

AN ADULT CASE OF CONGENITAL ADRENAL HYPERPLASIA DUE TO 21-HYDROXYLASE DEFICIENCY ASSOCIATED WITH BILATERAL ADRENAL MYELOLIPOMA: AN 8-YEAR OBSERVATION OF CLINICAL CHARACTERISTICS DURING STEROID REPLACEMENT THERAPY

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Abstract: We describe the case of a 44-year-old man with congenital adrenal hyperplasia (CAH; 21-hydroxylase deficiency) associated with bilateral adrenal myelolipoma. While undergoing computed tomography (CT) for the evaluation of persisting flank pain in May 1988, he was diagnosed incidentally as having a bilateral adrenal tumor. Histology of the right extirpated tumor revealed myelolipoma of the adrenal gland, and the other side of the tumor also was diagnosed as myelolipoma by the image diagnostic characteristics. The left side tumor was not extirpated. During examination of hyper-reninism, plasma renin activity (PRA) at 10.5 ng/ml/h, he was diagnosed as having congenital adrenal hyperplasia due to elevation of adrenocorticotropin (ACTH), progesterone, and 17 α -hydroxyprogesterone (17 α -OHP). Hydrocortisone with dexamethasone supplemented therapy was started, and the ACTH, progesterone, and 17 α -OHP were normalized, but plasma PRA persisted at high levels. The PRA in this case did not show the degree of sodium loss. During 8 years of observation of the left side myelolipoma by CT, the tumor size did not increase. This case provides an interesting natural history of the clinical characteristics of CAH that went undiagnosed for a long period and an interesting complication of bilateral adrenal myelolipoma.

Index Terms

congenital adrenal hypertrophy, 21-hydroxylase deficiency, late onset type, myelolipoma

Congenital adrenal hyperplasia (CAH) is characterized by a hereditary enzyme deficiency in steroid synthesis of the adrenal gland. Over 90 % of CAH cases are associated with 21-hydroxylase deficiency^{1,2)} and have a mutation in the CYP 21 gene³⁻⁶⁾. The majority of mutations result from recombination between the CYP 21 gene encoding the 21-hydroxylase enzyme and the closely linked, highly homologous pseudogene CYP 21 P^{7,8)}. Cases of CAH due to 21-hydroxylase deficiency are classified into three clinical phenotypes: salt losing, simple virilizing, and nonclassical forms or late onset type⁹⁻¹¹⁾. The molecular basis of the phenotypic heterogeneity associated with the mutation in the CYP 21 gene remains to be elucidated. For early diagnosis, newborn mass-screening for CAH was developed using measurement of 17 α -hydroxyprogesterone (17 α -OHP)^{12,13)}. Before mass-screening, many cases were not discover-

ed until the onset of precocious puberty. The case described herein was undiagnosed for more than 40 years and was discovered by chance during examination of adrenal myelolipoma. We discuss the clinical characteristics and whether hydrocortisone supplement therapy was necessary in this case.

ASSAY METHODS

The concentration of adrenocorticotropin (ACTH) was measured by immunoradiometric assay (IRMA) (Allegro HS-ACTH kit, Nihon Medi-Physics Co. Ltd., Nishinomiya, Japan). Cortisol was measured by a radioimmunoassay (RIA) (Gamma CoatTM Cortisol, INCSTER Co., Stillwater, MN, USA). The concentration of 11-deoxycorticosterone (DOC) and 11-deoxycortisol were measured by RIA (Ohtsuka Assay Co., Tokushima, Japan). The concentrations of progesterone, 17 α -hydroxyprogesterone and dehydroepiandrosterone-sulfate (DHEAS) were measured by RIA (DPC Progesterone KIT, DPC 17 α -OH Progesterone KIT and DPC DHEAS KIT, Nippon DPC Corporation, Tokyo, Japan), respectively. Plasma renin activity (PRA) was measured by RIA (Gamma Coat Plasma Renin Activity Kit, INCSTAR Co., USA). Active renin concentration was measured by IRMA (Renin IRMA "Daiichi", Daiichi Radioisotope Labos Ltd., Tokyo, Japan). Aldosterone was measured by RIA (SPACK-S Aldosterone Kit, Daiichi Radioisotope Labos Ltd., Tokyo, Japan).

CASE REPORT

The patient was born full term and had a normal birth. He did not suffer from dehydration or shock and had no apparent genital abnormality at birth. His growth and development in childhood were almost normal although his skin color was dark compared with his brother. Secondary sexual characteristics developed when he was nearing 10 years old, and his height growth stopped shortly thereafter with his final adult height being 153 cm. After graduation from university, he worked strenuously without feeling fatigued. In May 1988, bilateral adrenal tumors were discovered incidentally by CT examination for the evaluation of flank pain. On August 2, 1989, extirpation of the right adrenal tumor was performed to rule out malignancy (Fig. 1), and the histology of the tumor revealed myelolipoma (Fig. 2). In April 1990, he was referred to our department due to the findings of hyper-reninism (10.51 ng/ml/h) and hyperaldosteronism (459.3 pg/ml). His height was 153 cm, weight 63 kg and blood pressure 134/80 mmHg. No abnormality was found in appearance but his skin had a brownish tone. No abnormality was found in penis size or testicular volume (right, 25 ml and left, 25 ml). His intelligence level was high.

1) Urine and blood examinations, and basal hormone values

No abnormality was found by urinalysis or peripheral blood examination. Serum Na (138 mEq/l), K (4.0 mEq/l) and Cl (101 mEq/l) were within normal ranges. For plasma basal hormone values, ACTH was elevated to 149 pg/ml (normal range, 4.4 to 48.0 pg/ml), and cortisol was 11.4 μ g/dl (normal range, 2.4 to 15.5 μ g/dl). PRA and plasma aldosterone concentration were elevated markedly to 13.2 ng/ml/hr (normal range, 0.5 to 2.0 ng/ml/hr) and 370.3 pg/ml (normal range, 45.0 to 105.5 pg/ml), respectively. Urinary 17-ketosteroids (66.6 mg/day) and 17-ketogenic steroids (95.9 mg/day) were elevated but 17-hydroxysteroids (8.3 mg/day) were within normal levels.



Fig. 1. The extirpated right adrenal myelolipoma: the tumor was encapsulated by envelope, and the cut-surface revealed yellow and red colored adipose tissue.

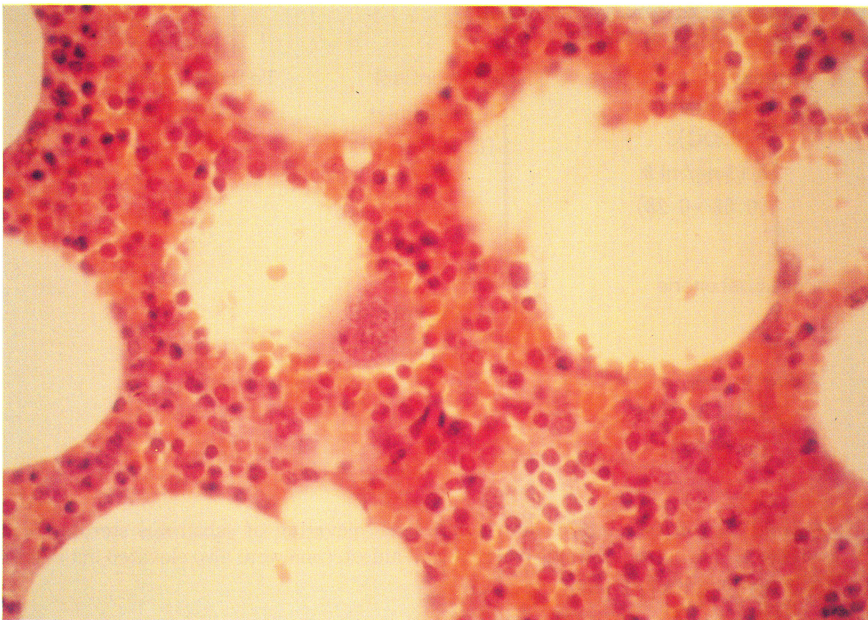


Fig. 2. Microscopic finding of the tumor of HE staining ($\times 400$): the tumor was consisted with adipocytes and myeloid cells which compatible with myelolipoma.

These data indicated that this patient had a mild form of CAH (21-hydroxylase deficiency). To confirm the diagnosis, the measurement of steroid biosynthesis intermediates, dexamethasone suppression test, and ACTH stimulation test were performed.

2) Steroid biosynthesis intermediates (Fig. 3)

Intermediates of steroid biosynthesis were measured and are shown in Fig. 3. Progesterone and 17 α -OHP were markedly elevated and DHEAS and androstenedione were both elevated. 11-deoxycortisol and cortisol were within normal levels. 11-deoxycorticosterone (DOC) and aldosterone were both elevated.

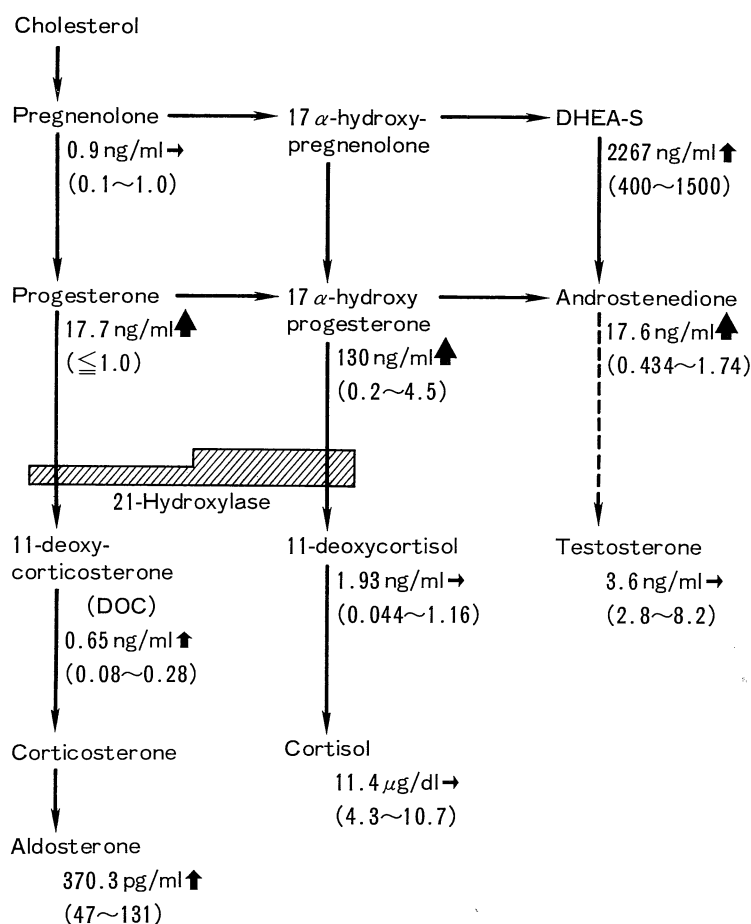


Fig. 3. Steroid biosynthesis intermediates shows the elevation of substrates steroids of 21-hydroxylase. 11-deoxycorticosterone and aldosterone were also elevated but cortisol was within normal ranges.

3) Dexamethasone suppression test and ACTH stimulation test (Fig. 4)

Dexamethasone, 1.0 mg, was administered at 11 : 00 pm, and plasma steroids were measured the next morning at 9 : 00 am. Progesterone, 17 α -OHP, DOC, aldosterone, and DHEAS were

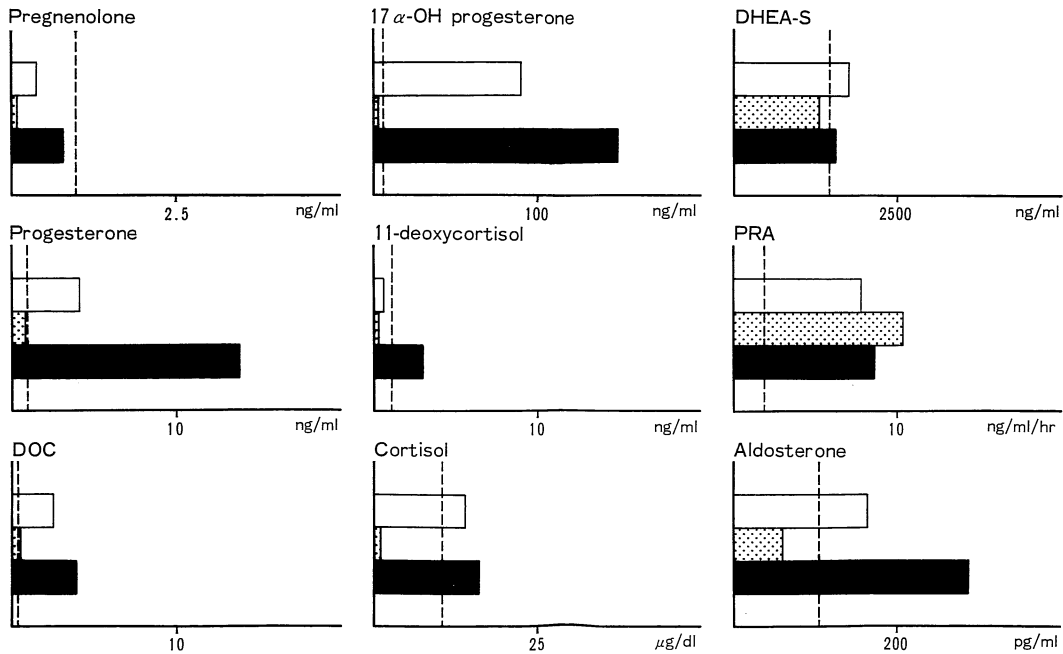


Fig. 4. Plasma steroids and PRA in dexamethasone suppression test and rapid ACTH test

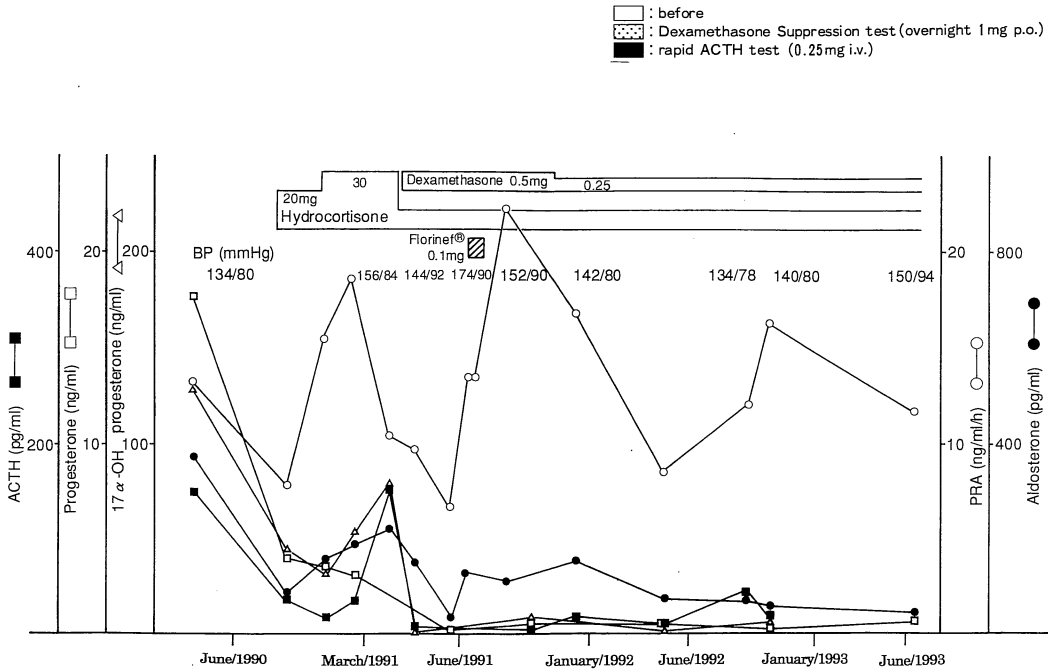


Fig. 5. Change in ACTH, progesterone, 17 α -OH progesterone, PRA and aldosterone levels during suppression therapy by hydrocortisone and dexamethasone

suppressed to normal ranges, but PRA was slightly elevated. ACTH test revealed prominent elevations in progesterone and 17 α -OHP to 13.8 ng/ml and 150.0 ng/ml, respectively. Cortisol was only slightly elevated (14.5 to 16.5 μ g/dl). DOC and aldosterone were both elevated.

These data indicated that the patient had a mild form of CAH due to 21-hydroxylase deficiency.

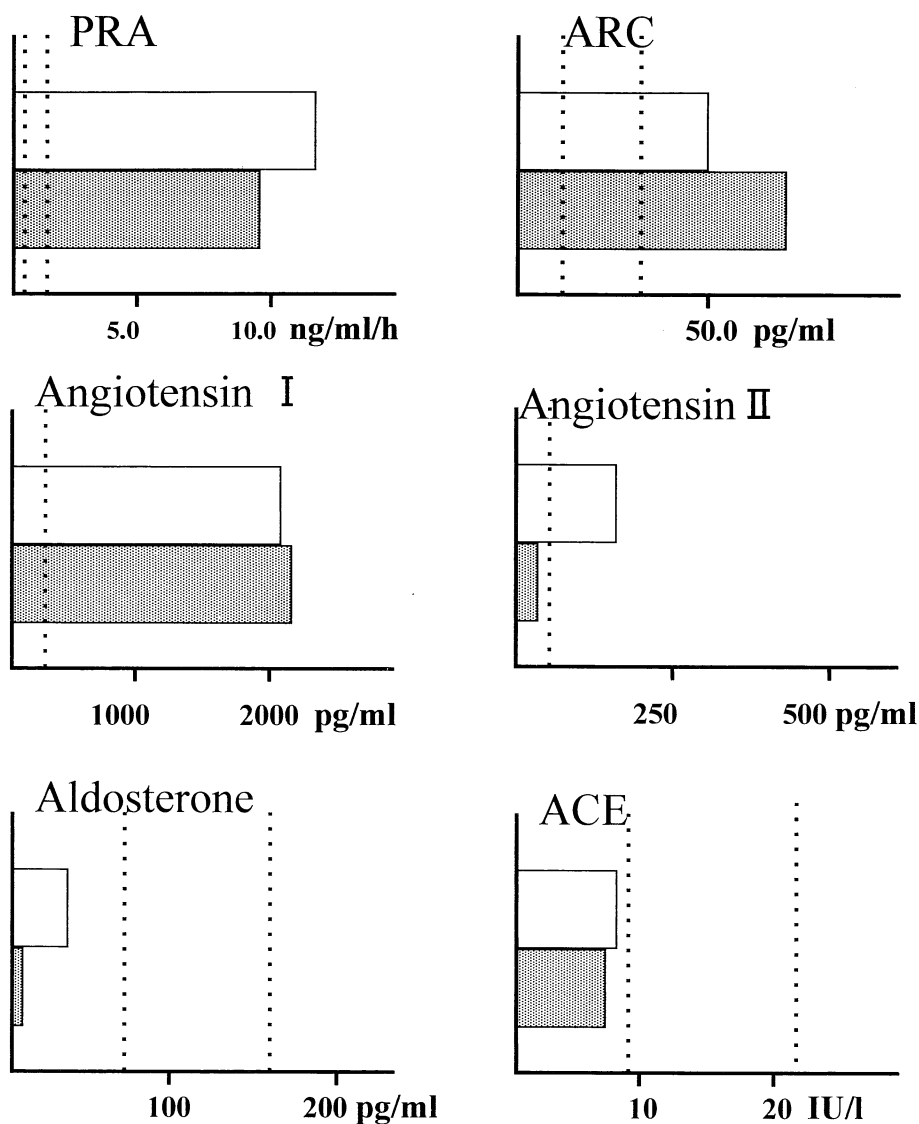


Fig. 6. Changes in renin-angiotensin-aldosterone parameters before and after 0.9% saline loading

□ : Before loading ▨ : After loading
 ∴ : Dotted lines indicate normal ranges

4) Clinical course and therapy (Fig. 5)

After the diagnosis of mild form of CAH, hydrocortisone supplement therapy was started, which successfully suppressed ACTH, progesterone, and 17 α -OHP to normal levels. Although ACTH was controlled by steroid replacement, PRA was not normalized from its high levels. Florinef (0.1 mg/day) was administered, but PRA did not decrease, thus Florinef was discontinued due to the accompanying hypertension.

5) 0.9 % Saline solution loading test (Fig. 6)

To clarify why PRA was not suppressed by steroid therapy, a saline solution loading test was performed. One thousand milliliters of 0.9 % saline solution was drip infused over 1 h; then PRA, active renin concentration (ARC), angiotensin I, angiotensin II, aldosterone, and angiotensin converting enzyme (ACE) were measured. PRA was only slightly lowered (11.7 to 7.89 ng/ml/hr). ARC was elevated rather than suppressed (72.2 to 98.7 pg/ml). Angiotensin II and aldosterone were suppressed, but angiotensin I and ACE were not suppressed.

6) Eight years of observation of left side myelolipoma and PRA

After the extirpation of right side adrenal myelolipoma, the size and characteristics of the left side tumor were followed by long term observation using CT. During the 8 years, the size and intensity of myelolipoma did not change. The PRA levels showed always over 5.0 ng/ml/h during this 8-year follow-up even though ACTH and 17 α -OHP were kept within normal ranges.

DISCUSSION

CAH due to 21-hydroxylase deficiency is classified into three forms clinically as salt-losing form, classical form, and non-classical form or late onset type (9-11). To classify our case, we considered the history and characteristics. This patient was incidentally diagnosed as having CAH at the age of 44 years. He had been healthy and well since birth and had no history of dehydration or shock due to adrenal insufficiency. He had not been diagnosed as having CAH before excision of the myelolipoma, and he did not need hydrocortisone replacement during or after operation, which indicated that 21-hydroxylase deficiency was mild and that his adrenal cortex could synthesize sufficient hydrocortisone.

Regarding the elevation of DOC and aldosterone, the 21-hydroxylase deficiency only mildly impaired the conversion of DOC to corticosterone in comparison to the impairment of 11-deoxycortisol conversion to cortisol. So he could tolerate physical stress both during his childhood and adult life, including the stress of the surgery. The only symptoms in this case were short stature and skin pigmentation. His short stature is probably due to precocious puberty induced from CAH¹⁴⁾ and the skin pigmentation is due to hypersecretion of ACTH. We could classify this case as nonclassical and late onset type due to the mild enzyme deficiency and the sole symptom of short stature induced by precocious puberty.

The relationship between CAH and bilateral adrenal myelolipoma in this case is interesting. Myelolipoma is characterized as a benign tumor consisting of mature adipose cells and hematopoietic elements; it resembles bone marrow¹⁵⁾. Reported cases have been associated with Addison's disease, Nelson's syndrome after adrenalectomy for Cushing's syndrome^{16,17)}, and CAH^{18,19)}. A review of these cases leads to the supposition that stimulation by ACTH may be part of the pathogenesis. The experimental work of Selye and Stone²⁰⁾ supports this

premise. They administered a crude anterior pituitary extract, rich in ACTH, that caused marked myelopoiesis in the adrenal gland of rats. In our case, CAH would have played a role in the tumorigenesis of this myelolipoma by hypersecretion of ACTH, especially since this was a bilateral myelolipoma and long term ACTH suppression therapy prevented further growth.

Another problem in this case is in deciding whether steroid replacement therapy is necessary. Although he had no history of adrenal insufficiency, he was administered hydrocortisone and dexamethasone because he underwent a right side adrenalectomy with extirpation of the myololipoma. He was given hydrocortisone to normalize PRA and checked by monitoring plasma ACTH and 17 α -OHP. Although the administration of 10 mg of hydrocortisone and 0.25 mg of dexamethasone successfully lowered plasma ACTH and 17 α -OHP to the normal ranges, the PRA continued to be high over 10 ng/ml/hr. When supplementary Florinef was added, hypertension and hypokalemia ensued, but PRA remained persistently high. These indicated that the PRA did not indicate the degree of salt loss. Although PRA and ARC were not sufficiently suppressed by the 0.9 % saline loading test, angiotensin II and aldosterone were both suppressed. We speculate that PRA in this case involves two elements. The activity suppressed by 0.9 % saline solution would be the element which controls angiotensin and aldosterone production. The mechanism related to the unsuppressed elements of PRA were not clear in this study. Our results indicate that angiotensin II and aldosterone were the markers of salt loss rather than PRA and ARC in this case. Therefore we conclude that PRA dose not always indicate the degree of salt loss in CAH.

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