Dexamethasone suppressible hyperaldosteronism in a child with nephrosclerosis

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Abstract. A 9 year old Mexican boy presented with severe hypertension, hypokalaemia and features suggesting acute glomerulonephritis. Nephrosclerosis was present on renal biopsy. Aldosterone levels were unresponsive to variations in dietary salt intake and plasma renin activity was suppressed. Following oral dexamethasone therapy (2 mg/day), plasma aldosterone decreased to undetectable levels, serum potassium normalized and plasma renin activity gradually increased. Dexamethasone also restored the normal responsiveness of the renin-aldosterone system to postural stimuli. The patient exhibited a marked response to a single dose of ACTH with a rise in plasma aldosterone. Long-term blood pressure control and normal potassium levels have been achieved with oral prednisone therapy (5 mg/day) for a period of one year. This case of dexamethasone suppressible hyperaldosteronism (DSH) illustrates that the degree of hypertension in this syndrome may produce severe renal microvascular lesions. DSH should be considered in all children who present with low renin hypertension.

Arterial hypertension resulting from overproduction of aldosterone is uncommon in the paediatric age group. Prior to 1967, only ten cases of primary aldosteronism had been described in children (New & Peterson 1968). Bilateral adrenal hyperplasia was the predominant pathologic abnormality, in contrast to adults where a hormone producing tumour is the usual aetiologic entity. A rare subgroup of hyperaldosteronism has been described among several families during the past decade (New et al. 1973; Giebink et al. 1973; Grim & Weinberger 1980). Its presenting clinical and biochemical features are similar to those of primary hyperaldosteronism, and include moderate hypertension in association with hypokalaemia and suppressed plasma renin activity. Urinary aldosterone excretion is frequently inappropriately elevated during periods of increased sodium intake. This syndrome is characterized by the ability of dexamethasone to promptly suppress aldosterone, resulting in normalization of the blood pressure and reversal of the biochemical abnormalities.

We are reporting a case of dexamethasone suppressible hyperaldosteronism who presented with clinical features suggesting acute glomerulonephritis, severe hypertension and renal biopsy findings of significant nephrosclerosis.

Case History

A 9 year old Mexican boy was hospitalized because of lethargy and high blood pressure. On the morning of admission he complained of abdominal cramping and paresthesias in all extremities. An unidentified antihista-mine medication was administered iv, immediately following which he suffered a cardio-pulmonary arrest. He was successfully re-suscitated and subsequently transferred to the University of Arizona Hospital.

There was no past history of renal or cardiac disease. His father had been treated for asymptomatic essential hypertension for several years.

On physical examination the blood pressure was 150/110 mmHg and the pulse rate 105/min. The chest revealed a hyperdynamic precordium. Heart and abdomen were otherwise normal. Funduscopic examination showed arteriolar narrowing and spasm. Neurologic
examination was normal apart from an altered mental status. Admission laboratory data included a normal blood count and platelets; BUN 16 mg/100 ml, creatinine 0.8 mg/100 ml, sodium 138 mEq/l, chloride 96 mEq/l, potassium 2.0 mEq/l, bicarbonate 33 mEq/l. Urinalysis revealed 1+ protein, 4+ blood, and many cellular casts. Subsequent data included a negative antinuclear antibody, normal complement components (C3 and C4), antistreptolysin titer 125 Todd units.

**Hospital course**

His blood pressure was initially controlled with iv sodium nitroprusside and he subsequently received oral propranolol, hydralazine, hydrochlorothiazide, aldactone and potassium supplementation. Because of continued proteinuria, microhaematuria, a rising BUN (88 mg/100 ml) and creatinine (1.8 mg/100 ml), a renal biopsy was performed. Subsequently his renal function improved spontaneously and he was discharged on the tenth hospital day. One month later his renal function had returned to normal (BUN 17 mg/100 ml, creatinine 0.7 mg/100 ml). Renal arteriogram showed kidneys of equal size and normal vascularity.

Blood for renal venous renin analysis was collected following discontinuation of all medications for five days. The patient was placed on a low salt diet and received furosemide 40 mg by mouth daily for two days prior to the study. The samples were analyzed by Bioscience Laboratories, Van Nuys, California. Values from left renal vein, right renal vein, superior vena cava and inferior vena cava were all 0.3 ng/ml/h. On a 24 h urine collection, urinary metanephrines were 1.1 µg/mg creatinine (normal 0–2.2). Urinary catecholamines were 2.0 µg/24 h (normal 0–135).

**Renal biopsy**

The glomeruli were normal as were the tubulo-interstitial structures. The major abnormalities in the biopsy were confined to the microvasculature. Well defined subintimal hyaline material was present in the afferent arterioles. In addition, the interlobular arteries showed moderate thickening. These changes were present throughout the biopsy.

Electron microscopic and immunofluorescent examination of the glomeruli was normal.

**Special studies**

The patient was re-admitted for metabolic balance studies on three occasions over the ensuing year.

**Materials and methods**

Plasma and urinary electrolytes (sodium and potassium) were measured by flame photometry. Creatinine was measured on an autoanalyzer using the Jaffé method. Plasma and urinary aldosterone, plasma cortisone, corticosterone and deoxycorticosterone (DOC) were measured by previously reported methods (New et al. 1966). Urinary aldosterone excretion was evaluated using a nomogram established with data on 230 normal children, where urinary aldosterone was plotted as a function of urinary sodium excretion (New et al. 1976a). Plasma renin was measured by the method of Haber et al. (1969).

**Experimental protocol**

Dietary intake was rigidly controlled and completeness of urinary collections was ensured by measurement of total creatinine excretion. Blood samples were obtained at 08.00 a.m., following 2 h of upright posture. Blood pressure were measured in the supine position every 4 h. The values reported in Fig. 1 are those obtained at 10.00 h.

**Results**

The results of the three metabolic study periods are depicted graphically in Fig. 1.

**Study period 1 (August 1978)**

This study period was designed to evaluate the effects of variable salt intake, and the short term effects of dexamethasone administration. Baseline plasma aldosterone (29.8 ng/100 ml) and urinary aldosterone (12.4 µg/24 h) were normal and showed no significant response to five days of salt restriction (10 mEq NaCl/day). On day 2 of the high salt diet (150 mEq NaCl/day), blood pressure rose to 160/120 mmHg, and he was treated with furosemide 40 mg iv. Thus the aldosterone response to high salt intake could not be completely evaluated.

During the latter four days of study, he received a normal salt intake (87 mEq NaCl/day) and oral dexamethasone 0.5 mg qid. A prompt suppression of both plasma and urinary aldosterone ensued, and plasma renin levels suppressed.

Baseline values of plasma cortisol, corticosterone and deoxycorticosterone were initially normal and increased following salt restriction. Urinary 17-ketosteroids and 17-hydroxysteroids remained in the normal range throughout this period.

**Study period 2 (November 1978)**

This study period (12 days) was designed to test the effects of prolonged oral dexamethasone administration (0.5 mg qid). Initial plasma aldosterone (13.0 ng/ml) was normal and plasma renin activity was low (0.12 ng/ml/h). While receiving dexamethasone, renin increased progressively and aldoste-
Metabolic response to variations in salt intake and dexamethasone administration. On day 7 of period 1 (August 1978), the patient received furosemide, 40 mg iv, indicated by +. Plasma renin and plasma aldosterone values depicted by cross hatched bars were obtained in upright posture. Values depicted by solid bars were obtained in supine position. On day 11 of period 3 (July 1979), plasma samples for renin and aldosterone were drawn prior to ACTH (*), and following ACTH (**), both in the upright position. Normal range of plasma aldosterone 5.2–17.7 ng/100 ml. Normal urinary aldosterone excretion 15 ± 10 µg/day (mean ± 1SD).

**Study period 3 (July 1979)**

Two parameters were evaluated during this study period: (a) the responsiveness of the renin-aldosterone system to postural stimuli, and (b) the acute effects of ACTH administration on renin and aldosterone. The patient had been taking prednisone 5 mg/day for eight months prior to this study and was maintained on dexamethasone (0.5 mg qid) during hospitalization. Plasma renin and aldosterone were initially within the normal range. On day 5 and 6 (normal salt intake) and on day 10 (low salt intake), both plasma renin and aldosterone exhibited a significant increase following 2 h
of upright posture. On day 11, 40 units of ACTH, administered in 250 ml of 5% dextrose over 4 h produced a dramatic rise in plasma aldosterone (32 to 141 ng/100 ml), and caused a suppression of plasma renin from 25 to 5 ng/ml/h. Plasma cortisol, corticosterone and deoxycorticosterone were initially normal and showed an appropriate increase following ACTH administration.

Discussion

Dexamethasone supressible hyperaldosteronism (DSH) is a syndrome characterized by low renin hypertension and clinical and biochemical features closely resembling primary aldosteronism. The response to dexamethasone provides a means to distinguish these two diseases. Acute glomerulonephritis was initially suspected in this patient, who presented with severe hypertension, an abnormal urine sediment and declining renal function. However, the occurrence of nephrosclerosis on kidney biopsy confirmed that the hypertension was not of recent onset. The transient deterioration of renal function may have resulted from renal ischaemia incurred during aggressive blood pressure control or following the cardiac arrest.

Primary aldosteronism was suggested by the presence of persistent hypokalaemia, bilaterally suppressed renal venous renin activity and the failure to completely suppress plasma aldosterone with salt loading. The prompt suppression of aldosterone following treatment with dexamethasone confirmed the diagnosis of DSH. Satisfactory blood pressure control was achieved on low dose prednisone (5 mg/day) during the year of out-patient observation.

The mechanisms responsible for the hyperaldosteronism in this syndrome are not completely understood. It has been suggested that the underlying pathophysiology in DSH results from an enhanced sensitivity of the adrenal cortex to ACTH (Grim & Weinberger 1980). In normal individuals, ACTH administration causes a transient elevation of aldosterone, but this effect is not prolonged, and aldosterone levels return to normal after several days (Newton & Laragh 1968). In one of the earliest reports of this syndrome (New & Peterson 1967), elevated ACTH levels were described, but this has not been a consistent feature. However, other studies in patients with DSH have indicated that the aldosterone response to ACTH administration is exaggerated and prolonged (Rauh et al. 1978). It is postulated that in this disorder, aldosterone production occurs through abnormal pathways in the zona fasciculata of the adrenal cortex.

Administration of dexamethasone to patients with primary hyperaldosteronism causes a transient and incomplete suppression of aldosterone, which may be a non-specific effect on synthesis. However, unlike patients with DSH, there is no reversal of renin suppression. The mechanism by which dexamethasone suppresses the hyperaldosteronism in DSH is not known. No specific enzyme defects in the metabolic synthetic pathways of glucocorticoids are apparent in this syndrome. It has been postulated that an unidentified hormone, which is sensitive to the suppressive effect of glucocorticoids, is responsible for the persistent stimulation of aldosterone in patients with DSH (New et al. 1976b).

In addition to its effect on aldosterone, dexamethasone restores the normal responsiveness of the renin-aldosterone axis to postural stimuli. In children, the rapidity with which blood pressure control is achieved on dexamethasone therapy is variable, and up to two weeks of therapy may be required. In adults, a longer period of time is needed before normalization of blood pressure occurs. In some cases the complications of chronic steroid administration preclude this form of therapy on a long term basis. The patient reported in this study has remained normotensive on prednisone (5 mg/day) with no evidence of steroid toxicity after one year.

Dexamethasone supressible hyperaldosteronism is a rare disease in childhood. A therapeutic trial of dexamethasone undertaken in conjunction with plasma renin and aldosterone measurements is worthwhile in young patients presenting with features of low renin hypertension. The present case report illustrates that untreated hypertension in this disease may be severe enough to produce renal injury, including nephrosclerosis.

Acknowledgments

This patient was studied on the Arizona Health Sciences Center NIH supported Clinical Research Center in Surgery (RR00714). Expert technical assistance was provided by Donna Mobley, Robin Perrin, Linda Lorenzen and Miguel Holguin.

The authors wish to express appreciation for secretarial assistance to Ms. Frances Campion and Ms. Carolina Ayala.
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Received on January 29th, 1980.