Short Reports

Acquired Partial Corticosterone Methyl Oxidase Type II Defect in Diabetes Mellitus

Case of Hyperreninemic Hypoaldosteronism

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The aim of this study was to investigate the pathogenesis of hypoaldosteronism in diabetes. Endogenous elevation of plasma renin activity and exogenous corticotropin were used to study steroidogenesis. Observations were made over 12 yr on the evolution and treatment of hyperkalemia in a diabetic subject. In 1977, potassium, baseline cortisol, aldosterone, and renin activity were normal; renin activity increased normally with posture; and cortisol responded normally to ACTH infusion. Nine yr later, persistent hyperkalemia was documented. Upright renin activity was elevated to 5.26 ng · L^{-1} · s^{-1}, with concomitant elevation of 18-hydroxycorticosterone (18-OHB) and a low-normal aldosterone level. One hour after administration of 0.25 mg i.m. cosyntropin, cortisol increased normally, aldosterone increased from 220 to 360 pM, and 18-OHB increased from 3700 to 4800 pM. During treatment with fludrocortisone, fludrocortisone with furosemide, and furosemide alone, improvement of hyperkalemia was noted. Endogenous hyperreninemia and basal elevations of 18-OHB, accompanied by limited aldosterone responsiveness to renin and ACTH, suggest the presence of a partial corticosterone methyl oxidase type II defect. Evolution of hyperkalemia between 1977 and 1986 suggests this defect was acquired. *Diabetes Care* 13:790–92, 1990

Two hereditary patterns of abnormality in the terminal steps of aldosterone biosynthesis have been described and defined as corticosterone methyl oxidase type I and type II defects, displaying increased ratios, respectively, of corticosterone to 18-hydroxycorticosterone (18-OHB) and 18-OHB to aldosterone. Acquired defects of aldosterone biosynthesis also occur and are included among the proposed mechanisms of mineralocorticoid deficiency occurring in diabetic subjects, but they have been difficult to demonstrate due to coexistent hyporeninemia in many diabetic subjects. Criteria for diagnosis in the absence of hyperreninemia have been elaborated (1–3). Abnormal ratios of measured levels of 17-desoxycorticosteroids have been interpreted as evidence of a metabolic block, and the observed patterns have suggested both acquired type I and type II defects (2,4). Reported herein is a case of corticosterone methyl oxidase type II defect in which hyperkalemia and hyperreninemia evolved during 9 yr of observation after the onset of orthostatic hypotension.

RESEARCH DESIGN AND METHODS

In 1977, renin activity was determined by kit (Schwartz-Mann, Orangeburg, NY) for the quantitative radioimmunoassay of angiotensin I generated in plasma. In 1986, the in vitro angiotensin I-Biotecx radioimmunoassay kit (Friendswood, TX) was used for quantitative measurement of plasma renin activity. Normal ranges were 110–860 pM for aldosterone, 170–690 nM for 0800 serum cortisol by radioimmunoassay, and 140–1130 pM for upright 18-OHB (5,6). During hospitalization in 1977, the patient received an 86-mmol sodium diet; postural studies and ACTH infusion inadvertently were performed on the same day. Forty units of ACTH

in 500 ml normal saline were infused over 8 h, cortisol was measured at 0 and 8 h, and renin activity and aldosterone were measured supine at 0 h and after sitting for 4 h. In 1986 and 1987, the patient was ambulatory and upright. In 1986, synthetic 1,24-ACTH was given intramuscularly, and hormones were assayed at 0 and 60 min.

CASE REPORT

In October 1986, a 69-yr-old (gravida 1, para 1) woman was evaluated for hyperkalemia of at least 8 mo duration, with a history of diabetes mellitus since the mid-1940s complicated by proliferative retinopathy and peripheral neuropathy, postoperative hypothyroidism diagnosed in 1976, levothyroxine and insulin treatment, and use of cigarettes and alcohol. One son had diabetes.

Orthostatic hypotension required evaluation in 1977. Her blood pressure supine was 130/65 mmHg and standing 80/52 mmHg. Serum concentrations were sodium 140 mM, potassium 5.0 mM, chloride 104 mM, and CO_2 combining power 24 mM. Renin activity expressed as angiotensin generation was 0.26 ng · L^{-1} · s^{-1} supine and 1.72 ng · L^{-1} · s^{-1} upright (normal ranges 0.14–0.42 ng · L^{-1} · s^{-1} supine on 110-mmol sodium diet and 1.12–2.22 ng · L^{-1} · s^{-1} upright on 10-mmol sodium diet). Aldosterone was 290 pM supine before ACTH and 550 pM upright during ACTH infusion. Cortisol before and after ACTH infusion was 550 and 880 nM, respectively. Orthostasis required no therapy. In 1985, her serum potassium was 4.9 mM.

Persistent hyperkalemia was noted after February 1986. Serum concentrations were creatinine 200 μM, sodium 137 mM, potassium 5.9 mM, chloride 107 mM, and serum CO_2 combining power 19 mM. In March 1986, an ankle fracture was pinned. In September 1986, she was briefly heparinized for deep venous thrombosis and a pacemaker was inserted for bradycardia-tachycardia syndrome. On physical examination in late 1986 blood pressure was 130/60 mmHg sitting and 118/70 mmHg standing. Advanced neurotrophic abnormalities of the joints and bones of the lower extremities were present. Serum concentrations were albumin 40 g/L (normal 30–52 g/L), thyroxine 69 nM (normal 64–154 nM), and thyroid-stimulating hormone 4.3 mU/L (normal 0.5–3.5 mU/L). Renin activity was 5.26 ng · L^{-1} · s^{-1} (normal upright on 10-mmol sodium diet 1.80–3.34 ng · L^{-1} · s^{-1}), aldosterone was 330 pM, and 18-OHB was 1570 pM. After administration of synthetic 1,24-ACTH, there were increases of cortisol from 470 to 830 nM, of aldosterone from 220 to 360 pM, and of 18-OHB from 3700 to 4800 pM (Fig. 1).

Fludrocortisone therapy 0.1 mg/day was initiated. The patient required the addition of furosemide and lanoxin due to congestive heart failure. While on these medications in 1987, renin activity was 7.38 ng · L^{-1} · s^{-1}. Mean ± SD ambulatory serum potassium levels were 5.6 ± 0.3 mM (n = 7) during the 9 mo before fludrocortisone treatment, 5.1 ± 0.3 mM (n = 7) during 12 mo of fludrocortisone treatment without and with addition of furosemide, 5.3 ± 0.3 mM (n = 4) during 12 mo of subsequent furosemide treatment without fludrocortisone, and 5.2 mM (n = 1) after resumption of fludrocortisone. Her medical problems were compensated until her death in late 1988 at a neighboring hospital with the clinical diagnosis of myocardial infarction and cardiogenic shock.

DISCUSSION

The case documents evolution over 9 yr of hyperkalemia and hyperreninemia, demonstrated in an angiotensin-generation system. The possibility that the patient was mineralocorticoid deficient is strongly suggested by her low aldosterone concentrations in the presence of elevated renin activity, her presentation with hyperkalemia, and the improvement of hyperkalemia during fludrocortisone administration.

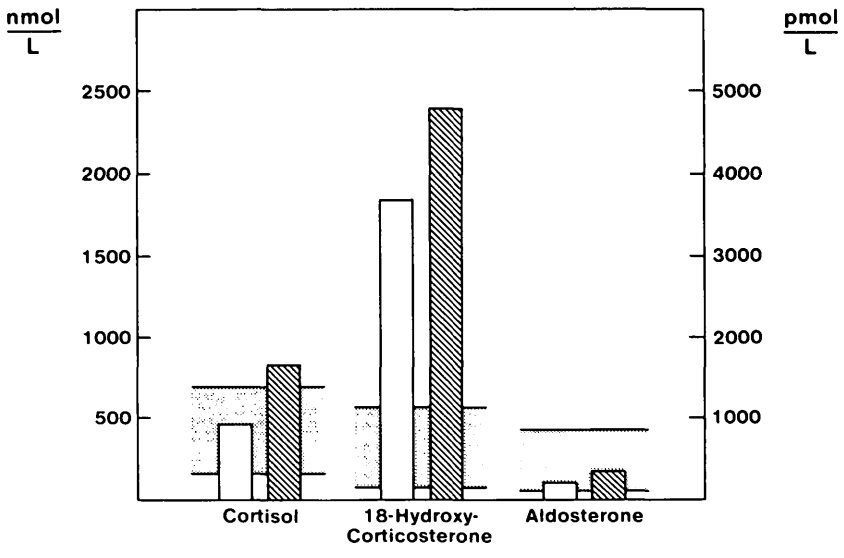

FIG. 1. Serum potassium level was 6.6 mM on day of ACTH test. Levels of cortisol are expressed in nanomoles per liter and 18-hydroxycorticosterone and aldosterone in picomoles per liter. *Open box*, baseline; *hatched box*, post-ACTH; *stippled areas*, normal range.

The hyperreninemia persisted despite mineralocorticoid treatment in 1987 and probably was multifactorial, due in part to congestive heart failure and diuretic therapy. In 1986, endogenous hyperreninemia provided a test of the function of the zona glomerulosa. The criteria met for diagnosis of partial corticosterone methyl oxidase type II defect were basal elevations of 18-OHB and limited aldosterone responsiveness to renin and ACTH.

The etiology of biosynthetic defects of aldosterone first detected in later life is unknown. Of relevance is the purification of a single bovine enzyme present in the zona glomerulosa and fasciculata that catalyzes 11-β-hydroxylation and both the corticosterone methyl oxidase I and II steps (7). Local factors in the zona glomerulosa probably influence the enzyme to activate its aldosterone synthetic capacity. In this case, it is reasonable to postulate acquired inhibition of biosynthesis by unknown factors perhaps related to renal disease or other complications of diabetes, causing alteration of function of proteins necessary for aldosterone biosynthesis, rather than an autoimmune or a congenital enzymatic defect.

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Received for publication 25 September 1989 and accepted in revised form 17 January 1990.

REFERENCES

1. Ulick S: Diagnosis and nomenclature of the disorders of the terminal portion of the aldosterone biosynthetic pathway. *J Clin Endocrinol Metab* 43:92–96, 1976
2. DeLeiva A, Christlieb AR, Melbee JC, Graham CA, Day RP, Luetscher JA, Zager PG: Big renin and biosynthetic defect of aldosterone in diabetes mellitus. *N Engl J Med* 295:639–43, 1976
3. Rosler A, Ulick S: Criteria for diagnosis of aldosterone biosynthetic defects (Letter). *N Engl J Med* 295:1383, 1976
4. Tuck ML, Mayes DM: Mineralocorticoid biosynthesis in patients with hyporeninemic hypoaldosteronism. *J Clin Endocrinol Metab* 50:341–47, 1980
5. Vetter W, Vetter H, Siegenthaler W: Radioimmunoassay for aldosterone without chromatography. *Acta Endocrinol* 74:558–67, 1973
6. Martin VI, Edwards CRW, Biglieri EG, Vinson GP, Bartter FC: The development and application of a radioimmunoassay for 18-hydroxycorticosterone. *Steroids* 26:591–604, 1975
7. Yanagibashi K, Haniu M, Shively JE, Shen WH, Hall P: The synthesis of aldosterone by the adrenal cortex: two zones (fasciculata and glomerulosa) possess one enzyme for 11-β, 18-hydroxylation, and aldehyde synthesis. *J Biol Chem* 261:3556–62, 1986

Abnormal Lipoprotein Composition in Normolipidemic Diabetic Patients

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To see whether there are any lipoprotein abnormalities in diabetic patients without hyperlipidemia, lipoprotein composition was examined in 75 strictly normolipidemic diabetic patients. Their plasma cholesterol (chol) and triglyceride (TG) were limited to <6.0 and <1.7 mM, respectively. Body-weight– and age-adjusted normolipidemic healthy subjects served as the control group. Plasma total chol and TG and low-density lipoprotein (LDL-) and high-density lipoprotein (HDL-) chol were identical in the diabetic and control subjects. Total apolipoprotein B (apoB) in the plasma of the diabetic subjects was significantly elevated. The chol-apoB ratio in the TG-rich (very-low-density + intermediate-density) lipoprotein fraction (Sf12–400) of the diabetic subjects was significantly higher than the control value, whereas LDL-apoB levels were increased and chol-apoB ratio in the LDL fraction was significantly suppressed in the diabetic subjects. Because each LDL particle contains only one apoB molecule, apoB and chol-apoB ratio in this fraction can represent particle number and chol loading of the LDL particles, respectively. Thus, these data suggest that LDL particle number is increased, and the particles are chol depleted in diabetic subjects even if they are normolipidemic.
***Diabetes Care* 13:792–96, 1990**

Diabetes mellitus is an important risk factor for coronary heart disease (1). Prolonged hyperglycemia may directly injure coronary arteries and thereby promote atherogenesis. Moreover, diabetic patients are frequently hyperlipidemic and are at higher risk even when normolipidemic (1,2). Therefore, factors associated with diabetes are presumably responsible for the higher incidence of cardiovascular complications. Several studies have described abnormalities in the composition of lipoproteins from normolipidemic diabetic patients. Our previous observation revealed an increased cholesterol (chol) concentration in the Sf20–