid***		
AST	33	U/L	Cell count	8/3	
LDH	146	U/L	IgG	2.8	ng/dL
ALP	291	U/L	Total protein	44	g/dL
γ-GTP	39	U/L	Glucose	66	mg/dL
Total protein	6.5	g/dL	LDH	17	U/L
Albumin	4.0	g/dL	HCG-β	< 0.2	ng/mL
Urea nitrogen	8.0	mg/dL	AFP	0.9	ng/mL
Creatinine	0.65	mg/dL	Herpes simplex virus-IgG	6	G.I.
Sodium	145	mmol/L	Varicella-zoster virus-IgG	< 1	G.I.
Potassium	4.3	mmol/L	Mumps-IgG	< 0.2	G.I.

ALT: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenese, ALP:alkaline phosphatase, γ-GTP: γ-glutamyl transpepetidase, FBG: fasting blood glucose, ACE: angiotensin converting enzyme, ESR: erythrocyre sedimentation rate, IgG: immunoglobulin G, IgM: immunoglobulin M, CRP: C-reactive protein, RF: rheumatoid factor, ANA: anti-nuclear antibodies, AFP: alpha-fetoprotein, HCG-β: human chorionic gonadotropin-β

Table 2. Endocrinological Data on Admission

GH	1.3	ng/mL	ACTH (early morning)	69.3	pg/mL
IGF-I	266	ng/mL	Aldosterone	169.2	pg/mL
Prolactin	12.1	ng/mL	PRA	7.7	ng/mL/hr
T3	369.2	ng/dL	LH	13.4	mIU/mL
T4	14.9	μg/dL	FSH	9.7	mIU/mL
TBG	15.3	μg/mL	Total testosterone	14.9	ng/mL
TSH	< 0.01	μIU/mL	Serum osmolarity	294	mOsm/kg
Thyroglobulin	353.8	ng/mL	Urine osmolarity	216	mOsm/kg
TRAb	29.5	%	AVP	0.49	pg/mL
TSAb	434	%	Anti-pituitary cytosol antibody	−	
Cortisol (early morning)	19.4	μg/dL			

GH: growth hormone, IGF- I: insulin-like growth factor- I, T3: tri-iodothyronine, T4: thyroxine, TBG: thyroxine binding globulin, TSH: thyroid stimulating hormone, TRAb: TSH receptor antibody, TSAb: thyroid stimulating antibody, ACTH: adrenocorticotropic hormone, PRA: plasma renin activity, LH: luteinizing hormone, FSH: follicle stimulating hormone, AVP: arginine-vasopressin

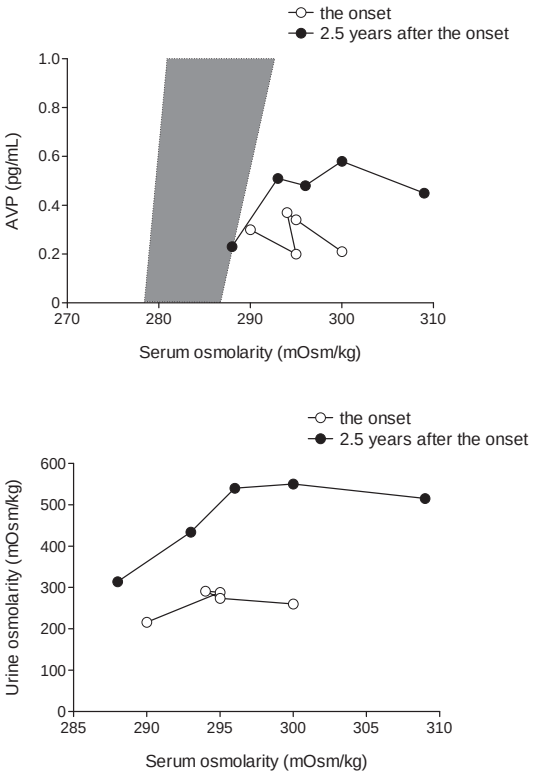

Figure 1. Hypertonic saline infusion test. AVP secretion and an increase in urinary osmolarity were abnormal at the onset of polyuria, but they were partially recovered and stabilized 2.5 years later. The shaded area shows normal range of AVP secretion responding to serum osmolarity.

pective of CDI (Table 2). The first 5% of hypertonic saline infusion test showed that AVP secretion was markedly reduced in spite of high serum osmolarity (Fig. 1). Intranasal DDAVP administration thereafter resulted in rapid elevation of urinary osmolarity (data not shown). Anti-pituitary cytosolic antibodies were negative. Secretion of hormones from the anterior pituitary was within normal range. Pituitary magnetic resonance imaging detected thickness of the pituitary stalk which deviated viscerally and swelling of the pituitary with indistinct high intensity signals of the posterior lobe on T1-weighted image. Posterior pituitary enhancement was also found, but not delayed (Fig. 2). For a reliable diagnosis, biopsy of the pituitary was performed. Macroscopically the pituitary was slightly swollen and the posterior lobe was relatively fibrous. Microscopically, fibrosis clarified with Azan stain was increased in the posterior pituitary. Pituicytes identified by immunostaining of glial fibrillary acidic protein (GFAP) were destroyed, and only a few barely remained. Neurons which are neurofilament-positive were also few. Inflammatory cells, mainly composed of lymphocytes, were highly infiltrated. The infiltration was partly in the anterior lobe and dura mater. No lymph follicle or granuloma formation was detected. Moreover, there was no atypicality or abnormal cellularity of infiltrated lymphocytes. CD3-positive cells were diffusely spread and CD20-positive cells were found in the region of follicle formation (Fig. 3). These histological findings were consistent with typical LINH. The clinical course is shown in Fig. 4. Therapy of GD was started with 30 mg/day of thiamazole (methimazole, MMI). After normalization of thyroid function, 100 μg of levothyroxine sodium was also given for the purpose of block and replacement therapy. MMI was gradually tapered off to 5 mg/day as TRAb titers were lowered. For CDI, 5 μg/day of DDAVP was also administered, resulting in decreasing urine volume to about 1.5 L/day. Treatment of LINH with glucocorticoid was not chosen because there were no symptoms resulting from the mass effect such as visual impairment, headache, or disorder in pituitary-adrenal axis. Around 1.5 years after the start of treatment of GD, the patient complained of reduced urine volume (approximately 1 L/day). Although the dose of DDAVP was gradually decreased, serum sodium concentrations were sometimes below 140 mmol/L. The administration of DDAVP was finally discontinued one year after his complaint. Neither adrenal failure nor morphological improvement of the pituitary on MRI was found. The second hypertonic saline infusion test 2.5 years after the onset of polyuria revealed that AVP secretion responding to elevated serum osmolarity seemed to be slightly recovered and stabilized although the response was still within impaired secretary range (Fig. 1). He has not received administration of DDAVP for about 5 years although the treatment of GD with MMI is continued.

Discussion

The pathogenesis of LINH still has not been elucidated. Histologically, lymphocytes, most of which consist of T cells, are diffusely infiltrated with scattered plasma cells, eosinophils, neutrophils and histiocytes in the posterior pituitary (3, 4). Allergic reactions to immunocomplex deposition in the small vessels and interstitial tissues are also supposed (4). In some cases, autoantibodies to AVP-secreting hypothalamic cells have been associated with the development and progression of the disease (5). Imura et al. (6) reported that the abnormalities in the pituitary stalk and/or neurohypophysis were observed on MRI only in the patients who had manifested CDI for less than 2 years and they improved during the follow-up. A case report of transient CDI due to LINH noted that inflammation might be limited within the infundibulum and might not involve the hypothalamic nuclei as a mechanism of the partial remission (7). However, LINH is not always self-limited and can progress from inflammation to fibrosis and atrophy. In a previous case report, progression to chronic hypophysitis with granuloma formation was described (8). In a review, LINH was not resolved spontaneously in any of the patients (2). The natural course of this disorder remains unclarified.

Autoimmune thyroid diseases can develop in the patients with LYH. Hashimoto's thyroiditis was mainly seen in 7.4% of total LYH patients, while GD appeared in 1.6% of them (2). Therefore the coexistence of GD with LYH is

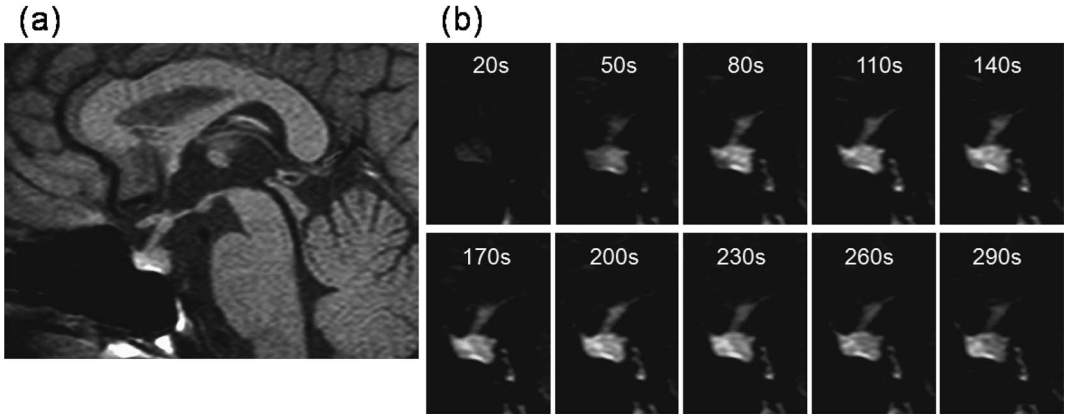

Figure 2. **Pituitary MRI. (a) The posterior pituitary was swollen and the thickened stalk was deviated viscerally. (b) Enhancement of the posterior pituitary was also detected. The serial images were obtained at the indicated seconds (s) after Gd-DTPA injection.**

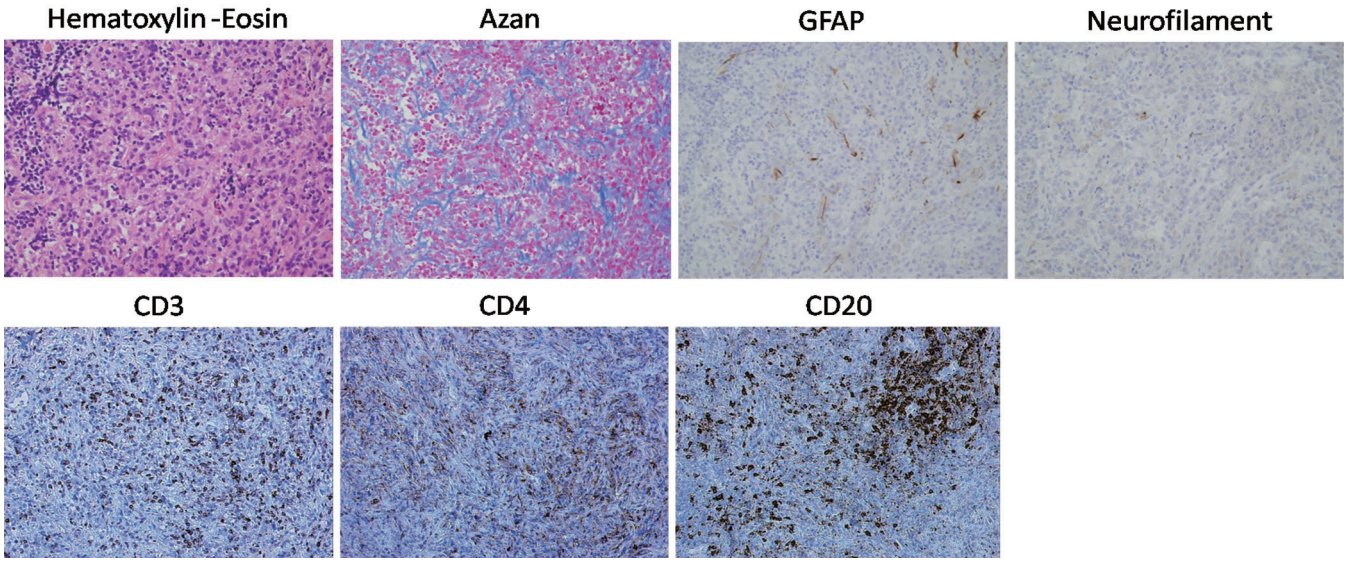

Figure 3. **Histology of the posterior pituitary. Azan stain demonstrated that fibrosis was noticeable. GFAP or neurofilament immunoreactivities suggested the involvement of pituicytes or neurons, respectively. T cells (CD3 positive) were diffusely spread and B cells (CD20-positive) formed colonies. Plasma cells and eosinophils were also scattered.**

rare. Some cases of LYH in the patients with GD have been reported (9-11).

The present case showed an interesting natural course in that polyuria related to LINH was improved and the administration of DDAVP was discontinued in a patient with GD which developed almost simultaneously. The recovery of renal sensitivity to AVP, which means the recovery from a "washout" of the renal medullary concentrating gradient caused by the water dieresis due to AVP deficiency, might be associated with the improvement of polyuria from the result that urine osmolarity was elevated despite of impaired AVP secretion in the hypertonic saline infusion test at the time of the remission of polyuria, Down-regulation of collecting tubule aquaporin-2 (AQP2) water channel is also supposed in the AVP-deficient state (12). It is known that prostaglandin E2 (PGE2) increases the retrieval of AQP2 from the membrane fraction to the intracellular fraction, thereby counteracting the action of AVP and that nonsteroidal anti-inflammatory drugs such as indomethacin enhance the shuttling of AQP2 by inhibition of prostaglandin E2 (PGE2) production (13, 14). Considering the potential of PGE2 inhibition of MMI, MMI may affect the remission of polyuria directly, resulting in assisting AVP action (15). However, the dose reduction of DDAVP was parallel to the remission of GD. In addition, fibrosis of the posterior pituitary was not complete and the hypothalamus might be intact based on findings of MRI although immunostaining was not performed with anti-AVP or anti-neurophysin antibody. Therefore, as another cause of the improvement of polyuria, it cannot be completely denied that AVP secretion respond-

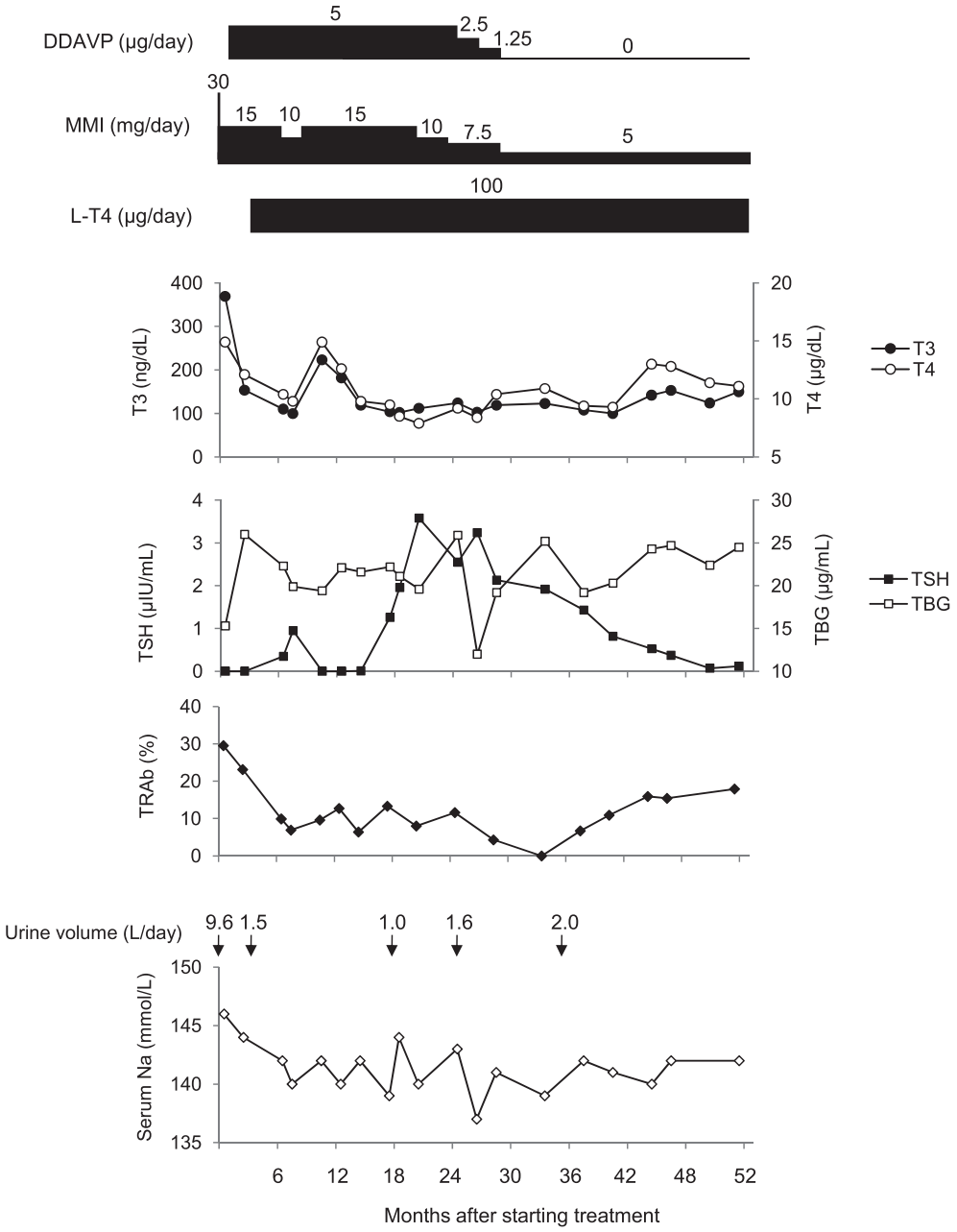

Figure 4. **Clinical course. The dose of DDAVP was gradually reduced as thyroid function was normalized and TRAb titers were decreased with MMI.**

ing to plasma osmolarity was slightly recovered or stabilized by some immunomodulation although AVP secretion was still within impaired range. Antithyroid drugs have the potential of immunomodulation. In patients taking them, both intracellular adhesion molecules 1 and soluble receptors of interleukin-2 or interleukin-6, decrease with reduction of TRAb. The drugs can also induce apoptosis of intrathyroidal lymphocytes and a decrease in HLA class II expression in thyroid follicular cells (16). It is noteworthy that MMI prevented induction or progression of the autoimmune diseases including experimental systemic lupus erythematosus and experimental autoimmune myocarditis in rodent models (17, 18). Therefore, in the present case MMI might have also induced immunomodulation directly or indirectly via the improvement of GD. Detailed immunological analysis is needed through case accumulation.

References

1. Molitch ME, Gillam MP. Lymphocytic hypophysitis. Horm Res **68** (Suppl 5): 145-150, 2007.
2. Caturegli P, Newschaffer C, Olivi A, Pomper MG, Burger PC, Rose NR. Autoimmune hypophysitis. Endocr Rev **26**: 599-614, 2005.
3. Rivera JA. Lymphocytic hypophysitis: disease spectrum and approach to diagnosis and therapy. Pituitary **9**: 35-45, 2006.
4. Waki K, Yamada S, Ozawa Y, Seki K, Endo Y. A case of lymphocytic infundibuloneurohypophysitis: histophathological studies. Pituitary **1**: 285-290, 1999.
5. Caturegli P, Lupi I, Landek-Salgado M, Kimura H, Rose NR. Pi-

tuitary autoimmunity: 30 years later. Autoimmun Rev **7**: 631-637, 2008.

6. Imura H, Nakao K, Shimatsu A, et al. Lymphocytic infundibuloneurohypophysitis as a cause of central diabetes insipidus. N Engl J Med **329**: 683-689, 1993.

7. Takahashi M, Otsuka F, Miyoshi T, Ogura T, Makino H. An elderly patient with transient diabetes insipidus associated with lymphocytic infundibulo-neurohypophysitis. Endocr J **46**: 741-746, 1999.

8. Amagasa M, Yuda F, Kojima H, Noshita N, Sato S. Natural course of lymphocytic infundibuloneurohypophysitis. Clin Neuropathol **20**: 229-232, 2001.

9. Yamamoto M, Murakami Y, Nishiki M, Kato Y. A case of autoimmune hypophysitis associated with Graves' disease. Endocr J **49**: 583-587, 2002.

10. Bayram F, Keleştimur F, Oztürk F, Selçuklu A, Patiroğlu TE, Beyhan Z. Lymphocytic hypophysitis in a patient with Graves' disease. J Endocrinol Invest **21**: 193-197, 1998.

11. Lidove O, Piette JC, Charlotte F, Cassoux N, Correas JM, Papo T. Lymphocytic hypophysitis with lachrymal, salivary and thyroid gland involvement. Eur J Intern Med **15**: 121-124, 2004.

12. Verbalis JG. Management of disorders of water metabolism in patients with pituitary tumors. Pituitary **5**: 119-132, 2002.

13. Zelenina M, Christensen BM, Palmér J, Nairn AC, Nielsen S, Aperia A. Prostaglandin E(2) interaction with AVP: effects on AQP2 phosphorylation and distribution. Am J Physiol Renal Physiol **278**: F388-F394, 2000.

14. Kim SW, Kim JW, Choi KC, et al. Indomethacin enhances shuttling of aquaporin-2 despite decreased abundance in rat kidney. J Am Soc Nephrol **15**: 2998-3005, 2004.

15. Lagorce JF, Moulard T, Rousseau A, Comby F, Buxeraud J, Raby C. Anti-inflammatory action of methimazole. Pharmacology **55**: 173-178, 1997.

16. Cooper DS. Antithyroid drugs. N Engl J Med **352**: 905-917, 2005.

17. Singer DS, Kohn LD, Zinger H, Mozes E. Methimazole prevents induction of experimental systemic lupus erythematosus in mice. J Immunol **153**: 873-880, 1994.

18. Song BC, Matsui S, Zong ZP, Katsuda S, Fu ML. Methimazole interferes with the progression of experimental autoimmune myocarditis in rats. Autoimmunity **34**: 265-274, 2001.