Schmidt's Syndrome: Autoimmune Polyglandular Disease of the Adrenal and Thyroid Glands

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It is known that immunoendocrine diseases often occur as polyglandular disorders. M.B. Schmidt [1], in 1926, was the first to describe a biglandular endocrine disorder (adrenal and thyroid insufficiency). Schmidt called it "thyreosuprarenal type" of polyglandular insufficiency. Two decades later, Demos et al. [2] named this type of autoimmune bi-glandular disease "Schmidt's Syndrome." In our previous study in 1988 [3] on the extra-adrenal endocrinopathies in 128 cases of Addison's disease, the incidence of Schmidt's syndrome was 12 of 42 cases of well-diagnosed idiopathic Addison's disease. However, comprehensive epidemiological studies of Schmidt's syndrome have not been carried out.

Recently, we confronted a patient who initially had partial Addison's disease associated with chronic thyroiditis, and during the subsequent 20 years developed a complete exhaustion of basal steroid secretion and thyroid insufficiency.

Case Description

The patient was a 53-year-old housewife with a 20 year history of increased skin pigmentation. Her father had died of pulmonary tuberculosis and her mother suffered from rheumatic heart disease. The patient had had acute glomerulonephritis at age 12 but had completely recovered. In 1976, she was suspected of having Addison's disease because of marked skin pigmentation. However, since no definite laboratory data supporting adrenocortical insufficiency were obtained, she was diagnosed with abnormal photosensitivity and treated with large doses of vitamin C.

In October 1982 she complained of general malaise with nausea, vomiting, diarrhea and headache. Blood pressure was 98/56 mmHg on admission. Urinary 17-KS and 17-OHCS were low (1.7 and 1.0 mg/24 hours, respectively), in contrast to elevated plasma adrenocorticotropic hormone concentration of 212 pg/ml. Thus, Addisonian crisis was suspected in spite of plasma cortisol within the normal range. The routine laboratory tests are shown in the Table. Since an intracutaneous test for ACTH was positive, the ACTH stimulation test was not done. Symptomatic treatment helped to relieve the symptoms and she was discharged after 2 weeks.

Two months later, she was readmitted with a recurrence of nausea and diarrhea. The rapid ACTH test done in the outpatient clinic before her hospitalization caused loss of consciousness with a drop in blood pressure (80 mmHg systolic). The routine laboratory tests gave almost the same results as those at the first admission [Table], and endocrinological tests revealed the characteristic data compatible with partial Addison's disease associated with chronic thyroiditis [Table]. Plasma ACTH was constantly elevated to ≥212 pg/ml, once reaching 3,010 pg/ml. The thyroid gland was moderately enlarged and of firm consistency, with fine nodules. Though serum free thyroxine and triiodothyronine levels were within the normal range, serum thyroid-stimulating hormone was increased. Microsomal antibody titers by hemagglutination test were 6,400x. No abnormal findings of the pituitary gland were seen on skull radiography and brain computerized tomography, and CT scan of the adrenals revealed no enlargement.

After discharge from the second hospitalization, the patient had been followed under replacement therapy with a physiological dose of hydrocortisone for several months — first in our clinic and thereafter in another hospital. In March 1996, 20 years after her first admission, the patient returned to our clinic because of increased facial skin pigmentation, enlargement of the goiter, and weight gain (4 kg). Physical examination at that time revealed dark brown skin pigmentation of the face, hands, elbows, abdominal belt zone and genital region. Brown flecks were also seen on the tongue and buccal mucous membrane. The goiter size was much larger than at the first visit in 1982, particularly the right lobe. Blood pressure was 128/80 mmHg. Values of routine and endocrinological tests are listed in the Table. Under hydrocortisone therapy (10 mg in the morning and 5 mg in the evening), the basal level of plasma cortisol at 08:00 — before she took the tablet — decreased to 1.0 g/dl; aldosterone was low normal, 32 pg/ml; plasma DHEA decreased to 0.2 ng/ml; and ACTH remained high, 190 pg/ml. The test for autoantibodies to the cytochrome P450 side-chain cleavage enzyme (P450scc) was strongly positive (13.4 U/ml), although the test for adrenal cortex autoantibodies was negative. The titer of antithyroid peroxidase antibody was high (5.6 U/ml), but tests for antibodies to smooth muscle cells, gastric parietal cells, glutamic

Laboratory data

	October-December 1982	July-August 1996	Normal range
Endocrinology			
pl-ACTH	212–3,010	195 pg/ml	(9–52 pg/ml)
Baseline pl-cortisol	10.5	1.0 g/dl	(4–18.3 g/dl)
Post-cortrosyn cortisol	11.2 (30')	—	
	11.2 (60')		
pl-corticosterone	2.4	1.5 g/dl	(0.2–8.5 g/dl)
pl-aldosterone	32–68	34.0 pg/ml	(30–160 pg/ml, recl)
PRA	3.5	1.6 ng/ml/h	(0.3–3.0 ng/ml/h, recl)
pl-DHEA	0.6	0.2 ng/ml	(0.8–7.0 ng/ml)
Urinary-17KS	1.3	1 mg/day	(2.4–11.0 mg/day)
Urinary-17-OHCS	2.4	0.6 mg/day	(2.2–7.3 mg/day)
Post-ACTH (250 g)			
IV infusion for 2 days:			
17 KS	1.5, 3.5		(3.5–10 mg/day)
17-OHCS	1.0, 2.4		(4.8–24 mg/day)
Thyroid			
p-TSH	2.6	7.2 U/ml	(0.34–3.5 U/ml)
s-T3	1.4	3.2 pg/ml	(2.47–4.34 pg/ml)
s-total T4	7.8 g/dl	—	(4.6–12.6 g/dl)
s-free T4	—	0.97 ng/dl	(0.97–1.79 ng/dl)
Thyroglobulin	—	11.0 ng/ml	(< 30 ng/ml)
anti-TPO ab	—	5.6 U/ml	(<0.3 U)
FBS	—	106 mg/dl	
Serology			
ESR	24/46 mm 30'/1h		
CRP	(-)	(-)	
ANA	x 5		
anti-DNA-ab	47 IU/ml		
anti-GLD-ab		negative	
anti-islet cell ab		negative	
anti-adrenal cortex ab		negative	
anti-21-hydroxylase ab		negative	
anti-17α-hydroxylase ab		negative	
anti-P450scc		positive	
HLA DR locus		DR4 DR14(6)	
Diagnostic imaging			
Pituitary gland CT		normal	
Thyroid gland CT and echography		diffusely swollen	

p-B = plasma corticosterone, p-aldo = plasma aldosterone, recl = in reclining position, ab = antibodies, TPO = thyroid peroxidase, GLD = glutamic dehydrogenase

dehydrogenase and pituitary were negative.

Comment

With regard to the adrenocortical function in the initial period, the present case satisfied the definition of so-called partial Addison's disease, which is characterized by normal plasma baseline cortisol levels but no response of plasma cortisol to exogenous ACTH stimulation. Moreover, plasma ACTH was consistently elevated in the period during which replacement steroid was withdrawn. Oelkers [4] stated in his recent review that in patients with primary adrenal insufficiency, plasma ACTH concentrations invariably exceed 100 pg/ml, even if the plasma cortisol concentration is in the normal range. Moreover, in our patient, elevated ACTH was suppressed to near the upper normal limit with concomitant amelioration of skin pigmentation, when hydrocortisone was switched for a month to betamethasone, a stronger ACTH-suppressive synthetic steroid, at a dose of 0.75 mg/day. This fact suggested that in this patient, functional capacity of the adrenal cortex was limited to the extent that it was not capable of further responding to exogenous ACTH stimulation; but normocortisolemia was maintained in the basal condition through markedly increased secretion of endogenous ACTH. This situation was combined with subclinical hypothyroidism in which an increased serum TSH was associated with normal serum concentrations of free thyroxine and triiodothyronine. However, during the 20 year course, the loss of adrenal cortical function had progressed, as indicated by a decrease in basal level of plasma cortisol (1.0 g/dl).

TSH = thyroid-stimulating hormone

In autoimmune Addison's disease, the markers of the autoimmune damage in the adrenal cortex that are of diagnostic value include: adrenal cortex autoantibodies or autoantibodies to 21-hydroxylase, 17a-hydroxylase or P450scc (side-chain cleavage enzyme) [5]. It has been reported that autoantibodies against P450scc enzyme as well as against 17a-hydroxylase are detected less often than those against 21-hydroxylase [6], and steroid replacement therapy may have a beneficial effect in inducing a reversal of adrenal antibodies with concomitant amelioration of adrenocortical function. In the case presented, only autoantibodies to P450scc were detected. At present, the authors have no answer to explain such a selective production of autoantibodies against the target organ elements. Genetic factors may play a role.

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