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BRIEF REPORT

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Transient hyporeninemic hypoaldosteronism in acute glomerulonephritis

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Abstract While hyporeninemic hypoaldosteronism (HH) has been well described in relation to chronic renal diseases, transient HH has rarely been reported. Here we present a 9-year-old boy with acute glomerulonephritis who developed hyperkalemia, which persisted for a period of 3 weeks despite normal values of creatinine clearance and an absence of acidosis. He was diagnosed as having HH because of low basal plasma renin activity and serum aldosterone level. Renal biopsy showed diffuse endocapillary proliferative glomerulonephritis. There were no apparent pathological changes in the juxtaglomerular apparatus (JGA). Rapid adrenocorticotropic hormone administration increased adequately both serum aldosterone and cortisol levels. Responses of both plasma renin activity and serum aldosterone level following the furosemide upright provocation were blunted in the hyperkalemic acute phase, but recovered in the normokalemic convalescent phase. Serum levels of human atrial natriuretic peptide were within normal range, both in the hyperkalemic and normokalemic phases. These results suggested that a transient dysfunction of the JGA, without volume expansion or structural damage of the JGA, caused HH in this patient.

Keywords Juxtaglomerular apparatus · Hyperkalemia · Renin-aldosterone axis · Pathogenesis · Post-infectious glomerulonephritis

Introduction

Hyporeninemic hypoaldosteronism (HH) is the most common form of isolated selective hypoaldosteronism [1], characterized by hyperkalemia due to a selective deficiency of aldosterone secretion by the adrenal gland, which is unassociated with abnormalities of glucocorticoid secretion [2, 3]. While most patients with HH have asymptomatic hyperkalemia, some patients show symptoms associated with hyperkalemia, such as muscle weakness or cardiac arrhythmias [1, 4]. Major underlying disorders of HH are chronic renal diseases with mild or moderate renal dysfunction, including diabetic glomerulosclerosis, interstitial nephritis, hypertensive nephropathy, gouty nephropathy, glomerulonephritis, and analgesic nephropathy [4]. Because HH usually tends to persist, transient HH is rare, having been described only in some patients with lupus nephritis [5, 6, 7] or with acute post-infectious glomerulonephritis [8]. While precise pathogenic mechanisms for the development of transient HH remain unclear, Don and Schambelan [8] reported transient HH in four patients with acute glomerulonephritis (AGN), suggesting that structural damage to the juxtaglomerular apparatus (JGA) with impaired release of renin by an inflammatory process, and/or physiological suppression of renin secretion by volume expansion caused transient HH. To clarify mechanisms for the development of transient HH, we performed pathological and endocrinological examinations on an AGN patient with transient HH.

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Case report

A 9-year-old boy was referred to the emergency department of our hospital on 3 October 2001 suffering from abdominal pain 2 days after being struck in the abdomen. He had suffered from common cold-like symptoms 2 weeks before, which subsided without any medication.

In the emergency department, the patient had upper abdominal pain and tenderness, mild abdominal bulging, and Brumberg's sign. Blood pressure was 130/88 mmHg. Body weight was 26 kg (+2 kg before the present illness). No edema was found in the eyelids or the legs. Abdominal computed tomography showed fluid collection in the right retroperitoneal and pelvic spaces. Laboratory study showed serum potassium (K) of 5.7 mEq/l, blood urea nitrogen (BUN) of 52.0 mg/dl, and serum creatinine of 0.7 mg/dl. Urinalysis showed microscopic hematuria without proteinuria or

casts. Complete blood cell counts, liver enzymes, serum electrolytes, except for K, and blood gas analysis were within the normal ranges. He was suspected of having a traumatic renal injury and was admitted to the Emergency and Critical Care Unit. He underwent intravenous infusion of K-free fluid and oral administration of furosemide and calcium polystyrene sulfonate. Two days later, he developed a generalized edema, oliguria, and hypertension (148/90 mmHg). The body weight increased to 27.7 kg. Laboratory study revealed serum K of 6.7 mEq/l, BUN of 31.5 mg/dl, serum creatinine of 0.6 mg/dl, and hypocomplementemia (C3 7 mg/dl, CH_{50} <12.0 CH_{50}U/ml). Urinalysis showed protein of 640 mg/day, 3+ occult blood, many red blood cells per high-power field, 10–19 white blood cells per high-power field, and various casts per high-power field. Serum sodium, serum chloride, and blood gas analysis were normal. Antinuclear antibody, double-stranded anti-DNA antibody, circulating immune complexes, hepatitis B virus antigen, anti-hepatitis C virus antibody, and anti-human immunodeficiency virus antibody were negative. Anti-streptolysin O and antistreptokinase titers were within the normal ranges. The throat swab culture grew no pathogenic agents. From these findings, he was diagnosed as having AGN. He underwent two courses of hemodialysis, a dietary restriction of NaCl (5 g/day) and K (<60 mEq/day), and anal administration of calcium polystyrene sulfonate. Thereafter, his urine output increased, and generalized edema and hypertension subsided. However, the serum concentrations of K continued to be high (5.5–6.4 mEq/l).

On 15 October, despite the normal creatinine clearance (103 ml/min per 1.73 m^2) and an absence of acidosis, the serum concentration of K was 6.4 mEq/l. Fractional excretion of K (FEK) was 3.68%. His body weight decreased to 24 kg, and his blood pressure was 102/48 mmHg. Serum aldosterone level and plasma renin activity after 2 h of bed rest were 3.4 (normal 3.6–24) ng/dl and <0.1 (normal 0.1–2.0) ng/ml per hour, respectively. From these findings, he was diagnosed as having HH.

On 23 October, he underwent percutaneous renal biopsy. Light microscopy showed diffuse endocapillary proliferative glomerulonephritis with focal and segmental tram track lesions (Fig. 1A). There were no apparent pathological changes, such as inflammatory cell infiltration or vasculitis in the JGA. The tubulointerstitial changes were absent. Immunofluorescence showed diffuse and granular depositions of C3 and IgG along the capillary walls and in the mesangium. Electron microscopy revealed subepithelial humps, segmental widening of subendothelial spaces, and segmental deposition of electron-dense deposits in the subendothelial spaces (Fig. 1B).

The patient's hyperkalemia gradually improved spontaneously, and disappeared on 30 October. The FEK was 11.70%. The concentration of C3 increased into the normal range, and proteinuria disappeared on 5 November. The patient was discharged from the hospital on 9 November. Two months later, the patient was fully recovered, having normal renal function and normokalemia.

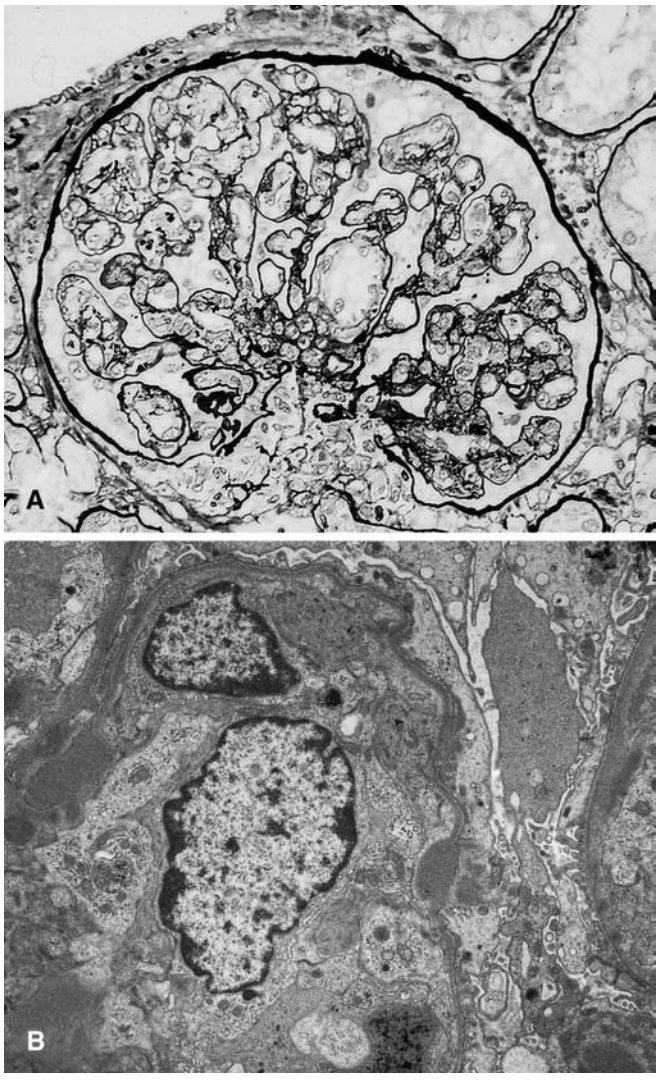


Fig. 1 **A** Light micrograph showing global endocapillary proliferation with focal and segmental tram track lesions (Periodic acid-methenamine silver, ×80). **B** Electron micrograph showing humps, widening of subendothelial spaces, and segmental effacement of foot process. Some subendothelial electron-dense deposits are also present (×4,130)

Methods

Written informed consent was obtained from the patient and his parents after explaining the aims and procedures of the studies. The patient was studied on a constant diet containing 5 g/day of NaCl and K <60 mEq/day. Blood samples for baseline concentrations of serum aldosterone, plasma renin activity, serum human atrial natriuretic peptide (hANP), and plasma cortisol were obtained at 9:00 a.m. after an overnight fast with bed rest.

For the rapid adrenocorticotropic hormone (ACTH) stimulation test, blood samples for baseline serum cortisol and serum aldosterone were taken; 250 μg of α-ACTH was then injected intravenously. One hour after the injection of ACTH, blood samples for serum cortisol and serum aldosterone were taken.

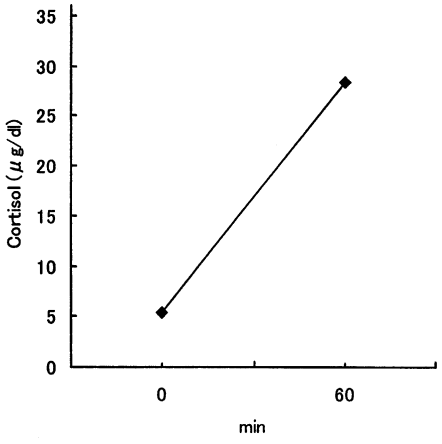
For the furosemide upright posture test, blood samples for baseline serum aldosterone and plasma renin activity were taken; 25 mg of furosemide was then injected intravenously, and the patient was kept standing for 120 min. Blood samples for stimulating serum aldosterone and plasma renin activity were obtained 120 min after furosemide injection and standing.

The rapid ACTH test was performed in the hyperkalemic phase (serum K was 5.5 mEq/l). The furosemide upright posture test and measurements of hANP, urinary aldosterone, and FEK were performed both in the hyperkalemic (serum K was 5.6 mEq/l) and the normokalemic phases (serum K was 4.3 mEq/l).

The patient was normotensive both in the hyperkalemic (104/48 mmHg) and the normokalemic (102/54 mmHg) phases. Body weight (24 kg, the same weight as before the present illness) did not change during the studies. The patient did not have edema in either phase. While the patient took calcium polystyrene sulfonate at the time of the study in the hyperkalemic phase, he had no antihypertensive drugs during the studies.

Results

Results of the rapid ACTH test are shown in Fig. 2. The basal level of serum aldosterone (2.7 ng/dl, normal



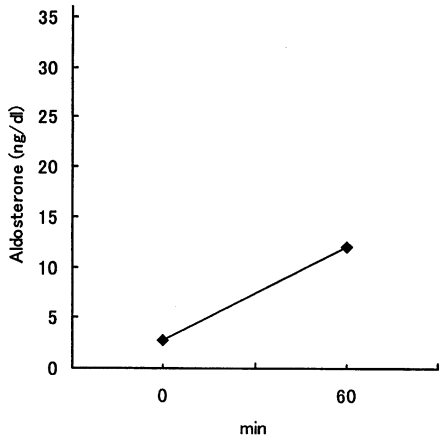
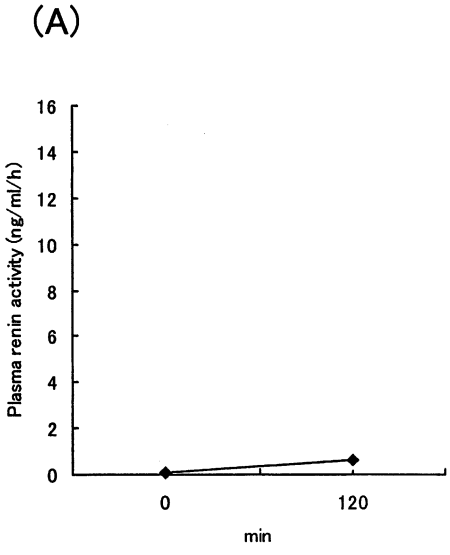
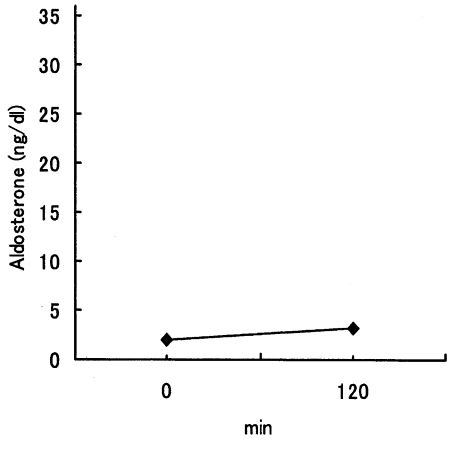
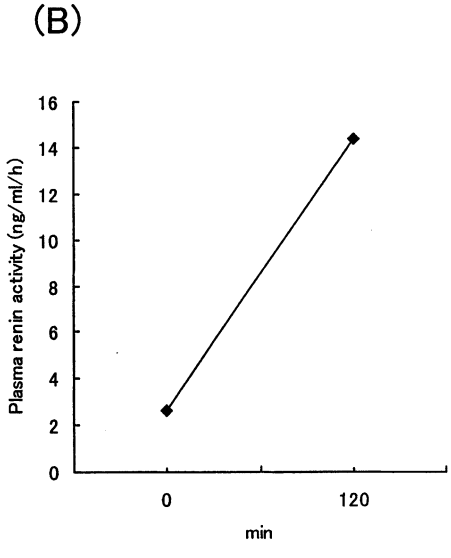


Fig. 2 Response of plasma cortisol and serum aldosterone levels to an intravenous administration of adrenocorticotropic hormone







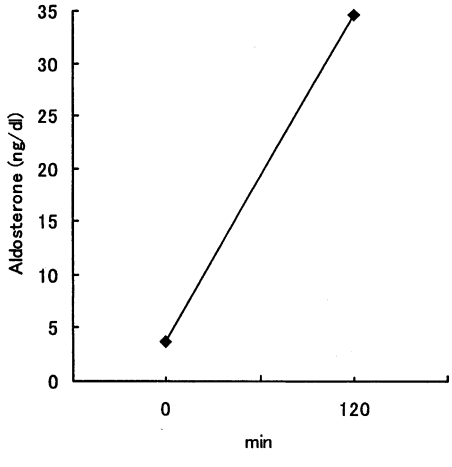


Fig. 3 Response of plasma renin activity and serum aldosterone level to furosemide upright posture in the hyperkalemic phase (**A**) and in the normokalemic phase (**B**)

3.6–24.0 ng/dl) was low. The basal cortisol level (5.4 μg/dl, normal 4.0–23.3 μ g/dl) was normal. Both responses of serum aldosterone (12.0 ng/dl) and plasma cortisol (28.3 μg/dl) levels to the administration of ACTH were normal.

The results of the furosemide upright posture test are shown in Fig. 3. In the hyperkalemic phase, both basal levels of serum aldosterone (2.1 ng/dl) and plasma renin activity (<0.1 ng/ml per hour, normal 0.1–4.0 ng/ml per hour) were low, and the responses of serum aldosterone (3.3 ng/dl) and plasma renin activity (0.6 ng/ml per hour) to the challenge of furosemide and upright posture were blunted (Fig. 3A). However, basal levels of serum aldosterone (3.7 ng/dl) and plasma renin activity (2.6 ng/ml per hour), and responses of serum aldosterone (34.7 ng/dl) and plasma renin activity (14.4 ng/ml per hour) to the challenge of the furosemide upright posture, normalized in the normokalemic phase (Fig. 3B).

Urinary excretion of aldosterone was low in the hyperkalemic phase (0.1 μg/day, normal 1.0–11.0 μg/day), and increased into the normal range in the normokalemic phase (1.8 μg/day).

FEK in the hyperkalemic phase and in the normokalemic phase were 4.30% and 11.23%, respectively. Serum concentrations of hANP were normal both in the hyperkalemic (30.0 pg/dl, normal <43.0 pg/dl) and the normokalemic (26.1 pg/dl) phases.

Discussion

The major physiological effect of aldosterone is K excretion via activation of the epithelial sodium channel, apical potassium channel, and the basolateral membrane Na^+/K^+ pump on the cortical collecting duct [9]. In addition, aldosterone stimulates H^+ secretion in the distal tubule and the collecting duct [4]. Therefore, hypoaldosteronism induces hyperkalemia, and 50% of patients with HH showed hyperchloremic metabolic acidosis [4].

Because almost all underlying renal diseases of HH are chronic and progressive conditions, HH usually tends to persist [8]. However, our patient with AGN showed HH from which he recovered completely 3 weeks after the onset of the illness. Transient HH in renal diseases is rare, and has been reported only in three patients with lupus nephritis [5, 6, 7] and in four patients with AGN [8]. Hyperkalemia in two lupus patients with HH subsided 3 months following administration of immunosuppression therapies, in accordance with clinical improvement [5, 6]. The renal histology of one showed vasculitis involving the afferent/efferent arterioles and JGA [6]. HH subsided within 5 days in another patient with lupus nephritis whose renal biopsy revealed no pathological changes in the JGA [7]. HH in patients with AGN improved spontaneously with resolution of glomerulonephritis within 4 weeks, as in our patient [8].

Several potential mechanisms for HH have been postulated, including a primary deficiency in renin secretion due to damage of the JGA [10, 11], acquired enzymatic defects in aldosterone biosynthesis [12, 13], extracellular fluid volume expansion resulting from impaired salt and water excretion [14], or impaired renal prostaglandin production [15]. In renal diseases, structural damage of the JGA and volume expansion are thought to be the most likely causes of HH [4, 11, 14].

While the precise pathogenesis of transient HH in AGN is unknown, Don and Schambelan [8] suggested that structural JGA damage due to the inflammatory process and/or physiological suppression of renin secretion by volume expansion were operative in AGN. In their report, volume expansion was present in two of the three patients in whom plasma volume determinations were obtained. However, they did not show the renal histological findings of their patients [8].

The present study demonstrated that no histological changes were found in the JGA; rapid ACTH administration increased both serum aldosterone and plasma cortisol levels; responses of both plasma renin activity and serum aldosterone level following the furosemide upright provocation were blunted in the hyperkalemic acute phase, but recovered in the normokalemic convalescent phase; and serum levels of hANP were within normal range both in the hyperkalemic and normokalemic phases. Normal results of the rapid ACTH test indicated no enzymatic defect of aldosterone biosynthesis. The results of the furosemide upright test confirmed transient HH in the patient. Because the stimulus for the secretion of hANP is atrial stretch or pressure, its normal value means an absence of plasma volume expansion [16]. These findings suggest that a transient dysfunction of the JGA, without structural damage of the JGA or volume expansion, caused HH in this patient. An absence of structural damage of the JGA may explain the prompt disappearance of HH, although the precise mechanisms for the development of the JGA dysfunction in the patient remain unclear.

References

1. Hudson JB, Chobanian AV, Relman AS (1957) Hypoaldosteronism. A clinical study of a patient with an isolated adrenal mineralocorticoid deficiency, resulting in hyperkalemia and Stokes-Adams attacks. N Engl J Med 257:529–536
2. Michelis MF, Murdaugh HV (1975) Selective hypoaldosteronism. Am J Med 59:1–5
3. Tan SY, Burton M (1981) Hyporeninemic hypoaldosteronism. Arch Intern Med 141:30–33
4. DeFronzo RA (1980) Hyperkalemia and hyporeninemic hypoaldosteronism. Kidney Int 17:118–134
5. Kiley J, Zager P (1984) Hyporeninemic hypoaldosteronism in two patients with systemic lupus erythematosus. Am J Kidney Dis 4:39–43
6. Kozeny GA, Hurley RM, Fresco R, Vertuno LL, Bansal VK, Hano JE (1986) Systemic lupus erythematosus presenting with hyporeninemic hypoaldosteronism in a 10-year-old girl. Am J Nephrol 6:321–324
7. Hataya H, Ikeda M, Ide Y, Kobayashi Y, Kuramochi S, Awazu M (1999) Distal tubular dysfunction in lupus nephritis of childhood and adolescence. Pediatr Nephrol 13:846–849
8. Don BR, Schambelan M (1990) Hyperkalemia in acute glomerulonephritis due to transient hyporeninemic hypoaldosteronism. Kidney Int 38:1159–1163

9. Stokes JB (1999) Disorders of the epithelial sodium channel: insights into the regulation of extracellular volume and blood pressure. Kidney Int 56:2318–2333
10. Schambelan M, Stockigt JR, Biglieri EG (1972) Isolated hypoaldosteronism in adults. A renin-deficiency syndrome. N Engl J Med 287:573–578
11. Weidmann P, Reinhart R, Maxwell MH, Rowe P, Coburn JW, Massry SG (1973) Syndrome of hyporeninemic hypoaldosteronism and hyperkalemia in renal disease. J Clin Endocrinol Metab 36:965–977
12. DeLeiva A, Christlieb AR, Melby JC, Graham CA, Day RP, Luetscher JA, Zager PG (1976) Big renin and biosynthetic defect of aldosterone in diabetes mellitus. N Engl J Med 295:639–643
13. Muto S, Akai Y, Ono S, Kusano E, Asano Y (2001) Selective hypoaldosteronism due to combined defects of the conversion from inactive renin to active renin and the aldosterone biosynthesis from corticosterone. Nephron 88:247–253
14. Oh MS, Carroll HJ, Clemmons JE, Vagnucci AH, Levison SP, Whang ESM (1974) A mechanism for hyporeninemic hypoaldosteronism in chronic renal disease. Metabolism 23:1157–1166
15. Nadler JL, Lee FO, Hsueh W, Horton R (1986) Evidence of prostacyclin deficiency in the syndrome of hyporeninemic hypoaldosteronism. N Engl J Med 314:1015–1020
16. Maack T (1996) Role of atrial natriuretic factor in volume control. Kidney Int 49:1732–1737