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A Case of Isolated ACTH Deficiency Who Developed Autoimmune-Mediated Hypothyroidism and Impaired Water Diuresis during Glucocorticoid Replacement Therapy

Yo KAGEYAMA

Department of Internal Medicine, Tochigi National Hospital, 1–10–37 Nakatomatsuri, Utsunomiya 320–8580, Japan

Abstract. A case of isolated ACTH deficiency who developed autoimmune-mediated hypothyroidism and still showed impaired water diuresis during glucocorticoid replacement therapy is reported. A 45-year-old woman was initially admitted for nausea, vomiting, and general malaise. Her serum sodium and plasma osmolality, ACTH and cortisol values were low, but her urine osmolality was high. Other pituitary hormone levels, thyroid hormone levels, and a computed tomogram of the pituitary gland were normal. The patient was treated with hydrocortisone and followed in the outpatient clinic; however, she was lost to follow up 18 months after admission. Three years later she presented with hypoglycemia and hyponatremia. Her serum or plasma ACTH, FT3, FT4, cortisol levels were low and her serum TSH level was high. Pituitary stimulation tests revealed a blunted response of ACTH to CRH and an exaggerated response of TSH to TRH. Plasma ADH was inappropriately high, and a water-loading test revealed impaired water diuresis and poor suppression of ADH. Although ADH was suppressed, impaired water diuresis was observed in the water loading test after hydrocortisone supplementation. Thyroxine supplementation completely normalized the water diuresis. Her outpatient clinic medical records revealed a gradual increase in TSH levels during follow up, indicating that she had developed hypothyroidism during glucocorticoid replacement therapy. The hyponatremia on the first admission was due to glucocorticoid deficiency, whereas the hyponatremia on the second admission was due to combined deficiencies of glucocorticoid and thyroid hormones.

Key words: Isolated ACTH deficiency, Hyponatremia, ADH, Autoimmune-mediated hypothyroidism

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ISOLATED ACTH deficiency is a rare cause of secondary adrenocortical insufficiency. Although in most cases the pathogenesis of isolated ACTH deficiency is uncertain, an autoimmune mechanism may be responsible, as suggested by the histological evidence of lymphocytic hypophysitis and by the frequent detection of anti-pituitary antibodies and association with other autoimmune disorders [1]. We describe a case of isolated ACTH deficiency associated with hypothyroidism due to autoimmune thyroiditis and hyponatremia due to impaired water diuresis. The impaired water diuresis was not improved by hydrocortisone replacement alone, but it was completely resolved after thyroxine supplementation. The hypothyroidism developed during replacement therapy with hydrocortisone for the preceding ACTH deficiency.

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Correspondence to: Yo KAGEYAMA, M.D., Department of Internal Medicine, Tochigi National Hospital, 1-10-37 Nakatomatsuri, Utsunomiya 320-8580, Japan

Materials and Methods

The following hormones and antibodies were measured by radioimmunoassay: insulin (Phadeseph Insulin RIA kit, Pharmacia), C-peptide (C-peptide RIA Shionogi kit II, Shionogi), aldosterone (Aldosterone RIA kit II, Dainabot), plasma renin activity (PRA) (Renin RIA kit II, Dainabot), cortisol (λ-coat Cortisol kit, Deid), free triiodothyronine (FT3)

(Amerlex-MAB FT3 kit, Amerlex), free thyroxine (FT4) (Amerlex-MAB FT4 kit, Amerlex), anti-thyroglobulin antibody (Tg Antibody kit, Eiken), anti-thyroid-peroxidase antibody (TPO Antibody kit, Eiken), and ADH (AVP RIA Mitsubishi, Mitsubishi). The following hormones were measured by immunoradiometric assay (IRMA), GH (GH kit, Daiichi), LH (SPAC-S LH kit, Daiichi), FSH (SPAC-S FSH kit, Daiichi), ACTH (ACTH II IRMA kit Mitsubishi, Mitsubishi), TSH (SPAC-S TSH kit, Daiichi) and PRL (SPAC-S Prolactin kit, Daiichi). Urinary free cortisol was measured by fluorescence polarization immunoassay with Dainabot cortisol kit (Dainabot). TSH receptor antibody was measured by radioreceptor assay with TRAB Cosmic II (Cosmic), and catecholamines were assayed by high-performance liquid chromatography.

Case Report

A 45-year-old woman was initially admitted to our hospital on December 27, 1994, because of nausea, vomiting, general malaise and poor appetite that she had first noted 10 days before. On admission, she was slightly drowsy, her body temperature was 35.4°C, pulse 78/min and regular, and blood pressure 84/64 mmHg. Her height was 160.4 cm, and she weighed 55.4 kg. The thyroid gland was not palpable, and the lungs, heart, and abdomen appeared normal. There was no peripheral edema or abnormal pigmentation. Axillary hair and pubic hair had been lost. The patient had menstruated 3 weeks before admission. Leukocyte count was 6300/mm^3, with 8.3% eosinophils. Serum sodium, potassium, and chloride values were 113, 4.8, and 79 mEq/l, respectively. Serum glucose, blood urea nitrogen, creatinine, and uric acid values were 72, 10, 0.3, and 2.6 mg/dl, respectively. Plasma osmolality was 243 mosm/l, but urine osmolality was 560 mosm/l. The results of chest and abdominal X-ray examinations were normal. Since the patient was admitted 2 days before the New Year's holidays, further examination could not be performed, and her serum and plasma samples were kept frozen for assay after the holidays. Based on the available data, intravenous administration of 500 ml saline supplemented with 40 ml of 10% sodium chloride solution and oral administration of demethylchlortetracycline hydrochloride 900 mg/day were started. Her serum sodium increased to 130 mEq/l on the 3rd hospital day and to 134 mEq/l on the 6th day. Her consciousness became normal, and her symptoms resolved as her serum sodium levels improved. Intravenous saline administration was discontinued on the 8th hospital day. Endocrinological laboratory studies on admission showed low serum or plasma levels of ACTH and cortisol. Her plasma ADH was 1.70 pg/ml, and was inappropriately high despite her low serum osmolality (Table 1). A computed tomography (CT) scan of the brain showed that the brain and especially the pituitary gland were normal. Oral hydrocortisone 20 mg/day was started, and demethylchlortetracycline hydrochloride was discontinued. The patient's serum sodium value became normal, and her urine osmolality decreased to 420–425 mosm/l. Since she refused further endocrinological testing, she was discharged on hydrocortisone 20 mg/day. The patient was followed in our outpatient clinic, and her serum sodium remained in the range 135–141 mEq/l. Follow-up in the outpatient clinic revealed gradually increasing TSH levels (Fig. 1). She continued to attend the outpatient clinic until June 1996, but was lost to follow-up thereafter.

Early in the morning of November 8, 1999, she was found to be confused and disoriented by her family, and was brought to our hospital by ambulance. She was lethargic, her blood pressure was 80/48 mmHg, pulse 90/min, and body temperature 35.5°C, but there were no abnormal physical findings except the consciousness disturbance. An emergency CT scan of the brain, electrocardiogram, and chest and abdominal X-ray films were normal. Because laboratory examination revealed a serum glucose value of 45 mg/dl, 50% glucose solution and 100 mg of hydrocortisone succinate were administered intravenously. The patient regained consciousness, but was admitted for further examination and treatment. She had been well after she discontinued medication in July 1996 and had entered menopause in early 1998. On admission, her serum sodium, potassium, and chloride were 120, 3.8 and 85 mEq/l, and serum blood urea nitrogen, creatinine, and uric acid were 23, 0.6, and 2.1 mg/dl, respectively. Plasma and urine osmolality was 250 mOsm/l and 566 mOsm/l, respectively. Intravenous administration of 500 ml of saline supplemented with 40 ml of

Table 1. Endocrinological data on the first and second admission

	First admission	Second admission
ACTH	<5 pg/ml	<5 pg/ml
GH	8.21 ng/ml	3.93 ng/ml
LH	18.8 mIU/ml	12.8 mIU/ml
FSH	44.9 mIU/l	35.4 mIU/ml
PRL	14.9 ng/ml	10.0 ng/ml
Free triiodothyronine	3.0 pg/ml	2.3 pg/ml
Free thyroxine	1.4 ng/ml	0.9 ng/dl
TSH	3.3 μU/ml	19.1 μU/ml
Anti-thyroid receptor antibody	Not examined	−5.2%
Anti-thyroglobulin antibody	Not examined*	6.5 U/ml***
Anti-thyroid peroxidase antibody	Not examined**	1.2 IU/ml****
Plasma renin activity	0.6 ng/ml/hr	0.9 ng/ml/hr
Aldosterone	7.1 ng/dl	4.6 ng/dl
Cortisol	3.1 μg/dl	1.5 μg/dl
Insulin-like immunoreactivity	Not examined	6 μU/ml
C peptide-like immunoreactivity	Not examined	2.3 ng/ml
Epinephrine	Not examined	<0.01 ng/ml
Norepinephrine	Not examined	0.68 ng/ml
ADH	1.70 pg/ml	2.29 pg/ml
Urinary cortisol excretion	Not examined	1.4 μg/day
Urinary aldosterone excretion	Not examined	0.8 μg/day
Urinary-C-peptide-like Immunoreactivity excretion	Not examined	40 μg/day

*, ***: Antithyroglobulin antibody (hemagglutination method) was negative, **, ****: antimicrosome antibody (hemagglutination method) was negative.

10% sodium chloride solution was started, and the patient's serum sodium became normal 4 days after treatment. Endocrinological examination on admission showed low serum or plasma levels of ACTH, FT3, FT4, cortisol, low urinary cortisol excretion, and high serum levels of TSH, anti-thyroglobulin antibody, and anti-thyroid-peroxidase antibody. Her plasma ADH was 2.29 pg/ml, and was inappropriately high despite her low plasma osmolality (250 mosm/l) (Table 1). Antithyrogloblin antibody (hemagglutination method) and antimicrosome antibody (hemagglutination method) were negative. No abnormal findings, such as tumor or empty sella, were found on a CT scan or magnetic resonance image of the pituitary gland. Dynamic tests for pituitary hormones secretion in response to combined stimulation with CRH, TRH, LH-RH and GRH revealed a blunted response of ACTH, exaggerated response of TSH and normal responses of PRL, LH, FSH and GH, while secretion of aldosterone and cortisol after ACTH stimulation were normal (Fig. 2). Water loading tests were performed before, and 10 days after hydrocortisone 20 mg/day replacement, and her body weight was 50 kg (Table 2). After hydrocortisone replacement her thyroid hormone levels became normal: FT3 2.6 pg/ml, FT4 1.1 ng/dl, TSH 1.3 μU/ml. The water loading test before glucocorticoid replacement showed that she excreted only 25% of the water load, and that her urine osmolality remained high; her plasma ADH was not suppressed despite the decrease in serum osmolality, and free water clearance was negative throughout the examination. The water loading test after glucocorticoid replacement showed suppression of ADH in accordance with the decrease in serum osmolality, and improvement of urine excretion to 39% of the water load; however, the urine osmolality was higher than that of the plasma, and free water clearance was negative except for the final 30-min period. Levothyroxine 100 μg/day was given, and the water loading test was performed 10 days later. After levothyroxine and hydrocortisone replacement, her

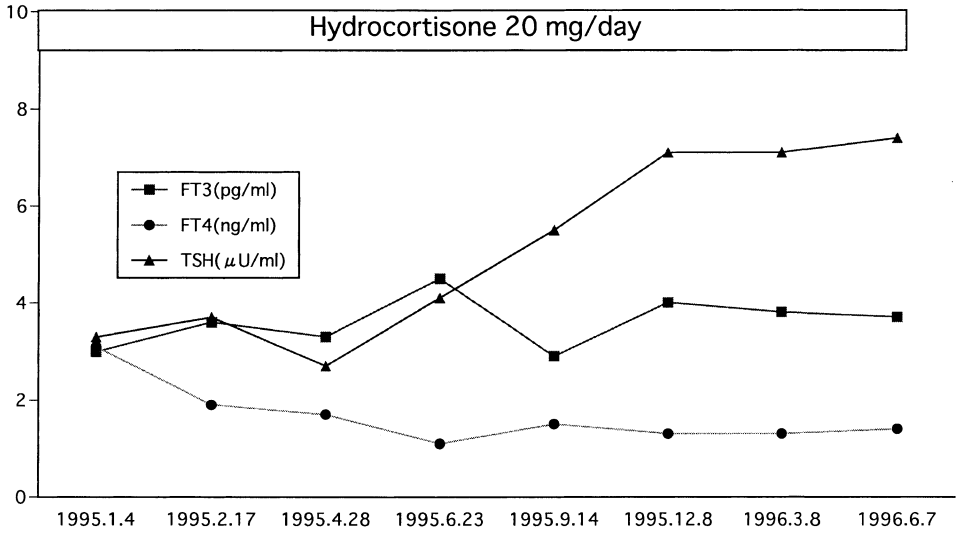

Fig. 1. Changes in patient's TSH and thyroid hormone levels during 1995–1996.

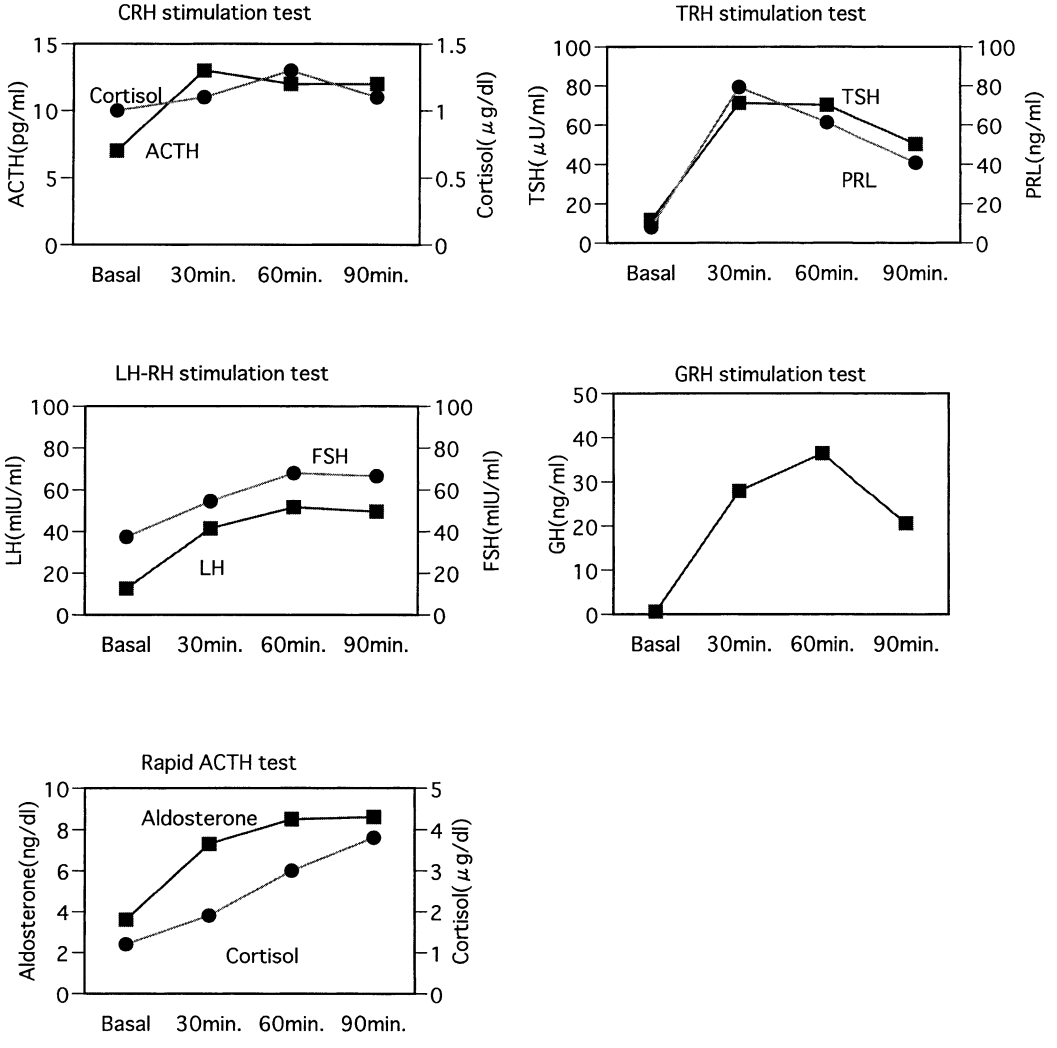

Fig. 2. Dynamic tests for secretion of pituitary and adrenal hormones.

Table 2. Water loading test

1. Before replacement

	UV (ml)	Na (mEq/l)	ADH (pg/ml)	Posm (mOsm/l)	Uosm (mOsm/l)	C_{H2O} (ml/min)
Basal		140	2.39	297	760	
0900–0930 h	10			292	755	−0.5
0930–1000 h	10	136	1.89	287	750	−0.5
1000–1030 h	10			285	735	−0.5
1030–1100 h	20	134	1.76	283	720	−1.1
1100–1130 h	40			282	716	−2
1130–1200 h	60	132	1.54	280	711	−3.1
1200–1230 h	50			275	538	−1.6
1230–1300 h	50	130	1.50	270	365	−0.6
Total	250					

2. After hydrocortisone 20 mg/day replacement

	UV (ml)	Na (mEq/l)	ADH (pg/ml)	Posm (mOsm/l)	Uosm (mOsm/l)	C_{H2O} (ml/min)
Basal		142	1.14	295	744	
0900–0930 h	25			290	696	−1.1
0930–1000 h	35	136	0.87	285	681	−1.7
1000–1030	30			284	667	−1.3
1030–1100 h	30	135	0.81	282	653	−1.3
1100–1130 h	30			281	646	−1.3
1130–1200 h	40	134	0.77	281	638	−1.6
1200–1230 h	70			281	443	−1.3
1230–1300 h	140	134	0.53	281	248	0.6
Total	390					

3. After hydrocortisone 20 mg/day and levothyroxine 100 μg/day replacement

	UV (ml)	Na (mEq/l)	ADH (pg/ml)	Posm(mOsm/l)	Uosm(mOsm/l)	C_{H2O} (ml/min)
Basal		141	2.02	292	720	
0900–0930 h	30			288	675	−1.3
0930–1000 h	30	137	1.15	283	630	−1.2
1000–1030 h	50			280	457	−1.1
1030–1100 h	60	136	0.91	276	283	−0.1
1100–1130 h	150			279	207	1.3
1130–1200 h	250	137	0.53	282	130	4.5
1200–1230 h	200			284	120	3.9
1230–1300 h	200	138	0.48	286	110	4.1
Total	970					

Serum and urine samples were obtained at the end of each period.

thyroid hormones were FT3 2.8 pg/ml, FT4 1.4 ng/ml, and TSH 2.9 μU/ml. When she excreted 97% of the water load, urine osmolality became lower than plasma osmolality 2 hours after water loading, and plasma ADH was suppressed as the plasma osmolality decreased.

Discussion

The patient presented with drowsiness due to hyponatremia on the first admission and consciousness disturbance due to hyponatremia and hypoglycemia on the second admission, and her clinical course and physical findings (loss of pubic

and axillary hair and episodes of hypoglycemia) strongly suggested a diagnosis of glucocorticoid deficiency. Her plasma ACTH and cortisol levels were low, but the levels of other pituitary hormones were normal. Although pituitary stimulation tests could not be performed during the first admission, a blunted response of ACTH to CRH was confirmed during the second admission, and the diagnosis of ACTH deficiency was confirmed. Secondary adrenocortical insufficiency due to ACTH deficiency impairs cortisol and adrenal androgen secretion but not aldosterone secretion. The usual symptoms are malaise, loss of energy, anorexia, weight loss, postural hypotension, orthostatic dizziness, and sometimes headache. Women tend to lose pubic and axillary hair and have decreased libido. Severe cortisol deficiency may result in hypoglycemia and hyponatremia [1].

Since the first report by Steinberg *et al.* [2], isolated ACTH deficiency has been increasingly associated with various autoimmune diseases, such as primary hypothyroidism due to autoimmune thyroiditis [3–11], Graves' disease [12], polyglandular failure [5, 9, 13], insulin-dependent diabetes mellitus [13], and autoimmune hypophysitis [10, 14]. These results strongly suggest that autoimmune mechanisms play important roles in the pathogenesis of isolated ACTH deficiency. Autoimmune thyroiditis has been the most common autoimmune disease associated with isolated ACTH deficiency, and it has been demonstrated histologically in all of the cases reported [5, 6, 9, 10, 11], or by the presence of thyroid autoantibodies [4, 7, 8]. Cortisol deficiency can also directly affect thyroid function [15, 16], and chronic glucocorticoid deficiency may impair the thyroid response to endogenous TSH or directly promote secretion of thyroid hormone [17–19]. However, in the present case, the low serum levels of thyroid hormones, increased serum TSH, presence of thyroid autoantibodies and exaggerated response of TSH to TRH suggest that the hypothyroidism was probably due to autoimmune thyroiditis. The autoimmune-mediated hypothyroidism in the present case developed during glucocorticoid replacement therapy (Fig. 1). Since antithyroglobulin antibody and antithyroid peroxidase antibody were not tested during the first admission, and antithyroglobulin antibody (hemagglutination method) and antimicrosome antibody (hemagglutination method) were negative during both admissions, we could not rule out the possibility that autoimmune thyroiditis had already been present during the first admission. In cases of isolated ACTH deficiency or adrenal glucocorticoid deficiency associated with autoimmune-mediated hypothyroidism, physiological doses of glucocorticoid have been variously reported to improve [20, 21] or not to improve thyroid function [7, 16, 17]. The development of autoimmune-mediated hypothyroidism during glucocorticoid replacement therapy in isolated ACTH deficiency is quite rare, and only two cases have been reported to date [3, 5]. Accumulation of similar cases will be needed to explore the mechanisms of this response and development of hypothyroidism following glucocorticoid replacement therapy in adrenal insufficiency.

Our patient developed hyponatremia with high urinary osmolality in the presence of hyponatremia, and serum hypoosmolality was observed. Despite the hyponatremia and serum hypoosmolality, the serum level of ADH was inappropriately high, indicating that free water generation was impaired. Impaired free water generation was confirmed by a water-loading test during the second admission. However, despite the improvement in thyroid hormone levels after glucocorticoid replacement therapy, the impaired water excretion persisted and the patient excreted only 39% of the water load in the second water load test. It has been reported that the thyroid hormone levels of patients with isolated ACTH deficiency complicated by autoimmune-mediated hypothyroidism do not return to normal levels when glucocorticoid replacement is provided [7, 15]. As long as the patient had impaired water excretion, she had the possibility of developing hyponatremia, and for that reason levothyroxine was administered and the water loading test was performed. Since her water excretion became normal after levothyroxine supplementation, the pathogenesis of the development of hyponatremia in the first and the second admissions seems to have been different. The above findings suggest that the hyponatremia on the first admission was due to glucocorticoid deficiency, whereas the hyponatremia on the second admission was due to a combination of glucocorticoid and thyroid hormone deficiencies. Glucocorticoids have been found to act directly on the hypothalamus and tonically inhibit ADH release

by magnocellular neurosecretory neurons [22], and plasma ADH has been found to increase in glucocorticoid deficiency [23]. These findings suggest that sustained and nonsuppressive ADH secretion because of the glucocorticoid deficiency may have played a role in the pathogenesis of hyponatremia in the present case; however, that fails to fully explain the impaired water diuresis on the second admission. Although the patient's serum thyroid hormones normalized after hydrocortisone replacement, the fact that the impaired water diuresis became normal after thyroxine supplementation indicates that thyroid hormone deficiency was also responsible for the impaired water diuresis on the second admission. While the contribution of inappropriate secretion of ADH has been reported [24, 25], the mechanisms of impaired water diuresis in hypothyroidism are considered to be non-ADH dependent including a decrease in glomerular filtration rate [26, 27], a decrease in cardiac output [28], changes in renal tubular function [29], and decreased distal delivery of the filtered load in the kidney [30]. The mechanism responsible for the impaired water diuresis observed in our case after hydrocortisone replacement is unclear, because we did not investigate whether she had the abnormalities described above. Montenegro *et al.* [31] reported that impaired water diuresis corrected by administration of thyroid hormone is frequently subtle and difficult to diagnose, because most patients have normal serum creatinine levels.

References

1. Thorner MO, Vance ML, Laws ER Jr, Horvath E, Kovacs K (1998) The anterior pituitary. In: Wilson JD, Foster DW, Kronenberg HM and Larsen PR (eds), Williams Textbook of Endocrinology, WB Saunders, Philadelphia, 249–340.
2. Steinberg A, Schechter FR, Segal HI (1954) True pituitary Addison's disease, A pituitary unitrophic deficiency. *J Clin Endocrinol* 14: 1519–1529.
3. Yamamoto T, Ogihara T, Miyai K, Kumahara Y, Hirata Y (1976) Co-existent primary hypothyroidism and isolated adrenal deficiency. *Acta Endocrinol (Copenh)* 82: 467–474.
4. Roosens B, Maes E, Van Steirteghem A, Vanhaelst L (1982) Primary hypothyroidism associated with secondary adrenocortical insufficiency. *J Endocrinol Invest* 5: 251–254.
5. Kojima I, Nejima I, Ogata E (1982) Isolated adrenocorticotropin deficiency associated with polyglandular failure. *J Clin Endocrinol Metab* 54: 182–186.
6. Horii K, Adachi Y, Aoki N, Yamamoto T (1984) Isolated ACTH deficiency associated with Hashimoto's thyroiditis: Report of a case. *Jap J Med* 23: 53–57.
7. Shigemasa C, Kouchi T, Ueta Y, Mitani Y, Yoshida A, Mashiba H (1992) Evaluation of thyroid function in patients with isolated adrenocorticotropin deficiency. *Am J Med Sci* 304: 279–284.
8. Escobar-Morreale H, Serrano-Gotarredona J, Varela C (1994) Isolated adrenocorticotropic hormone deficiency due to probable lymphocytic hypophysitis in a man. *J Endocrinol Invest* 17: 127–131.
9. Nagai Y, Ieki Y, Ohsawa K, Kobayashi K (1997) Simultaneously found transient hypothyroidism due to Hashimoto's thyroiditis, autoimmune hepatitis and isolated ACTH deficiency after cessation of glucocorticoid administration. *Endocrine J* 44: 453–458.
10. Richtsmeier AJ, Henry RA, Bloodworth JBM Jr, Ehrlich EN (1980) Lymphoid hypophysitis with selective adrenocorticotropic hormone deficiency. *Arch Intern Med* 140: 1243–1245.
11. Kamijo K, Kato K, Saito A, Kawasaki K, Suzuki M, Yachi A (1982) A case with isolated ACTH deficiency accompanying chronic thyroiditis. *Endocrinol Japon* 29: 183–189.
12. Stephens WP, Goddard KJ, Laing I, Adams JE (1985) Isolated adrenocorticotropin deficiency and empty sella associated with hypothyroidism. *Clin Endocrinol (Oxf)*: 22: 771–776.
13. Starke AAR, Valverde I, Bottazzo GF, Tsotsalas M, Zimmermann H (1983) Glucagon deficiency associated with hypoglycemia and the absence of islet cell antibodies in the polyglandular failure syndrome before the onset of insulin-dependent diabetes mellitus: a case report. *Diabetologia* 25: 336–339.
14. Sauter NP, Toni R, McLaughlin CD, Dyess EM, Kritzman J, Lechan RM (1990) Isolated adrenocorticotropin deficiency with an autoantibody to a corticotroph antigen that is not adrenocorticotropin or other proopiomelanocortin-derived peptides. *J Clin Endocrinol Metab* 70: 1391–1397.
15. Yoshida T, Arai T, Sugano J, Yarita H, Yanagisawa H (1983) Isolated ACTH deficiency accompanied by

'primary hypothyroidism' and hyperprolactinaemia. *Acta Endocrinol (Copen)* 104: 697–401.
16. Proto G, Bertolissi F (1988) Reversible hypothy roi-dism in idiopathic adrenal insufficiency. *J Endocrinol Invest* 11: 227.
17. Topliss DJ, White EL, Stockigt JR (1980) Significance of thyrotropin excess in untreated primary adrenal insufficiency. *J Clin Endocrinol Metab* 50: 52–56.
18. Barnett AH, Donald RA, Espeiner EA (1982) High concentration of thyroid-stimulating hormone in untreated glucocorticoid deficiency: indication of primary hypothyroidism? *Br Med J* 285: 172–173.
19. Nicoloff JT, Fisher DA, Appleman MD Jr (1970) The role of glucocorticoid in the regulation of thyroid function in man. *J Clin Invest* 49: 1922–1929.
20. Gharib H, Hodgson SF, Gastineau CF, Scholz DA, Smith LA (1972) Reversible hypothyroidism in Addison's disease. *Lancet* II: 734–736.
21. Candrina R, Giustna G (1987) Addison's disease and corticosteroid-reversible hypothyroidism. *J Endocrinol Invest* 10: 523–526.
22. Silverman AJ, Hoffman D, Gadde CA, Krey LC, Zimmermann EA (1981) Adrenal steroid inhibition of the vasopressin-neurophysin neurosecretion system to the median eminence of the rat. *Neuroendocrinology* 32: 129–133.
23. Linas SL, Berl T, Robertson GL, Aisenbery GA, Schrier RB, Anderson RJ (1980) Role of vasopressin in the impaired water excretion of glucocorticoid deficiency. *Kid Int* 18: 58–67.
24. Laczi F, Janaky T, Ivanyi T, Julesz J, Laszlo FA (1987) Osmoregulation of arginine-8-vasopressin secretion in primary hypothyroidism and in Addison's disease. *Acta Endocrinol (Copenh)* 114: 389–395.
25. Iwasaki Y, Oiso Y, Yamauchi K, Takatsuki K, Kondo K, Hasegawa H, Tomita A (1990) Osmoregulation of plasma vasopressin in myxedema. *J Clin Endocrinol Metab* 70: 534–539.
26. Allon M, Harrow A, Pasque CB, Rodriguez M (1990) Renal sodium and water handling in hypothyroid patients: The role of renal insufficiency. *J Am Soc Nephrol* 1: 205–210.
27. Ojamaa K, Balkman C, Klein IL (1993) Acute effect of triiodothyronine on arterial smooth muscle. *Ann Thorac Surg* 56: S61–S67.
28. Boykin J, De Torrente A, Erickson A, Robertson G, Schrier RW (1978) Role of vasopressin in impaired water excretion of glucocorticoid deficiency. *J Clin Invest* 62: 738–744.
29. Koide Y, Oda K, Shimizu K, Shimizu A, Nabeshima I, Kimura S, Maruyama M, Yamashita K (1982) Hyponatremia without inappropriate secretion of vasopressin in a case of myxedema coma. *Endocrinol Japon* 29: 363–368.
30. Deruberitis FR Jr, Michelis MF, Bloom ME, Mintz DH, Fields JB, Davis BB (1971) Impaired water excretion in myxedema. *Am J Med* 51: 41–53.
31. Montenegro J, Gonzalez O, Saracho R, Aguirre R, Gonzalez O, Martinez I (1996) Changes in renal function in primary hypothyroidism. *Am J Kid Dis* 27: 195–198.