INTERNAL MEDICINE

□ ORIGINAL ARTICLE □

History of Stress-related Health Changes: A Cue to Pursue a Diagnosis of Latent Primary Adrenal Insufficiency

Toshihide Yamamoto

Abstract

Objective Routine delays in the diagnosis of primary adrenal insufficiency (PAI) are well known and conceivably attributable to the absence of cues, other than anti-adrenal autoantibodies, to pursue subclinical PAI. Subclinical PAI is latent unless the afflicted patient encounters stress such as an acute illness, surgery, psychosocial burden, etc. It remains to be demonstrated whether a history of stress-related health changes is a useful cue to pursue a diagnosis of latent PAI.

Methods The patients were selected for a history of recurrent symptoms, i.e., gastrointestinal symptoms, fatigue, or lassitude, aggravated by stress and alleviated by the removal of stress, and signs, i.e., weight loss, hypotension, and hyperpigmentation. As the early morning cortisol levels were low or low-normal and the adrenocorticotropic hormone (ACTH) levels were within the reference ranges, provocation tests, i.e., insulin-induced hypoglycemia tests and low-dose (1 μg) corticotropin tests (LDTs), were used to estimate the hypothalamus-pituitary-adrenal (HPA) axis status. Patients with the HPA axis dysfunction on two provocation tests were supplemented with physiologic doses of glucocorticoids (GCs). The effects of GC supplementation on stress-related health changes were observed.

Results The ACTH levels after insulin-induced hypoglycemia were higher and the cortisol levels were lower in the patients than in the control subjects. The cortisol levels in the patients were increased less significantly by LDT than those observed in the control subjects. Stress-related health changes ceased to recur and signs, i.e., a low body weight, hypotension, and hyperpigmentation, were ameliorated following GC supplementation.

Conclusion A history of stress-related health changes is useful as a cue to pursue latent PAI in patients with low or low-normal early morning cortisol levels.

Key words: ACTH, cortisol, insulin-induced hypoglycemia test, insulin tolerance test, low-dose corticotropin test, stress

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Introduction

Delays in the diagnosis of primary adrenal insufficiency (PAI) are well known (1, 2). If subclinical or latent PAI could be detected earlier, then more doctors would pay attention to patients with latent PAI, and afflicted patients would be better managed. Progression to PAI has been documented in patients with positive anti-adrenal autoantibodies (3-6). Tests for anti-adrenal autoantibodies are used to screen for subclinical PAI, especially in Europe. These tests, however, are not available in Japan: therefore other means are needed to pursue a diagnosis of subclinical or latent PAI. The author reported the latent nature of isolated adrenocorticotropic hormone (ACTH) deficiency (IAD) in the sense that most patients with IAD, although doing well in their non-stressful daily lives before *being diagnosed and treated*, are often brought to the hospitals after developing anorexia, abdominal pain, diarrhea, dehydration, hyponatremia, or hypoglycemia following acute illnesses, overwork, surgery, etc. (henceforth collectively designated as *stress*) (7). In an endocrinology textbook published in the

Yamamoto Internal Medicine Clinic, Japan
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Correspondence to Dr. Toshihide Yamamoto, tynaika@qf7.so-net.ne.jp

Table. Demographic, Clinical, and Endocrine Findings

patients‡	1	2	3	4	5	6	7	8	9	10
age (years)	26	73	47	71	64	69	45	39	30	56
gender	F	M	F	F	F	F	F	F	F	F
hyperpigmentation							O			O
body mass index <20				O	O					
systolic BP <100 mmHg				O	O					O
blood glucose at time of stress (mg/dL)		60	61							
early morning cortisol (μg/dL) (4.6-18.1)†	3.4	4.5	5.3	6.4	6.5	6.7	6.9	6.9	7.2	10.1
early morning ACTH (pg/mL) (7.2-63.3)†	23.3	46.3	8.7	11.0	11.0	27.2	12.5	14.3	22.4	16.1
autoimmune thyroid diseases	G	H		H			H	H		G'
history relevant to adrenal gland						HA				
hydrocortisone (mg/day)	10	10	15	7.5	25	20	20	15	15	15

‡: patients are arranged in the order of rising basal cortisol levels, † reference ranges (samplig time unspecified).
Abbreviations: BP: blood pressure, M: male, F female: BP: blood pressure, H: Hashimoto thyroiditis (with positive anti-thyroid peroxidase antibodies), G: Graves' disease (with positive anti-TSH receptor antibodies), G': status postopertive subtotal thyroidectomy for Graves' disease, HA: hemiadrenalectomy for pheochromocytoma
Modest adrenal atrophy was found in abdominal computor tomography (CT) scan in patient 2. No significant adrenal abnormalities were detected in abdominal CT scan in patients 1,4,5.

1980's, latent Addison's disease was described as "always manifesting in situations of stress, such as infection, overexertion, surgery, and trauma" (8). Hence, a history of stress-related health changes appears to be a useful cue to pursue a diagnosis of latent PAI. In the present study, the subjects were selected from among patients with stress-related health changes. As the early morning cortisol levels were low or low-normal and the ACTH levels were within the reference range, the function of the hypothalamus-pituitary-adrenal (HPA) axis was investigated using provocation tests. Patients demonstrating insufficient cortisol responses to the provocation tests were supplemented with physiologic doses of glucocorticoids (GCs). The efficacy of GC supplementation for treating stress-related health changes was observed.

Materials and Methods

Subjects

The patients were evaluated for recurrent gastrointestinal or constitutional symptoms characterized by occurrence or worsening during physical or psychosocial stress. If a candidate patient exhibited an early morning cortisol level above 11 μg/dL, he or she was excluded. Patients with chronic fatigue syndrome or post-traumatic stress disorder were also excluded because their complaints of fatigue, lassitude, and weakness were *persistent*. Sixteen patients were selected for the study, none of whom had been treated with pharmacologic doses of GC for prolonged periods. As the basal levels of cortisol and ACTH were normal in the majority of the patients (Table), the function of the HPA axis was examined using two provocation tests, i.e., an insulin-induced hypoglycemia test (IHT) and a low-dose (1-μg) i.v. corticotropin test (LDT).

Volunteers were recruited to define the reference ranges of the ACTH and cortisol responses to the IHT and LDT examinations. The IHT was modified by limiting the test time to 60 minutes (hereafter referred to as *the short IHT*). The subjects were questioned about their current health as well as any changes in their health following stress. A good health status and the absence of stress-related health changes were confirmed. None of the volunteers exhibited hyperpigmentation, weight loss, or hypotension. Any potential hypoglycemic reactions during the test and the management thereof were explained beforehand. Fifteen subjects, consisting of nine men and six women, were selected as normal controls for the short IHT. The average age of the men was 36.6 years (range, 23 to 71) and that of the women was 38.7 years (range, 19 to 60). An additional 15 subjects, consisting of five men and ten women, voluntarily participated in the LDT. The average age of the men was 41.2 years (range, 25 to 74 years) and that of the women was 50.0 years (range, 30 to 73). The volunteers provided their signed consent prior to the test. The project was approved by the clinic's ethical committee (consisting of the authors, part-time doctors, and an endocrinologist not associated with the clinic).

Endocrine studies

The short IHT was carried out after overnight fasting. Both the short IHT and LDT began before 9:30 a.m. After obtaining initial blood samples for the short IHT, a dose of regular insulin (Humalin®, Eli Lilly, Tokyo, Japan) of 0.1 U/kg of body weight was injected intravenously. The IHT was shortened to limit blood drawing to 30 and 60 minutes after the insulin injection. The blood glucose level was immediately measured with a glucose analyzer (Antsense III, Horiba, Kyoto, Japan; coefficient of variance, <5%). The handling of the blood samples before the hormone assays and the assay methods have been described elsewhere (7). The cortisol and ACTH assays were performed by Special Reference Laboratories (Hachioji, Japan). The lower and upper reference ranges for the cortisol and ACTH levels were 4.6 and 18.1 μg/dL and 7.2 and 63.3 pg/mL, respectively (data provided by Special Reference Laboratories). When the blood glucose level remained below 60 mg/dL at 60 minutes, small chunk of crude cane sugar was given to hasten the subject's recovery. The post-hypoglycemic cortisol

response at 60 minutes was judged based on a cutoff level (CL) of a positive response set at 20 μg/dL (9). For the LDT, blood for cortisol measurement was drawn before, and at 30 and 60 minutes after a 1-μg intravenous injection of corticotropin (Cortrosyn®, Daiichi-Sankyo Pharmaceutical Co., Tokyo, Japan). In patients already being supplemented with GC, the GC was withheld for two days prior to the second test, either the short IHT or the LDT. The responses to the LDT were judged based on a 30-minute cortisol level, with a CL of a positive response set at 18 μg/dL (10).

GC supplementation

The patients were treated with hydrocortisone at a dose of 7.5 to 25 mg per day (50% for morning use with the remainder divided for noon and evening use). The subjects were instructed to increase the dose of GC whenever expecting stress, i.e., the common cold, uncomplicated gastroenteritis, a hard and long work schedule, a prolonged very hot atmospheric temperature, travel to unfamiliar places, etc.

Results

Six of the sixteen patients were excluded due to a discordance between the two tests (cf. discussion section). The demographic, clinical and endocrine findings are summarized in Table. Patient 1 developed anorexia and began feeling unwell after several days of hot temperature in the summer. When Patient 2 came to the clinic during an episode of the common cold, the patient's consciousness was obtunded, with an attention span reduced to less than one minute and a blood glucose level of 60 mg/dL. The patient's consciousness became clear following the administration of an i.v. glucose infusion. Patient 3 complained of fatigue and arthralgia and stiffness of the finger joints without deformities. Blood tests for rheumatoid arthritis and systemic erythematodes were negative. The arthralgia was alleviated by a nonsteroidal anti-inflammatory agent. When the patient had a dry cough that lasted approximately one week, she developed orthostatic dizziness and reported cold sweats after working long hours without food intake. Her glucose level three hours after breakfast happened to be 61 mg/dL on one occasion. Patients 4 and 9 required i.v. fluid supplementation for anorexia and diarrhea on more than two occasions during episodes of the common cold. Patients 5-8 and 10 were troubled by anorexia, abdominal pain, diarrhea, and lassitude when their tight work schedules lasted for days. Recurrent diarrhea in Patients 4 and 5 was attributed to the sequela of past pelvic surgeries. In response to specific inquiries regarding symptoms in reference to concurrent stress, the patients reported that anorexia, abdominal pain, diarrhea, tiredness, and malaise often recurred following stress, the degree of worsening of the symptoms seemed disproportionate to the severity of the stress, and that the recovery was quick after the stress was relieved. Hyperpigmentation, a low body mass index (≤20) and low blood pressure (systolic blood pressure ≤100 mmHg) were observed in a few patients.

Endocrine studies

The early morning cortisol levels were low in two patients (3.4, 4.5 μg/dL) and low-normal (5.3-10.1 μg/dL) in the other patients. The early morning ACTH levels of the patients were within the reference range (Table). The changes in the glucose, ACTH, and cortisol levels following insulin injection are illustrated in Fig. 1. The glucose levels were reduced at 30 minutes to below 40 mg/dL in 13 of the 15 control subjects and in nine patients (Fig. 1, section A). The blood glucose levels at 30 minutes following insulin injection were not statistically different between the patients and the control subjects (Mann-Whitney U test, $p>0.05$). The maximal ACTH levels of 12 of the control subjects were greater than 127 pg/mL (twice the upper reference range) while the maximal ACTH levels of the other three controls were 79 to 112 pg/mL (Fig. 1, section B). The maximal ACTH levels at 30 minutes in two of the patients and at 60 minutes in the other patients were in the range of 201 and 415 pg/mL, respectively. The 60-minute ACTH levels of the patients were higher as a group than those of the controls (Mann-Whitney U test, $p<0.01$). The basal and the maximum ACTH levels of two patients with hyperpigmentation were not different from those of the other patients. The 60-minute cortisol levels were increased above the CL (20 μg/dL) in all the control subjects, including the subjects whose maximum ACTH level did not rise above twice the upper reference range, while the 60-minute cortisol levels of the patients were not increased above the CL (Fig. 1, section C).

The 30-minute cortisol levels were increased following LDT above the CL set at 18 μg/dL in all control subjects: however, the patients' levels were not raised above the CL (Fig. 2).

Response to GC supplementation

Gastrointestinal symptoms as well as pain and stiffness of the finger joints ceased to recur within a few weeks after the initiation of GC supplementation. Systolic blood pressure rose above 100 mmHg, and two to three months were required for weight gain. Pigmentation of the gum and palm creases became lighter following GC supplementation for more than three months. Patient compliance with GC supplementation was good.

Discussion

The present patients lacked the usual triad of hyperpigmentation and, low cortisol and elevated ACTH levels and were asymptomatic in their daily lives. Their symptoms appeared to be related to stress: gastrointestinal symptoms occurred following stress and remitted quickly after the stress was relieved, while stress causing anorexia, abdominal pain, diarrhea, or lassitude was not very severe, e.g., a garden-variety common cold. When asked about symptoms in the

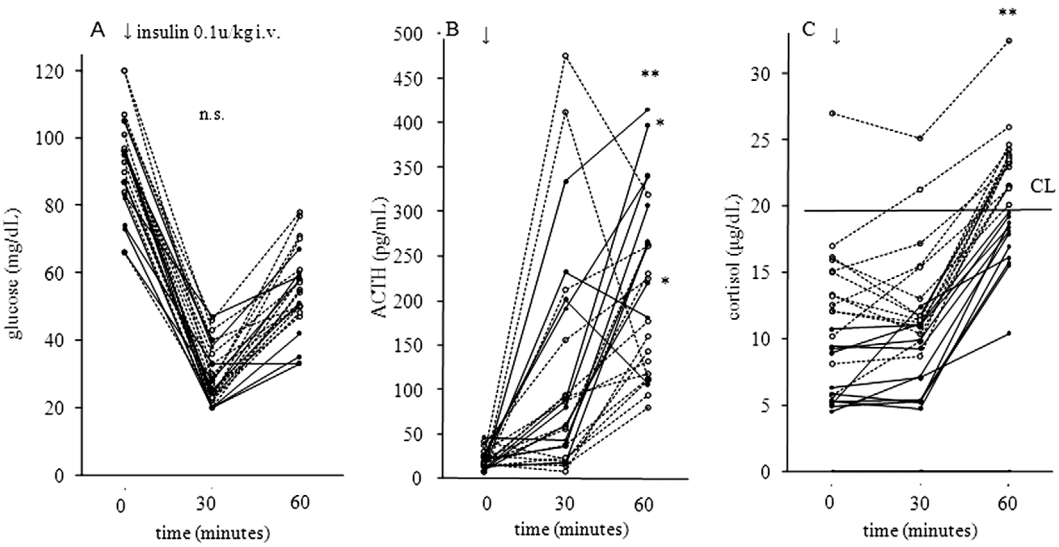

Figure 1. **Response of ACTH and cortisol to insulin-induced hypoglycemia in controls and patients with latent primary adrenal insufficiency. Regular insulin (Humalin®) 0.1 U/kg was injected after fasting blood sample had been drawn. Data of controls are shown with open circles connected by dotted lines and those of patient with solid circles connected by straight lines. Cutoff line (CL) of positive cortisol response is shown with a horizontal line (section C). ACTH data of two patients with hyperpigmentation are indicated by asterisks on the right sides of the data (section B). The statistical significance of differences in glucose (at 30min), ACTH (at 60min), and cortisol levels (at 60min) between controls and patients was tested with the Mann-Whitney U test (n.s., p>0.05; **, significant, p<0.01).**

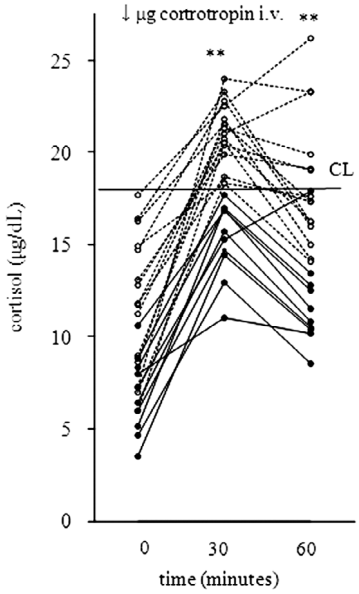

Figure 2. **Cortisol responses to 1-μg corticotropin in controls and patients with latent primary adrenal insufficiency. Data of controls are shown with open circles connected by dotted lines and those of patient with solid circles connected by straight lines. Cutoff line (CL) of positive cortisol response is shown with a horizontal line. Statistical significance of differences in cortisol levels at 30min and 60min between controls and patients was tested with the Mann-Whitney U test (**, significant, p<0.01).**

past, the patients reported similar health changes occurring under similar circumstances. A history of stress-related health changes has seldom been mentioned in reference to adrenal insufficiency in reviews and textbooks in recent decades. According to a current veterinary textbook (11), "the destruction of the adrenal gland [in dogs] is usually a gradual process, with a partial deficiency syndrome characterized by inadequate adrenal reserve occurring first and with clinical signs manifested only during times of stress (e.g., boarding, travel, surgery) and that the most common clinical manifestations include lethargy, anorexia, vomiting, and weight loss." Provided that latent PAI is a functional disorder characterized by impaired stress preparedness resulting from failed stress-mediated activation of the HPA axis, the occurrence of stress-related health changes disproportionate to the severity of the stressor and a quick recovery following the resolution of the stress is consistent with a diagnosis of latent PAI. Latent PAI in humans manifesting with stress-related gastrointestinal symptoms is seldom referred to in contemporary medical literature. The prevalence of stress-related gastrointestinal manifestation remains to be investigated. The author prefers the term *latent* PAI to subclinical PAI for the following reasons: subclinical hypo- and hyperthyroidism do not pose immediate problems but may cause accelerated atherosclerosis, osteoporosis or cardiac dysrhythmia etc. in the years ahead while *latent* PAI may become manifest at any time following stress.

Although seven of the 10 patients had autoimmune thyroid disorders, the author refrains from discussing an autoimmune pathogenesis in the absence of measurements of anti-adrenal autoantibodies. As for late-onset congenital adrenal hyper- or hypo-plasia, the author understands that the

former is often referred to as 21-hydroxylase deficiency in patients with the polycystic ovary phenotype while the latter is often referred to as hypoadrenalism appearing in childhood or adolescence. The present patients did not exhibit features common to these disorders.

The normal basal cortisol and ACTH levels of the present patients appear to contradict the features of PAI. The cortisol levels, however, are reportedly normal in most patients with a condition designated as preclinical, subclinical or asymptomatic PAI, as are the basal ACTH levels (12-15). Betterle et al. schematized the natural history of autoimmune adrenal insufficiency in four advancing stages: Stages 1 through 4, with Stage 2 being characterized by a normal basal cortisol level and an impaired cortisol response following stimulation (6). Hence, the use of stimulation tests is necessary to detect less advanced cases of PAI. The choice of the stimulation tests remains a question that has yet to be clearly elucidated. The IHT is believed to be the most reliable for testing the integrity of the HPA axis (16, 17). The IHT is, however, seldom employed lately for fear of acute myocardial infarction or cerebral ischemic injury due to prolonged hypoglycemia. In this study, the short IHT was employed in order to prevent prolonged hypoglycemia. The finding of less cortisol secreted by more ACTH in the present patients is interpreted as an indication of a reduced adrenal reserve. This finding is consistent with the observation of Giordano et al. (18), i.e., that patients with subclinical PAI exhibit less secretion of cortisol due to more ACTH (the area under the curves) in response to IHT.

An explanation is needed for a few methodological issues regarding the short IHT before accepting the present findings, i.e., the duration of hypoglycemia, timing of cortisol peaks, and CL of a positive cortisol response. First, Borm et al. (19) circumvented the development of prolonged hypoglycemia by means of concurrent glucose infusion after hypoglycemia had been attained and found similar cortisol responses with or without glucose infusion. Their observations implicitly proved that the induction per se but not the duration of hypoglycemia is sufficient to stimulate the HPA axis. Second, a post-hypoglycemic cortisol peak is reported to occur at 60 minutes in response to an ACTH peak at 45 minutes (18, 20). The cortisol level increases above the CL later than 60 minutes in some patients (designated as *slow responders*). Following a corticotropin injection of 1 μg, the plasma ACTH level reportedly increases above 400 or 1,000 pg/mL within five minutes after i.v. injection, while the cortisol level attains a maximum at 30 minutes (21, 22). In the present study, the patients were doubly studied using the short IHT and the LDT; therefore the chance of a slow responder being classified as having PAI was reduced. Third, Grinspoon et al. (16) and Dorin et al. (17) recommended a CL of 18 μg/dL for a positive cortisol response to IHT, while Oelkers advised the use of 20 μg/dL to reduce underdiagnosis of PAI (9). In this study, 20 μg/dL was adopted as the CL in order to detect latent PAI. On the other hand, 18 μg/dL was employed as the CL to judge the 30-minute cortisol level following corticotropin, according to Pura et al. (10). They derived this figure from the mean - two standard deviations of the data of 110 subjects with a wide age and weight distribution. The definition of the CLs is admittedly different in the two tests, which may cause discordance between two test results. Six patients were excluded from receiving a diagnosis of latent PAI due to discordance, i.e., an impaired cortisol response in the short IHT and a normal response in the LDT. This discordance is attributable to partial ACTH deficiency, a slow cortisol response to the IHT, or misclassification due to the post-corticotropin CL set at 18 μg/dL. Three patients who exhibited insufficient post-hypoglycemia ACTH levels were considered to have partial ACTH deficiency and received supplementation with GC. Three other patients are currently being followed without GC supplementation.

Lastly, the basal morning cortisol level was set to less than 11 μg/dL for a selection criterion for patients with latent PAI. This level was chosen based on the early morning peak cortisol levels of normal subjects in the contemporary literature, 11.7-20.6 μg/dL [95% reference range, n= 33 (23)]. This level appears to be reasonable because the average increments of the cortisol level following the administration of insulin and low-dose corticotropin were 10.1 μg/dL and 8.0 μg/dL, respectively. The cortisol response to provocation tests is influenced by the basal cortisol levels. However cortisol levels of all control subjects including four (the short IHT) and five (the LDT) with a pre-test cortisol levels less than 11 μg/dL were increased above the respective CLs by the provocation tests. The comparison of the responses would be improved if the basal cortisol levels were not significantly different between two groups.

The GC supplementation used in this study was not administered in a double-blind therapeutic trial. It was difficult to separate medicinal effectiveness from the placebo effect or spontaneous recovery. The patients experienced recurrent gastrointestinal or joint symptoms when they withheld the dose of GC. The efficacy of GC supplementation was supported by good compliance, weight gain, amelioration of low blood pressure and fading hyperpigmentation.

Conclusion

A history of stress-related health changes is a useful cue to pursue a diagnosis of latent PAI. Once latent PAI is recognized as a clinical entity within the spectrum of PAI, the delay in the diagnosis of PAI will be reduced, and patients with latent PAI will receive due attention and medical care.

The author states that he has no Conflict of Interest (COI).

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