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Four Patients with Polyendocrinopathy with Associated Pituitary Hormone Deficiency

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Abstract. Four cases of polyglandular endocrine disorders associated with pituitary hormone secretion failure are reported. Three of them had both insulin dependent diabetes mellitus (IDDM) and Hashimoto's disease. Each of these patients (cases 1–3) showed isolated deficiency of ACTH, TSH or gonadotropin, respectively. Another patient (case 4) had both Hashimoto's disease and isolated ACTH deficiency. Anti-pituitary antibody to AtT-20 cells was detected in case 1. Serum gamma-globulins from patients 1 and 4 attenuated corticotropin releasing hormone-induced ACTH release in monolayer cultured rat anterior pituitary cells. Gamma-globulins from patients 1 and 2 decreased baseline TSH release but stimulated baseline prolactin release in pituitary cell cultures. It is possible that pituitary hormone deficiency in these patients may be caused by autoimmune disorders.

Key words: IDDM, Hashimoto's disease, Isolated ACTH deficiency, TSH, Gonadotropin

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THE COEXISTENCE of multigland diseases was suggested as early as 1908 [1], and the clinical classification of polyglandular autoimmune syndrome (PGA) was first presented by Neufeld *et al.* in 1980 [2]. This syndrome was classified into three types by their classification. Type 1 is defined by the presence of at least two of the following diseases: chronic mucocutaneous candidiasis, acquired hyoparathyroidism, and idiopathic or autoimmune Addison's disease. Criteria for PGA Type II include Addison's disease plus autoimmune thyroid disease and/or insulin-dependent diabetes mellitus (IDDM). Patients with PGA Type III syndrome have autoimmune thyroid disease without Addison's disease but with at least one associated organ-specific autoimmune disease, such as IDDM or pernicious anemia.

Hypophysitis is also a component of the PGA syndrome, although rarely is the pituitary involved. Lymphocytic infiltration of the anterior hypophysitis was first correlated with hormone deficiencies in 1962 by Goudie and Pinkerton [3]. It has been suggested that some autoimmune disorders are at least partly involved in isolated ACTH deficiency and pregnancy-related hypophysitis [4–6]. PGA syndromes associated with isolated pituitary hormone (ACTH, GH or gonadotropin) secretion failure have been reported [7–9]. Here we report two patients with isolated ACTH deficiency, one patient with isolated TSH deficiency and one patient with gonadotropin deficiency associated with other autoimmune endocrine disorders. We examined the effects of these patients' gamma-globulins on ACTH, TSH and PRL release in rat anterior pituitary cell cultures.

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Materials and Methods

Anterior pituitary function test

Pituitary functions of the present patients were evaluated with a combined anterior pituitary function test consisting of an intravenous injection of corticotropin-releasing hormone (CRH) (CRF, 100 μg), growth hormone-releasing hormone (GRH) (GRF, 100 μg), TRH (500 μg) and LH-RH (100 μg). Blood samples were collected before and at 15, 30, 60 and 90 min after injection. Plasma ACTH and cortisol and serum GH, TSH, PRL, LH and FSH were measured with commercially available IRMA and RIA kits [ACTH-II IRMA kit (Mitsubishi Petrochemicals, Tokyo, Japan); AMEREX CORTISOL Kit (Amersham, Tokyo, Japan); Ab Bead HGH Kit (Eiken Chemical, Tokyo, Japan); TSH RIA BEAD II, PROLACTIN RIA BEAD (Dainabot, Tokyo, Japan); SPAC-S LH Kit and SPAC-S FSH Kit (Daiichi Radioisotope Lab., Tokyo, Japan), respectively]. In each case of isolated TSH or gonadotropin deficiency, the TRH test or LH-RH test was repeated after continuous daily administration of 500 μg TRH or 400 μg LH-RH for 6 days.

Preparation of cultured pituitary cells

Male Wistar rats weighing 200–250 g were decapitated. Their anterior pituitaries were removed immediately, minced into small pieces and placed in Hanks-HEPES buffer (pH 7.4). The pituitary cells were then dispersed with collagenase and cultured as described previously [10].

Gamma-globulin extraction

Five milliliters of plasma from each patient or control subject was diluted with the same volume of 0.01 M phosphate buffered saline. Twenty m*l* of saturated ammonium sulfate was then added to the diluted serum and mixed for 30 min. After keeping the mixture at room temperature for 30 min it was centrifuged at 1,200 ×g for 20 min at 16°C. The supernatant was decanted and a small amount of PBS was added to dissolve the sediment. The dissolved sediment was then placed into the dialysis membrane (Seamless Cellulose Tubing, 8/32", Union Carbide Corp, USA) and dialyzed against phosphate buffered saline for 24 h while being agitated gently in a cold room at 4°C. The residual gamma-globulin was then lyophilized.

Experiments with cultured cells

After 4 days of culture, the cells were washed twice with fresh DMEM and the gamma-globulin-containing DMEM was added to the cultured cells (final concentration, 2.5 mg/m*l*) with or without CRH (10 ng/m*l*) and incubated for 37°C. The ACTH concentration in the medium was measured with an immunoradiometric assay kit. TSH and PRL concentrations in the medium were measured with kits provided by NIDDM (Bethesda, USA). Synthetic human CRH was purchased from the Protein Foundation in Osaka, Japan. These materials were dissolved and diluted with DMEM immediately before use.

Statistical analyses

Data from culture experiments were evaluated statistically by analysis of variance followed by Duncan's multiple range test.

Case Presentation

Case 1

A 47-yr-old woman admitted to our clinic due to repeated syncope. Her early clinical course was once reported [11]. Briefly, in 1977 she was diagnosed as having IDDM for which she was given insulin therapy (approximately 40 U/day). She then serially developed relapsing polychondritis, Hashimoto's disease and secondary adrenal insufficiency from 1984 to 1987. Since then she has been treated with 10 mg/day of hydrocortisone. In August, 1991 she was readmitted due to pneumonia. At that time a combined anterior pituitary function test was performed. Plasma ACTH and cortisol did not respond, whereas serum GH, PRL and FSH responded normally, and TSH and LH were hyperresponsive (Fig. 1). Therefore, she was diagnosed as having isolated ACTH deficiency.

Case 2

A 37-yr-old man who was admitted due to general edema and ascites. His father had diabetes

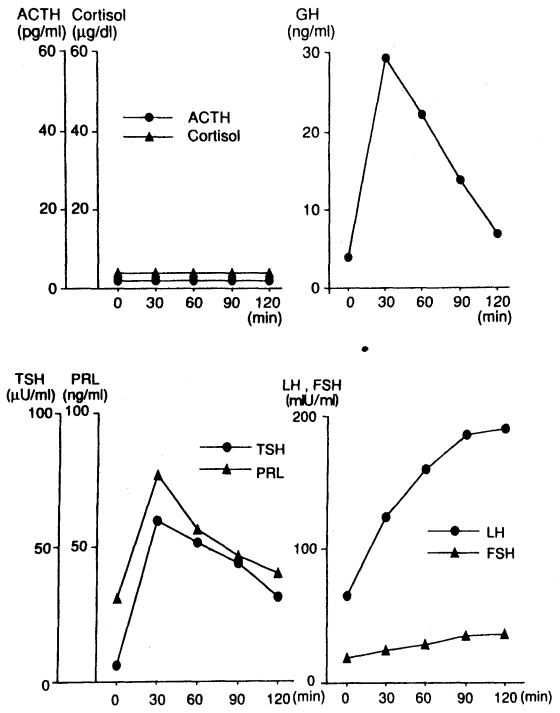

Fig. 1. Combined anterior pituitary function test in case 1 (IDDM + Hashimoto's thyroiditis + isolated ACTH deficiency) with CRH (100 μg), GRH (100 μg), TRH (500 μg) and LH-RH (100 μg).

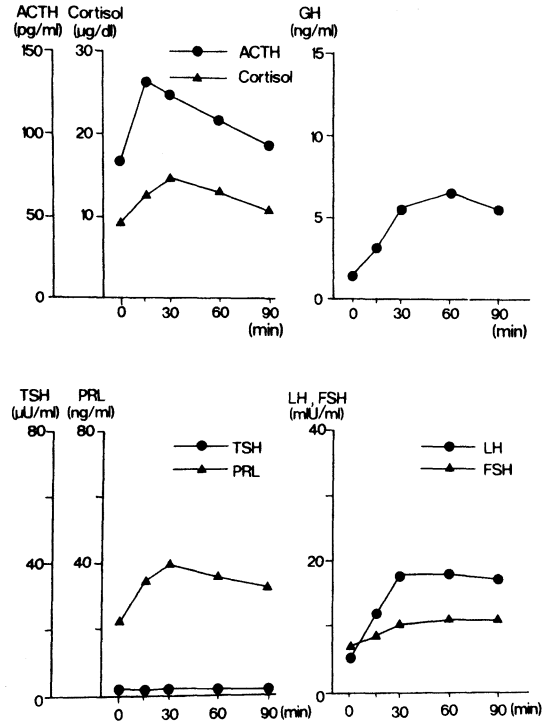

Fig. 2. Combined anterior pituitary function test in case 2 (slowly progressive IDDM + Hashimoto's thyroiditis + isolated TSH secretion failure) with CRH (100 μg), GRH (100 μg), TRH (500 μg) and LH-RH (100 μg).

mellitus and liver cirrhosis. His mother had Hashimoto's disease. In 1976 he complained of thirst and general malaise, was diagnosed as having diabetes mellitus and given an antihyperglycemic drug (Sulfonyl urea). In 1977 insulin therapy was started due to his impaired insulin secretion. In 1982 he was diagnosed as having diabetic retinopathy, and in 1988 he had proteinuria and was diagnosed as having diabetic nephropathy. In 1991 he was admitted to our clinic due to general malaise and edema. On admission his blood pressure was 220/116 mmHg. He had goiter but no lymph node swelling. Laboratory data are shown in Table 1. He was diagnosed as having nephrotic syndrome and chronic renal failure due to diabetic nephropathy. Hormonal examination revealed low urinary and serum CPR levels (Table 2). The plasma ACTH level was high but the cortisol level was normal. Serum TSH, T_3, free T_3, and free T_4 levels were low with a high TRH level. ^{123}I-uptake by the thyroid gland was low (1.8%). Serum thyroglobulin hemoagglutinin test (TGHA), MCHA and TSH receptor antibody (TRAb) were all positive. TSH-stimulating antibody (TSAb) was also positive. ICA, ICSA and anti-GAD antibody were positive. He was diagnosed as having slowly progressive IDDM and autoimmune thyroid disease. Although it has not been concluded whether his autoimmune thyroid disease is low thyroid Graves' disease or Hashimoto's disease, laboratory data suggest that Hashimoto's disease is more probable. On the combined anterior pituitary function test, TSH did not show any response to TRH, whereas PRL responded normally (Fig. 2). Plasma cortisol, GH, LH and FSH responded normally, and ACTH was hyperresponsive. TSH did not respond to 500 μg TRH after repeated daily administration of 500 μg TRH for 1 week (TSH remained undetectable throughout the test). He was therefore also diagnosed as having isolated TSH deficiency.

Case 3

A 32-yr-old woman who complained of thirst and polyuria. In 1981, she was diagnosed as having diabetes mellitus and given a sulfonyl urea.

Table 1. Laboratory data

		Case 1	Case 2	Case 3	Case 4
Urinary protein	(mg/dl)	5	600	200	5
glucose	(mg/dl)	50	300	30	0
Peripheral blood					
Hb	(g/dl)	10.0	8.9	9.0	10.6
RBC	($\times 10^4$/mm^3)	335	317	312	342
WBC	(/mm^3)	4500	8500	4100	5500
Plt	($\times 10^4$/mm^3)	15.4	28.9	23.0	25.9
Blood chemistry					
FBG	(mg/dl)	42	321	275	71
T-cho	(mg/dl)	83	456	271	166
TG	(mg/dl)		298	279	91
BUN	(mg/dl)	8	49	21	11
Crn	(mg/dl)	0.7	3.1	1.9	0.9
UA	(mg/dl)	3.2	7.5	6.6	3.7
Na	(mEq/l)	115	137	142	131
K	(mEq/l)	4.4	4.4	4.0	4.1
Cl	(mEq/l)	82	110	108	100
Ca	(mEq/l)	4.1	3.5	4.0	
P	(mEq/l)	1.7	3.1	2.6	
Proteinogram					
TP	(g/dl)	6.7	4.5	4.9	6.5
Alb	(g/dl)	4.1	1.8	2.8	3.8
HLA					
		A24	A11	A2	
		A26	A26	A31	
		BW61	BW54	B62	B54
		B39	BW61	B48	
		CW3	CW1		CW1
		CW7	CW3		
		DR4	DR4	DR4	DR2
		DRW13	DRW8	DR9	DR8

Two years later insulin therapy was started. In March, 1993, she had fever and general malaise for which she was admitted to a hospital where she was found to have diabetic ketoacidosis and was transferred to our hospital. Amenorrhea had been continuing since 1981. On admission, her blood pressure was 165/105 mmHg. She had a small and smooth goiter. Pretibial pitting edema was noted. Numbness was noted in both feet. Vibration sense was impaired on both hands and lower extremities distal to the knees. Serum HbA1c was 9.2% and serum CPR levels before and after glucagon (1 mg) injection were <0.2 and 0.29 ng/ml, respectively. ICA was positive and the anti-GAD antibody level was high. Hormonal examination showed low serum T_3 and free T_4 concentrations with a high TSH level (Table 2). Serum and urinary estrogen were low. ^{123}I-scintigraphy of the thyroid gland showed low (2.9%) and diffuse uptake. On the combined anterior pituitary function test, ACTH, cortisol, TSH and PRL showed normal response while the GH response was exaggerated (Fig. 3). Serum LH and FSH responses to LH-RH were low. LH and FSH did not respond to 100 μg LH-RH even after repeated daily administration of 400 μg LH-RH (LH: 2.5, 3.6, 5.1 , 6.5 and 7.8 mIU/ml; FSH: 4.7, 4.6, 4.7, 4.7 and 4.8 mIU/ml at 0, 15, 30, 60 and 90 min, respectively). She was therefore diagnosed as having isolated gonadotropin deficiency.

Case 4

A 71-yr-old man who was admitted to our hospital due to loss of consciousness. In October, 1990 he experienced loss of consciousness and thereafter repeated syncope attacks. He was admitted in June, 1991. On admission he had low blood pres-

Table 2. Hormonal examination

		Case 1	Case 2	Case 3	Case 4	Normal Range
Urinary						
17-OHCS	(mg/day)	0.5	3.2	2.3	0.2	1.9–6.1
17-KS	(mg/day)	0.8	6.8	3.7	0.4	3.1–8.8
CPR	(μg/day)	<2.1	2.7	<2.1		24–97
Plasma or Serum						
CPR	(ng/ml)	<0.3	0.92	<0.2		1.2–2.0
ACTH	(pg/ml)	16	84.3	54.2	<10	7.4–55.7
Cortisol	(μg/dl)	0.4	12.4	14.6	3.7	5.7–19.2
CRH	(pg/ml)	55.6	7.8		6.4	3.7–11.9
TRH	(pg/ml)		33.2			
TSH	(μU/ml)	57.4	<0.05	5.6	94.5	0.34–3.50
T_3	(ng/dl)	47	51	48	69	93–181
FT_3	(pg/ml)		1.9		2.2	3.0–5.8
T_4	(μg/dl)	0.4	7.2		2.1	5.8–12.0
FT_4	(ng/dl)		0.6	0.6	0.5	0.8–1.8
PRL	(ng/ml)	29	21.6	10.5	34.9	0.1–26.0
GH	(ng/ml)	1.3	2.7	3.4	2.1	<5.0
LH	(mIU/ml)	14.2	5.2	<0.25	2.8	0.9–15.5
FSH	(mIU/ml)	15.3	7.0	0.9	10.1	3.1–23.9
TGHA		<×100	<×400	×100	<×12800	<×100
MCHA		×6400	<×800	×100	<×409600	<×100
TRAb	(%)	(−)	50.9	2.3		<15
TSAb	(μU/ml bTSH)		0.9			<0.3
ICA		(−)	(−)	(+)		(−)
ICSA		$(+)_{to}(-)$	(−)	(−)		(−)
Anti-GAD Ab	(U/ml)	4.9	51.3	2391	<4	<8
Anti-pituitary Ab						
Cytoplasm		(−)	(−)	(−)	(−)	(−)
Cell membrane						
AtT-20		(+)	(−)	(−)	(−)	(−)
GH_3 cell		(−)	(−)	(−)	(−)	(−)

sure (94/64 mmHg). He did not have anemia, goiter or edema. Laboratory data are shown in Table 1. Hormonal examination showed low urinary 17-OHCS and KS (Table 2). Plasma ACTH and cortisol were low. Serum T_3, free T_3, T_4 and free T_4 were low and was TSH high. The baseline prolactin level was also high. TGHA and MCHA were highly positive. On a combined anterior pituitary function test, plasma ACTH and cortisol did not respond to CRH, serum GH, LH and FSH responded normally and TSH and PRL responded strongly (Fig. 4). On the basis of these results he was diagnosed as having isolated ACTH deficiency with Hashimoto's disease.

Results

Serum gamma-globulins from cases 1 and 4, who had isolated ACTH deficiency, attenuated CRH-induced ACTH release in pituitary cell cultures compared to gamma-globulins from control subjects (Fig. 5). Gamma-globulin from Case 2 tended to decrease CRH-induced ACTH release. Gamma-globulins from cases 1, 2 and 4 tended to decrease basal ACTH release. Gamma-globulins from cases 1 and 2 decreased basal TSH release while they stimulated basal PRL release in pituitary cell cultures (Fig. 6). Gamma-globulin from case 3 affected neither ACTH, TSH nor PRL release (data not shown).

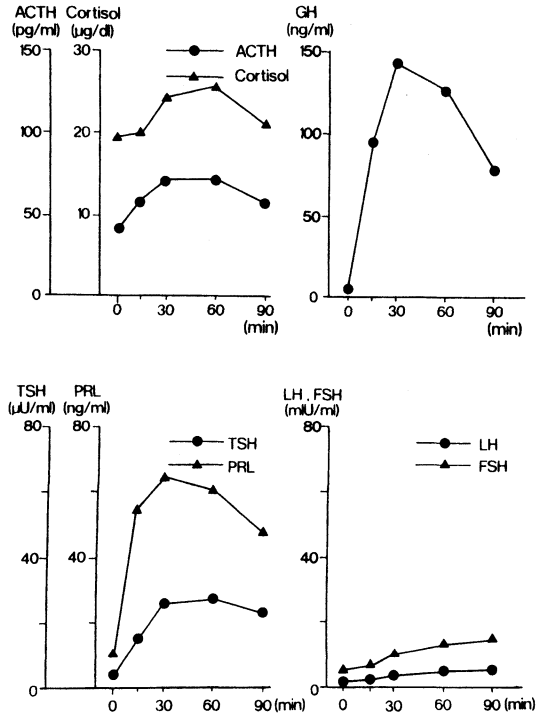

Fig. 3. Combined anterior pituitary function test in case 3 (slowly progressive IDDM + Hashimoto's thyroiditis + isolated gonadotropin secretion failure) with CRH (100 μg), GRH (100 μg), TRH (500 μg) and LH-RH (100 μg).

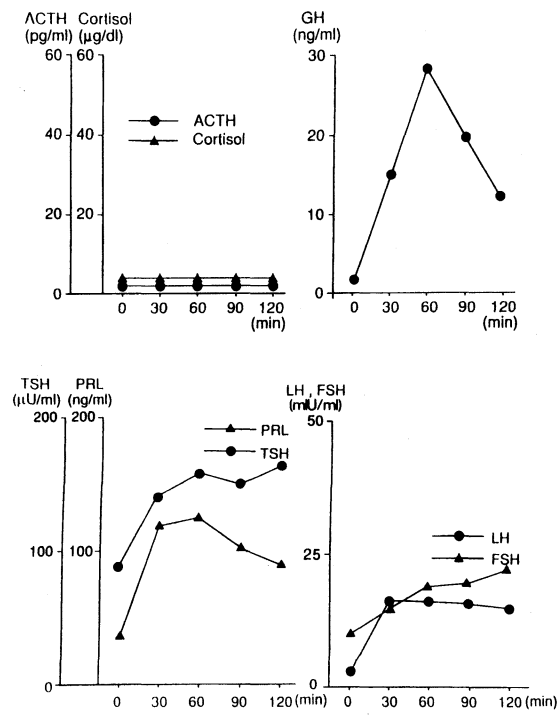

Fig. 4. Combined anterior pituitary function test in case 4 (isolated ACTH deficiency + Hashimoto's thyroiditis) with CRH (100 μg), GRH (100 μg), TRH (500 μg) and LH-RH (100 μg).

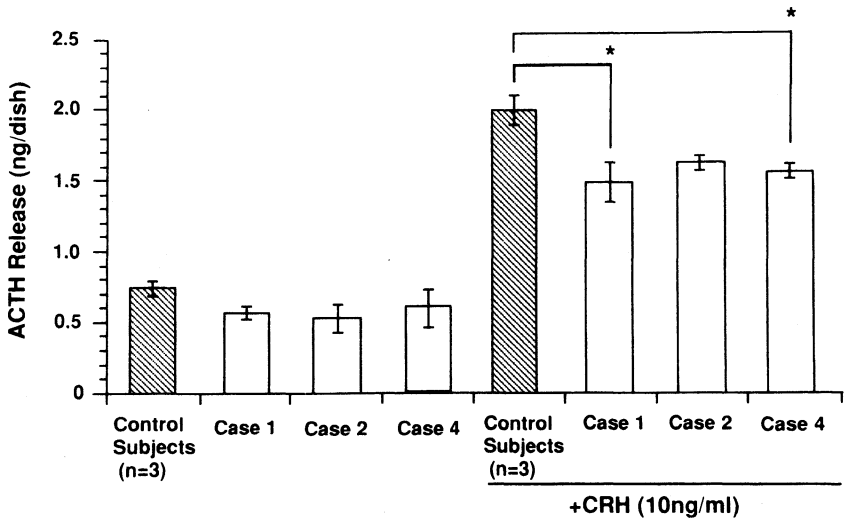

Fig. 5. Effects of serum gamma-globulins from cases (C) 1, 2 and 4 on baseline and CRH-induced ACTH release by cultured rat pituitary cells. Each column and bar represent the mean ± SEM. *, $P<0.05$.

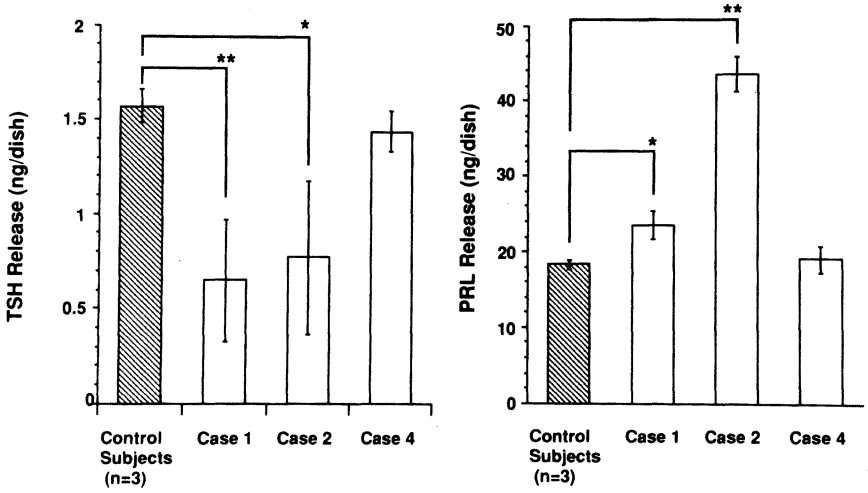

Fig. 6. Effects of serum gamma-globulins in cases 1, 2 and 4 on baseline TSH and prolactin release by cultured rat anterior pituitary cells. Each column and bar represent the mean ± SEM. *, $P<0.05$; **, $P<0.01$.

Discussion

IDDM and autoimmune thyroid disease are common in type III PGA. Garzelli *et al.* [12] reported human monoclonal autoantibodies that reacted with both pancreatic islets and thyrocytes. All 4 cases presented with autoimmune thyroid disease, probably Hashimoto's disease, and cases 1–3 developed IDDM. Cases 1 and 4 also developed isolated ACTH deficiency. Cases 2 and 3 developed isolated TSH and gonadotropin deficiency, respectively. Type II PGA syndrome is associated with HLA-B8, DW3 [13] and DR3 [14] in Caucasian patients. In Japan, patients with PGA syndrome do not have these HLA antigens. The present three patients (cases 1–3) did not have HLA B8 or DR3, but they had DR4. Although there may be no essential difference between types II and III, cases 1–3 can be classified as type III according to Neufeld's classification as these patients did not develop Addison's disease but did develop isolated pituitary hormone deficiency.

Neufeld reported hypophysitis to be a component of the PGA syndrome [2]. However, clinically evident-hypophysitis has been reported to be very rare in PGA. It is well known that IDDM, Hashimoto's disease and relapsing polychondritis are caused by autoimmune mechanisms. Although isolated pituitary hormone deficiency may be evoked by multiple causes, an autoimmune disorder may be at least partly responsible for the pathogenesis. In our study of 241 Japanese cases of isolated ACTH deficiency, 28 (11.6%) were associated with Hashimoto's disease [15]. Anti-pituitary cell antibody and pituitary cell surface antibody (PCSA) to AtT 20 cell membrane were detected in 15 (36.6%) of 44 cases and 13 (50%) of 26 cases, respectively. In the present cases, PCSA was found only in case 1. The negative results in the remaining three cases do not refute the autoimmune etiology of their isolated pituitary hormone failure, as the sensitivity and specificity of anti-pituitary antibody tests are not yet satisfactory. Sauter *et al.* [5] reported that isolated ACTH deficiency was associated with an autoantibody to a corticotroph antigen that is not ACTH or any other proopiomelanocortin-derived peptide. Recently, Crock and Goding [16] reported anti-pituitary autoantibodies to a 49 kDa pituitary protein in lymphocytic hypophysitis and isolated ACTH deficiency. Their method for detecting anti-pituitary antibody seemed to have better specificity but we did not use this method in the present cases.

In vitro, gamma-globulins from case 1 attenuated CRH-induced ACTH increase, and it decreased the basal secretion of TSH, but stimulated basal PRL secretion. Gamma-globulins from case 2 attenuated TSH basal secretion *in vitro*. Gamma-globulins from case 4 attenuated CRH-induced ACTH release, but did not affect TSH or PRL secretion. It is therefore possible that isolated pitu-

itary hormone deficiency in these 3 cases (cases 1, 2 and 4) may be caused by some autoimmune disorders. As LH and FSH release into the medium were not measured in the present investigation, we cannot conclude that isolated gonadotropin secretion failure in case 3 was evoked by an autoimmune disorder, but there still remains the possibility that autoimmune disorder might be responsible for it.

In case 1, plasma TSH responded well to TRH. The serum TSH response to TRH was exaggerated in 34.7% cases of isolated ACTH deficiency in Japan [15]. Low plasma cortisol and low thyroid hormone were responsible for high basal TSH and/or the exaggerated response of TSH to TRH in these cases. Low blood cortisol and thyroid hormone in case 1 also explain the exaggerated TSH response to TRH in case 1, although her gammaglobulin attenuated baseline TSH levels *in vitro*. Gammaglobulins from patients 1 and 2 stimulated basal PRL release in pituitary cell cultures. Bottazo and Doniach detected antibodies to PRL secreting cells in 10 out of 82 cases of polyendocrinopathy [17]. This antibody may stimulate PRL release *in vitro*. In Japan, 78 (32.3%) out of 241 patients with isolated ACTH deficiency had high basal PRL and/or exaggerated PRL response to TRH [15]. Low cortisol and low thyroid may also be responsible for this, but in these cases one third of the patients had hyperprolactinemia even after hydrocortisone replacement. The incidence of positive antipituitary antibody was higher (70.0%) in patients with hyperprolactinemia than in those without (37.1%) hyperprolactinemia. It is possible that a PRL-stimulating antibody is responsible for hyperprolactinemia in these patients. Gamma-globulins in cases 1 and 2 may therefore contain PRL-stimulating antibody. In conclusion, the present results suggest that abnormal pituitary hormone secretion associated with PGA syndrome may be caused by an autoimmune mechanism.

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References

1. Claude H, Gourgerot H (1908) Insuffisance pluriglandulaire endocrinience. *J Physiol Pathol Gen* 10: 469–480.
2. Neufeld M, Maclaren H, Blizzard R (1980) Autoimmune polyglandular syndromes. *Pediatr Ann* 9: 154–162.
3. Goudie RB, Pinkerton PH (1962) Anterior hypophysitis and Hashimoto's disease in a young woman. *J Pathol Bacteriol* 83: 584–585.
4. Richtsmeier AJ, Henry RA, Bloodworth JMB, Ehrlich EN (1980) Lymphoid hypophysitis with selective adrenocorticotropic hormone deficiency. *Arch Intern Med* 140: 1243–1244.
5. Sauter NP, Toni R, Mclaughlin CD, Dyess EM, Kritzman J, Lechan RM (1990) Isolated adrenocorticotropin deficiency associated with an autoantibody to a corticotroph antigen that is not adrenocorticotropin or other proopiomelanocortin-derived peptides. *J Clin Endocrinol Metab* 70: 1391–1397.
6. Cosman F, Kalman DP, Holub DA (1989) Lymphocytic hypophysitis. Report of 3 new cases and review of the literature. *Medicine (Baltimore)* 68: 240–256.
7. Kojima I, Nejima I, Ogata IE (1982) Isolated adrenocorticotropin deficiency associated with polyglandular failure. *J Clin Endocrinol Metab* 54: 182–186.
8. Bottazzo GF, Mcintosh C, Stanford W, Preece M (1980) Growth hormone cell antibodies and partial growth hormone deficiency in a girl with Turner's syndrome. *Clin Endocrinol* 12: 1–9.
9. Barkan Al, Kelch RP, Marshall JC (1985) Isolated gonadotrope failure in the polyglandular autoimmune syndrome. N *Engl J Med* 312: 1535–1540.
10. Hashimoto K, Yunoki S, Takahara J, Ofuji T (1979) Effect of neurogenic peptides and neurotransmitter substances on ACTH release induced by hypothalamic corticotropin releasing factor (CRF). *Endocrinol Japon* 26: 103–109.
11. Takamatsu K, Nishiyama T, Nakauchi Y, Yamano T, Ohno F (1989) A case of insulin dependent diabetes mellitus associated with relapsing polychondritis, Hashimoto's thyroiditis and pituitary adrenocortical insufficiency in succession. *Jpn J Med* 28: 232–236.
12. Garelli C, Taub FE, Jenkins MC, Drell DW, Ginsberg-Fellner F, Notkins AL (1986) Human monoclonal autoantibodies that react with both pancreatic islets and thyroid. *J Clin Invest* 77:1627–1631.

13. Eisenbarth G, Wilson P, Ward F, Lebovitz HE (1978) HLA type and occurrence of disease in familial polyglandular failure. *N Engl J Med* 298: 92–94.
14. Farid NR, Bear JC (1981) The human major histocompatibility complex and endocrine disease. *Endocr Rev* 2: 50–86.
15. Hashimoto K, Nishioka T, Iyota K, Nakayama T, Itoh H, Takeda K, Takamatsu K, Numata Y, Ogasa T (1992) Hyperresponsiveness of TSH and prolactin and impaired responsiveness of GH in Japanese patients with isolated ACTH deficiency. *Folia Endocrinol* 68: 1096–1111 (In Japanese).
16. Crock PA, Goding JW (1993) Antipituitary autoantibodies to a 49 kDa pituitary protein in lymphocytic hypophysitis and isolated ACTH deficiency. 75th Annual Meeting of the Endocrine Society, Las Vegas, USA, p.241 (Abstract).
17. Bottazzo GF, Doniach D (1978) Pituitary autoimmunity: a review. *J Royal Soc Med* 71: 433–436.