Clinicians Sometimes Miss Cases of Latent Primary Adrenal Insufficiency Involving Stress-related Health Changes

Tetsuo Nishikawa, Masao Omura, Jun Saito and Yoko Matsuzawa

Key words: cortisol, ACTH, insulin-induced hypoglycemia, gastrointestinal symptoms

(Intern Med 53: 169-170, 2014)
(DOI: 10.2169/internalmedicine.53.1527)

In this issue of Journal, Yamamoto (1) reported the occurrence of latent primary adrenal insufficiency (PAI) in patients with low or low-normal early morning cortisol levels. It has previously been reported that the presence of gastrointestinal symptoms and anemia, especially in conjunction with autoimmune disorders, should alert the physician regarding the possibility of Addison’s disease (2). It is currently well known that autoimmune adrenalitis is the most common cause of primary adrenocortical failure. Antibodies against the steroidogenic enzyme 21-hydroxylase are commonly found in blood samples in more than 50% of affected patients (3). Therefore, clinicians must repeat ACTH-stimulating tests for the early diagnosis of primary adrenal failure, although a low cortisol level and/or low response of cortisol to various provocative tests are not always reflective of clinically manifested Addison’s disease. Recently, microRNAs selected from the blood mononuclear cells of patients with autoimmune PAI were amplified via PCR, the results of which demonstrated that miRNA 181a_1 is significantly increased, while miRNA 200a_1 and miRNA 200a_2 are significantly decreased, in CD4+ T-cells (4). We completely agree with Yamamoto’s report, which concluded that doctors would pay attention to patients with latent PAI and afflicted patients would be better managed if subclinical and latent PAI were detected earlier (1). The usual triad of hypopigmentation with low cortisol and elevated ACTH levels was not always present in the patients in that study (1). It is very interesting that gastrointestinal symptoms, such as anorexia, abdominal pain, diarrhea and lassitude, occurred following stress and remitted quickly after the stress was relieved (1). We previously compared the adrenocortical function in detail in two cases of Schmidt’s syndrome and found that zona fasciculata tissue in the adrenals may be destroyed first followed by the zona glomerulosa in cases of Schmidt’s syndrome (5). Therefore, these results suggest that stress causing anorexia, abdominal pain, diarrhea and lassitude is easily induced by a slightly impaired steroidogenic function of cortisol production in the zona fasciculata in patients with latent PAI without reducing mineralocorticoid steroidogenesis.

The biggest problem in this study (1) is that some normal healthy subjects with a blood cortisol level of less than 11 μg/dL in the morning may demonstrate the same responsiveness of cortisol to an insulin stress test as that observed in patients with latent PAI. It can be speculated that normal healthy subjects do not experience stress causing anorexia, abdominal pain, diarrhea and lassitude. Furthermore, it has been reported that several single-nucleotide polymorphisms of NR3C1 induce an increase in the sensitivity of glucocorticoid receptors to cortisol and/or relative cortisol resistance (6). It is, therefore, very interesting to compare the sensitivity of glucocorticoid receptors for which their genotypes have been recently clarified as being various between normal healthy subjects and latent PAI patients with a blood cortisol level of less than 11 μg/dL in the morning. Moreover, it is well known that cortisol is metabolized to the inactive form of cortisol, cortisone, by 11βHSD2. Researchers should therefore also focus on the involvement of 11βHSD2 in the pathogenesis of latent PAI compared with that observed in normal healthy subjects with a blood cortisol level of less than 11 μg/dL.

Yamamoto (1) also reported that the ACTH levels were higher and the cortisol levels were lower after insulin-induced hypoglycemia in their patients than in the control subjects. Clinicians always examine the hypothalamo-pituitary function in order to analyze the reserve capacity of ACTH and GH production following insulin-induced hypoglycemia, while Yamamoto’s report clearly demonstrated that the presence of insulin-induced hypoglycemia is also useful for definitively diagnosing the overt and latent forms of PAI.

Flexion contractures have been described in patients with...
Table. Sequential Protocol for Diagnosing Latent Primary Adrenal Insufficiency

1. Genetic study: HLA-B8, HLA-OR3, etc
2. Immunological assessment:
   - Cytoplasmic adrenal antibodies (Cy-Ad-Abs)
   - Surface reactive adrenal antibodies
   - Cortical adrenal autoantigen (CYP17, CYP21)
   - Other tissue antibodies (anti-Tg antibody)
3. Endocrinological function test:
   - ACTH-stimulating test
   - CRH-loading test
   - Insulin tolerance test

Addison’s disease (7). The condition is reported to be relieved by the administration of glucocorticoids, not mineralocorticoids (7).

On the other hand, patients who are ultimately diagnosed with latent PAI exhibit recurrent symptoms, i.e., gastrointestinal symptoms and fatigue (1). Therefore, Yamamoto emphasized that a history of stress-related health changes, including gastrointestinal symptoms, is a useful cue to pursue a diagnosis of latent PAI (1). Perhaps physicians should also assess musculoskeletal symptoms, including flexion contractures, to make an early diagnosis of latent PAI. Such symptoms should also be evaluated during glucocorticoid replacement therapy in order to assess the appropriate amount of glucocorticoids.

Finally, we would like to propose a flowchart for screening and definitively diagnosing subclinical and latent PAI, as shown in Table. First, physicians must screen patients complaining of stress-related health changes, including muscle weakness, fatigability, weight loss, gastrointestinal symptoms and so on. Subsequently, the basal cortisol level should be assessed in the morning. Furthermore, the possibility of latent PAI should be examined if the basal cortisol level is less than 11.0 μg/dL. Addison’s disease is primarily caused by tuberculosis, and it has recently been reported that immunological impairments are closely related to its pathogenesis. Therefore, clinicians must examine the clinical characteristics of each case of latent PAI by analyzing the genetic, immunological and endocrinological findings in order to precisely diagnose latent PAI.

In conclusion, general physicians, as well as endocrinologists, should therefore evaluate the possibility of latent PAI in patients complaining of stress-related health changes, as suggested by Yamamoto (1).

The authors state that they have no Conflict of Interest (COI).

Acknowledgement

This work was partly supported by a Grant for Research on Intractable Diseases provided by the Japanese Ministry of Health, Labour and Welfare.

References