

# Comorbid Latent Adrenal Insufficiency with Autoimmune Thyroid Disease

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## Key Words

Hypoadrenalism · Graves' disease · Hypothyroidism

## Abstract

**Background:** Autoimmune thyroid disease (ATD) has been occasionally observed in patients with primary adrenal insufficiency (PAI). In contrast, less than 20 cases of comorbid PAI with ATD have been found in the English literature. One conceivable reason is difficulty in detecting latent PAI. **Objective:** Information of clinical presentation and diagnostics is sought to facilitate diagnosis of latent PAI. **Methods:** Latent PAI was pursued in 11 patients among 159 ATD patients. All of them were maintained in a euthyroid state. Except for one patient with nonrheumatic musculoskeletal symptoms, the other patients, who were asymptomatic in their daily lives, presented with recurrent nonspecific gastrointestinal symptoms or fatigue in stress-associated circumstances. Morning cortisol level  $<303$  nmol/l was used as an inclusion criterion. Their basal adrenocorticotrophic hormone levels were normal. The adrenal status was examined by a provocation test, either an insulin-induced hypoglycemia test or a 1- $\mu$ g intravenous corticotrophin test. Eleven patients showed subnormal cortisol response. They were supplemented with hydrocortisone of doses  $\leq 15$  mg/day. After a few months of supplementation, PAI was confirmed by another provocation test. Three patients were excluded because of dissociation of two provocation tests. **Results:** Comorbid latent PAI

with ATD was pursued from the symptoms stated above and proven by two provocation tests; it was found in 5% (8/159) of the patients. **Conclusion:** When patients with ATD are troubled by recurrent stress-associated gastrointestinal or constitutional symptoms or nonrheumatic musculoskeletal symptoms which have remained unrelieved by adjustment of thyroid medication, these symptoms may be a manifestation of comorbid latent PAI. It is worth investigating such patients for latent PAI.

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## Introduction

Variable occurrence of autoimmune thyroid disease (ATD) in patients with primary adrenal insufficiency (PAI) has been reported: 24% of 148 patients with Addison's disease in Poland [1], 47% of 664 patients in Norway [2], and 10 of 3,286 patients (0.3%) in the United Kingdom [3]. In contrast, less than 20 cases of comorbid PAI with ATD have been found in the English literature: 3 ATD patients with elevated plasma adrenocorticotrophic hormone (ACTH) levels were proven to have subclinical PAI by a provocation test [4, 5], and several ATD patients preliminarily screened by antiadrenal autoantibody tests were shown to have PAI by a provocation test [6, 7]. PAI is usually pursued in the advanced stage (i.e. patients with

weakness, fatigue, anorexia, hyperpigmentation, etc.) in current endocrine practice as symptoms of PAI at less advanced stages are vague or nonspecific and hyperpigmentation is absent in some patients [8]. Consequently, the diagnosis of PAI is often delayed [9, 10]. Information on clinical presentation and diagnostics is needed to facilitate diagnosis of less advanced PAI.

Decades ago, latent Addison's disease was described as follows: 'A latent insufficiency always manifests in situations of stress, such as infection, overexertion, surgery, and trauma. However the patients are still capable of leading a normal life without maintenance therapy. They may feel healthy and even the important symptom of fatigue may be absent or inconspicuous [sic]' [11]. In short, latent PAI could be paraphrased as a 'state of impaired stress preparedness' as a result of adrenal dysfunction. Anti-21-hydroxylase autoantibodies, adrenal-specific autoantibodies [12], have been found in patients with preclinical or subclinical primary hypoadrenalism [6, 7], the measurement of which, however, is not widely available outside Europe and North America. The author considered history of stress-related health change as a manifestation of 'impaired stress preparedness', screened patients with recurrent gastrointestinal or constitutive symptoms in stress-associated circumstances, and diagnosed latent PAI by provocation tests in 10 patients [13].

Following the same diagnostic approach, comorbid latent PAI was sought in ATD patients. This report investigates how frequently latent PAI occurs in patients with ATD.

## Methods

Eleven patients were selected from the ATD patients medically treated for either Graves' disease (GD) or hypothyroidism from Hashimoto thyroiditis at the author's clinic. GD with hyperthyroidism and Hashimoto thyroiditis with hypothyroidism were diagnosed based on serum free thyroid hormones, thyrotrophic hormone (TSH), anti-TSH receptor antibodies measured with DYNtest TRAK human™ (B.R.A.H.M.S AG, Berlin, Germany), and antithyroglobulin and antithyroid peroxidase antibodies. GD was treated with antithyroid drugs, either thiamazole or propylthiouracil, with no addition of L-tyrosine. The antithyroid drug was maintained according to the guideline for drug treatment of GD of the Japanese Thyroid Association [14]. First, the dose is to be tapered in patients after having responded to the drug and to be maintained at the minimal level for the period of 6 months or more before discontinuing it. Second, in case of difficulty in reducing the dosage within 1.5–2 years, changing to an alternative treatment, either surgery or radioiodine, is to be considered. Patients with hypothyroidism were supplemented with L-thyroxine. Serum TSH levels were measured 3 months after dosage adjustment. Doses to keep serum TSH levels within the reference range

were maintained. All of them had stayed in a euthyroid state and had never been treated with medication containing glucocorticoids (GC). Seven patients, although asymptomatic in their daily lives without abnormalities in basal clinical laboratory tests, presented with a variety of nonspecific gastrointestinal or constitutional symptoms under stress-associated circumstances. One patient developed swelling as well as pain in the forearms and hands, and swelling of the feet. Their basal morning cortisol levels were low or in the low normal range (<303 nmol/l) and their ACTH levels were not elevated, they were evaluated by a provocation test for latent PAI. They were numbered as 1–8 according to rising early morning cortisol levels (table 1). Patients 9–11 were excluded from the cohort after two provocation tests (see Results). Patients 1–3 and 5–8 had positive tests to serum anti-TSH receptor, antithyroglobulin, or antithyroidal peroxidase autoantibodies. Patient 4, who had hypothyroidism following radioiodine treatment for GD in her 30s, had a negative test to anti-TSH receptor auto-antibodies.

As an initial provocation test, either an insulin-induced hypoglycemia test (IHT) or a low-dose (1 µg) intravenous corticotrophin test (LDT) was employed. For IHT, regular insulin of 0.1 U/kg body weight was injected intravenously after blood samples had been drawn for basal levels of glucose, ACTH, and cortisol. The test was modified to limit blood drawing to 30 and 60 min after the insulin injection to avoid prolonged hypoglycemia (designated as short IHT). The responses of glucose, ACTH, and cortisol were determined in 15 normal volunteers for comparison. The posthypoglycemic cortisol response at 60 min was judged by a cutoff level (CL) set at 552 nmol/l [15]. For LDT, blood for cortisol measurement was drawn before and at 30 and 60 min after intravenous injection of 1-µg corticotrophin (Cortrosyn™, Daiichi-Sankyo Pharmaceutical Co., Tokyo, Japan). The responses of cortisol were determined in another 15 normal volunteers. The cortisol response to LDT at 30 min was judged by a CL set at 497 nmol/l [16]. The assays of levels of cortisol, ACTH, aldosterone, TSH, and free thyroxine were performed by a commercial laboratory (Special Reference Laboratories SRL, Hachioji, Japan). Blood for aldosterone measurement was drawn without specifying position and prior sodium intake. The methods of the hormone assays and the profiles of volunteers for IHT and LDT have been described elsewhere [13]. The present study was approved by the clinic's review board. Volunteers for the IHT and the LDT gave informed written consent prior to the tests.

When latent PAI appeared probable from an insufficient cortisol response to the initial provocation test, the patients were supplemented with hydrocortisone at a dose of 5–15 mg/day (50% for the morning use with the remainder divided for noon and evening use). After a few months of the supplementation, they were tested by another provocation test while the supplementation was withheld for 2 days prior to the test.

In the period of 5 years from April 2009 until closure of the clinic in March 2014 when the 11 patients were evaluated and treated, 159 patients with ATD thyroid illness were treated at the author's clinic, i.e. 98 patients (73 women and 25 men) with GD, 52 patients (43 women and 9 men) with hypothyroidism, 7 women with postradioiodine hypothyroidism, and 2 women with hypothyroidism after remission from GD. The occurrence of latent PAI in ATD patients was calculated as a ratio of the number of patients with latent PAI to the number of the total ATD patients.

**Table 1.** Demographic findings, selected features of symptoms and signs, and endocrine data

	Patient No.								Mean
	1	2	3	4	5	6	7	8	
Age at first provocation test, years	26	60	74	56	71	45	39	71	55.3
Gender	F	F	F	F	F	F	F	M	
BMI $\leq 20$					yes				
Systolic BP $\leq 100$ mm Hg			yes	yes					
Hyperpigmentation				yes		yes			
Cortisol, nmol/l <sup>a</sup>									
Preliminary (before provocation test)	94	132	132	143	190	190	279	287	169.1
Basal level before short IHT	174	97	246	174	135	146	146	353	183.9
Basal level before LDT	97	160	160	143	199	166	127	348	175
Aldosterone, pmol/l <sup>b</sup>	316	486	394	79	352	366	388	344	340.6
ATD	GD	H	H	G'	H	H	H	H	
TSH, mU/l <sup>c</sup>	0.25	0.86	1.27	0.87	2.18	0.63	1.03	4	1.4
Free T <sub>4</sub> , pmol/l <sup>d</sup>	12.6	21.5	17.8	19.3	19	17.4	18.3	14.7	17.6
Dose of hydrocortisone, mg/day	10	5 or 10	10	15	15	5 or 10	10	15	

Patients are arranged in the order of rising cortisol levels. BP = Blood pressure; H = Hashimoto thyroiditis; G' = postradioiodine hypothyroidism; T<sub>4</sub> = thyroxine. Reference ranges: <sup>a</sup> 121–499 nmol/l (sampling time not specified); <sup>b</sup> 100–666 pmol/l (prior salt intake and position not specified); <sup>c</sup> 0.3–4.0 mU/l; <sup>d</sup> 9.0–21.9 pmol/l.

## Results

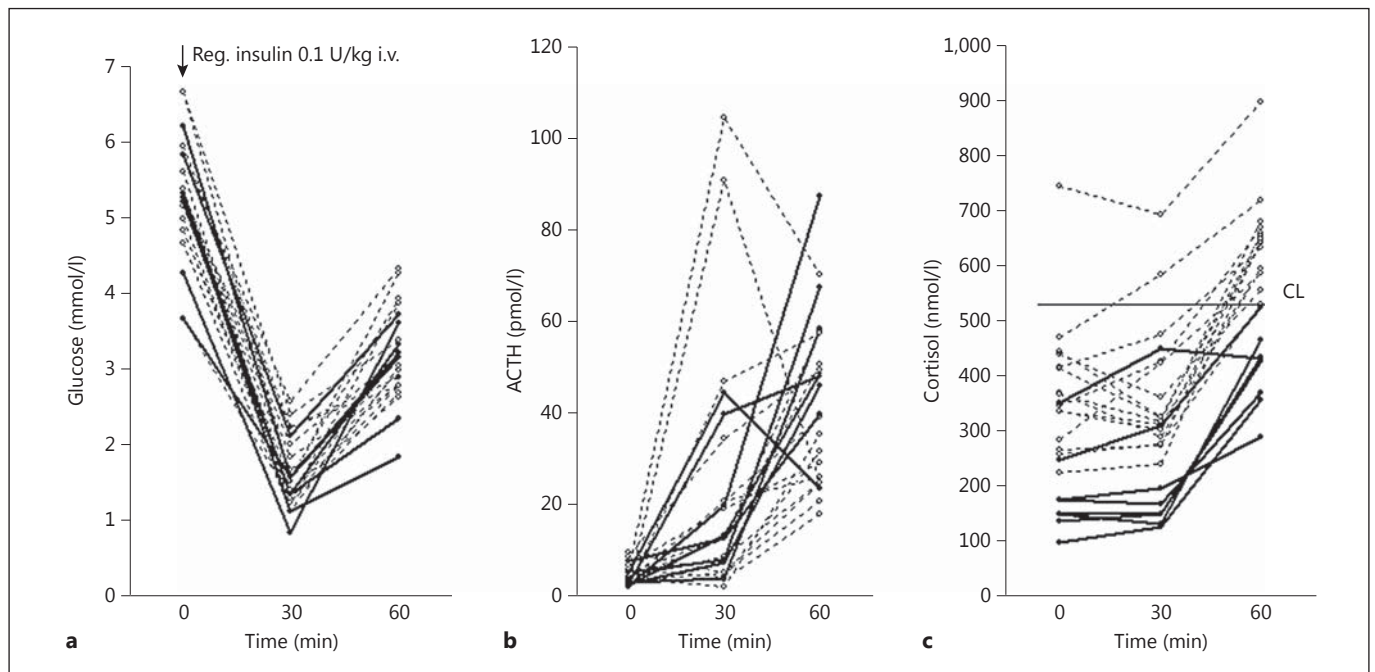
Demographic findings, selected features of Addison's disease, and endocrine findings of the patients are summarized in the table 1. Patients 1 and 3–7 were troubled by recurrent episodes of various combinations of anorexia, abdominal discomfort, abdominal pain, constipation, diarrhea, or fatigue in circumstances associated with physical (e.g. common cold or overwork; heat or cold wave) or psychosocial stress (e.g. bereavement). Patient 8 had several hypoglycemia-like episodes: the episodes occurred in the evening when he was lecturing at college for hours without having lunch, he felt very tired and had bouts of cold sweat during the episodes, and his symptoms were allegedly alleviated by nibbling sweets. However, the symptoms were not reproduced by a Whipple test in a later period. Patient 2 presented with swelling from the elbow to the fingers on both sides and swelling of the feet as well as joint pain in the swollen parts. Her serum tests for rheumatoid arthritis and scleroderma were negative. Her symptoms were not ameliorated by nonsteroidal anti-inflammatory drugs. Serum levels of thyroid and TSH of the 8 patients were within the respective reference ranges. The serum level of aldosterone was low only in patient 4, who did not have hyperkalemia.

The results of provocation tests are illustrated in figures 1 and 2. The levels of glucose were reduced at 30 min to

below 2.22 mmol/l in the 13 control subjects and in all patients (fig. 1a). The areas under the curves (AUC) of glucose and ACTH were calculated. The AUC of the glucose and ACTH curves were not significantly different between the controls and the patients (Mann-Whitney U test,  $p > 0.05$ ; fig. 1a, b). The postinsulin cortisol levels at 60 min were increased above the CL (552 nmol/l) in 14 of the control subjects, while the levels of the 8 patients remained below the CL (fig. 1c). The AUC of the patients' cortisol curves were significantly less than those of the controls (Mann-Whitney U test,  $p < 0.01$ ). Following LDT, the controls' cortisol levels were raised above the CL (497 nmol/l) at 30 min, but the patients' levels remained below the CL.

Gastrointestinal symptoms, fatigue, and pain and swelling of the fingers and feet ameliorated within a few weeks after the initiation of GC supplementation. The fatigue and hypoglycemia-like symptoms of patient 8 ceased to recur. Systolic blood pressure rose above 100 mm Hg in patients 1, 3, and 4. Two to 3 months were required for weight gain. It took more than 3 months for pigmentation to become lighter. The pain and swelling of the fingers remitted following GC supplementation (patient 2).

Patients 9–11 were excluded from the 11 patients for the following reasons: postinsulin blood glucose level was not reduced below 2.22 mmol/l in patient 9, patient 10 did not show sufficient rise in ACTH level in response to hypoglycemia, and patient 11 showed subnormal cortisol



**Fig. 1.** Response of ACTH and cortisol to insulin-induced hypoglycemia in controls and patients with latent PAI. The arrow indicates i.v. injection of regular insulin 0.1 U/kg of body weight after fasting blood samples were drawn. Data of controls are shown with open circles connected by dotted lines and those of patients with solid circles connected by uninterrupted lines. Data of glucose, ACTH, and cortisol are illustrated in **a–c**, respectively. **c** The CL

(552 nmol/l) of a positive cortisol response is shown with a horizontal line. The AUC of glucose and ACTH were not significantly different between the patients and the controls (Mann-Whitney U test,  $p > 0.05$ ), while the AUC of the patients' cortisol curves were significantly less than those of the controls (Mann-Whitney U test,  $p < 0.01$ ).

response to the short IHT but normal response to LDT. After the 3 patients were excluded, 8 patients with ATD were considered to have latent PAI, i.e. 5.0% (8/159).

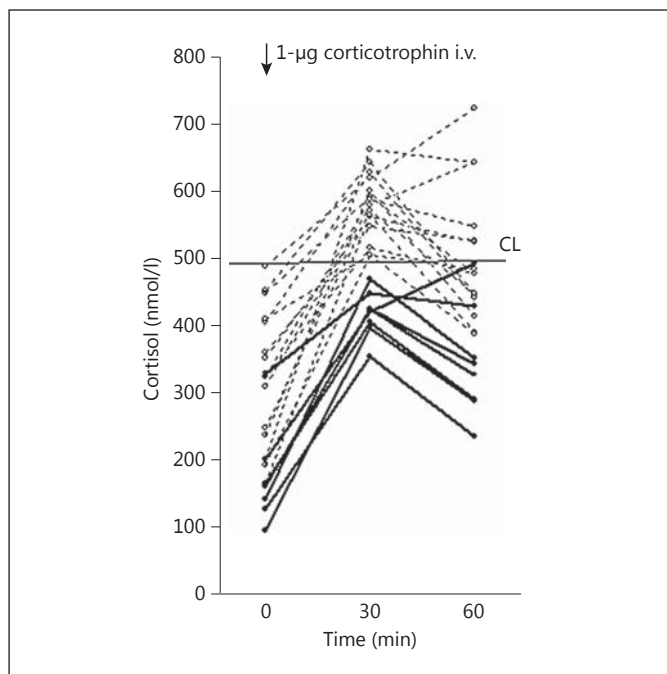
## Discussion

Patients 1 and 3–8 were asymptomatic in their daily lives and presented with a variety of nonspecific symptoms in stress-associated circumstances. On the other hand, symptoms of adrenal fatigue ([http://en.wikipedia.org/wiki/Adrenal\\_fatigue](http://en.wikipedia.org/wiki/Adrenal_fatigue); last viewed in January, 2015) are persistent. Though some clinical features of Addison's disease were observed in a few patients (table 1) and their morning cortisol levels were lower than those of 33 normal subjects reported in contemporary literature, i.e. 323–568 nmol/l [17], the levels were not extremely low. The basal ACTH levels were not elevated either. Hence, they cannot be considered to have Addison's disease in the usual sense.

Betterle et al. [18] described progression of autoimmune adrenal insufficiency in four stages: stage 1 is char-

acterized by impaired aldosterone production, stage 2 is characterized by impaired peak cortisol response to provocation, stage 3 is characterized by reduced basal cortisol and increased basal ACTH levels, and stage 4 is manifested by further reduction of cortisol and a further increase in ACTH levels [18]. PAI in the early stage has been proven by provocation tests or antiadrenal autoantibody tests. It has been described by a variety of terms, i.e. 'asymptomatic' [4], 'subclinical' [5, 7], 'preclinical' [6], 'hidden' [8], 'early' [19], 'occult' [20], and 'biochemical' [21] adrenal insufficiency. As clinical features were not thoroughly explored in the patients from these reports, clinical presentation of the present patients cannot be compared with those of these patients. The basal endocrine findings of the present patients, i.e. low or low-normal cortisol levels, normal ACTH levels, and a low level of aldosterone only in one patient, are not very different from the respective values of these patients at transitional stages, i.e. normal basal cortisol levels, basal ACTH levels either normal or elevated [4–7, 21], and the aldosterone levels either low [18] or normal [4, 7]. Hence, the





**Fig. 2.** Cortisol responses to 1- $\mu$ g corticotrophin in controls and patients with latent primary adrenal insufficiency. The arrow indicates i.v. injection of 1- $\mu$ g corticotrophin after basal blood samples were drawn. Data of controls are shown with open circles connected by dotted lines and those of patients with solid circles connected by uninterrupted lines. The CL (497 nmol/l) of positive cortisol response is shown with a horizontal line.

disorder of the present patients is consistent with PAI at a transitional stage. The author prefers the terms 'latent' or 'hidden' PAI, meaning manifesting at any time in stress-associated circumstances. A couple of recent reviews refer to musculoskeletal symptoms as a manifestation of Addison's disease [22, 23].

As the present patients had normal basal ACTH levels, they were studied by IHT and LDT to rule out secondary adrenal insufficiency by IHT as well as to eliminate misinterpretation of delayed posthypoglycemic responses of ACTH and cortisol by LDT. A combination of IHT and the corticotrophin test was employed to prove subclinical adrenal insufficiency in other studies of patients including those with normal basal ACTH levels [7, 19]. LDT was originally introduced as a diagnostic test for secondary adrenal insufficiency [24, 25]. Its usefulness for diagnosis of mild or subclinical PAI has been described [16, 26]. The results of provocation tests of the present patients are similar to but different from those of some patients with subclinical or biochemical hypoadrenalism [7, 26]. These studies included several patients with elevated basal

ACTH levels. Their cortisol levels could not be raised by LDT because of raised basal ACTH levels. Other methodological issues of the provocation tests have been discussed in a previous report [13].

The amelioration of symptoms and signs is not attributable to a pharmacologic effect because the doses employed for the present patients are almost equal to the daily secretion rate of cortisol in normal subjects, i.e.  $9.9 \pm 2.7$  mg/day [27].

There could have been a few more ATD patients with latent PAI from the 159 patients; perhaps they were not worried by nonspecific symptoms or were treated as having a different illness. Hence, the occurrence of latent PAI in ATD patients is considered to be at least 5%. Though latent PAI afflicts ATD patients infrequently, such patients benefit by latent PAI being diagnosed in two ways, i.e. amelioration of symptoms and signs not achieved by adjustment of thyroid medication and better preparedness for acute illness, injury, surgery, or psychosocial stress. When ATD patients have such symptoms and signs, they had better be screened for latent PAI with an antiadrenal antibody test. When the test turns out positive, latent PAI can be proven by LDT because a concurrent ACTH deficiency is supposedly rare in PAI patients with positive antiadrenal autoantibodies.

The sera of 8 patients as well as of 2 patients with full-blown Addison's disease gave negative tests to a radioimmunoassay for anti-21-hydroxylase autoantibody using an assay kit imported from RSR Ltd. (Cardiff, UK). The assay was performed by Cosmic Corporation (Tokyo, Japan). The causes of the negative results have not been investigated.

## Conclusion

Latent PAI occurs in 5% of ATD patients. In a few patients with ATD whose thyroid disorders are adequately treated, recurrent nonspecific gastrointestinal or constitutional symptoms in stress-associated circumstances or musculoskeletal symptoms mimicking rheumatic disease may be a manifestation of latent PAI even if the morning cortisol level is not very low and the ACTH level is not elevated. It is worth investigating whether such patients have latent PAI.

## Disclosure Statement

The author declares no conflicts of interest.

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