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Aldosterone hyperplasia
congenital renal alkalosis

A Short Communication. Congenital Renal Alkalosis

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Summary

Patients with idiopathic hypokalemic metabolic alkalosis and hyperreninemia have been lumped under the heading of Bartter's syndrome. However, the clinical picture is not totally uniform. Recently, Gullner *et al.* described a familial disorder with hypokalemic metabolic alkalosis, hyperreninemia, and aldosteronism, but without juxtaglomerular hyperplasia. They suggested that this family had a condition other than Bartter's syndrome. The present report details the followup from infancy to adulthood of a patient with hypokalemic metabolic alkalosis, salt wasting, and hyperreninemia, but with normal aldosterone level and without juxtaglomerular hyperplasia. The authors suggest that this new condition be termed renal alkalosis. The studies suggest that the distal tubular reabsorptive capacity was defective in this patient.

Speculation

Idiopathic hypokalemic metabolic alkalosis may be due to different pathologic entities. The disorder may be on a developmental basis.

Bartter's syndrome is a disorder characterized by hypokalemia, metabolic alkalosis, hyperreninemia with normal blood pressure, resistance to pressor effects of angiotensin II, hyperplasia of the juxtaglomerular apparatus and hyperaldosteronism (2). The pathyphysiologic mechanism of this disorder is a subject of great controversy. Several postulates have been forwarded including defective sodium transport in various segments of the renal tubule, defective chloride transport in the ascending limb, defective potassium handling by the kidney, resistance to angiotensin II, generalized defect in cation transport, and abnormalities of prostaglandin and kinin metabolism (6, 7, 12–15, 20, 21, 26–28, 36, 40).

Although patients with idiopathic hypokalemic metabolic alkalosis and hyperreninemia have been lumped under the heading of Bartter's syndrome, the clinical picture is not totally uniform. The renal response to salt restriction has been variable (2, 6, 17, 28, 31). Recently, Robson *et al.* (30) showed that the ability to conserve salt in Bartter's syndrome may be age-related, with younger patients demonstrating greater salt wasting than patients over age 3. The variability of the manifestations may also be noted in the reports of normal levels of urine and plasma aldosterone (3, 4, 17, 18). Several investigators have suggested that variations in the clinical presentation of patients with idiopathic hyperkalemia alkalosis may indicate a spectrum of a single pathologic entity or represent multiple etiologic conditions (1, 4).

This report describes the followup of a patient, from early infancy to adulthood, with hyperreninemic hypokalemic metabolic alkalosis, but with normal plasma and urinary aldosterone levels and absence of juxtaglomerular hyperplasia. It has been suggested that this represents a new entity distinct from Bartter's syndrome (23).

CASE REPORT

R. S. was admitted to the Buffalo Children's Hospital for the first time in 1960 at the age of 2 yr, 7 months for evaluation of excessive thirst, polyuria, unexplained febrile episodes, and growth failure. Height and weight were below the 3rd percentile for age. Blood pressure was 100/60 mm Hg. Laboratory studies included: BUN (15 mg/dl), serum calcium (10.1 mg/dl), serum phosphorus (4.4 mg/dl), alkaline phosphatase (8.8 B.U.), CO_2 content (32 mEq/liter), potassium (1.8 mEq/liter), sodium 136 mEq/liter), and chloride (82 mEq/liter). Venous pH was 7.45 units. Urine output was greater than 150 ml/kg/day. Twenty-four-hr excretion rates of 17 ketosteroids and hydroxycorticosteroids were normal for this age (22, 24). On a sodium intake of 3 mEq/kg/day, the fractional excretions of sodium, chloride, potassium, and phosphorus were 1.8, 3.6, 86 and 22%, respectively. After 3 days of sodium intake of 1.3 mEq/kg/day, potassium 2.1 mEq/kg/day, and chloride 3.3 mEq/kg/day, weight loss and azotemia occurred. Venous pH decreased slightly from 7.45 to 7.41, sodium fell from 136 to 126 mEq/liter, chloride from 82 to 75 mEq/liter, potassium increased from 1.8 to 2.2 mEq/liter, and serum CO_2 content from 32.5 to 34.3 mEq/liter. The fractional excretions of sodium, chloride, and potassium were 0.13, 0.47, and 30.33%, respectively.

A percutaneous renal biopsy showed changes compatible with potassium depletion. In a sample of at least 49 glomeruli (kindly performed by Bartter and McCardle), juxtaglomerular hyperplasia was not noted. Potassium citrate was begun at 6 mEq/kg/day. After 3 months, the dose was increased to 12 mEq/kg/day without normalization of serum or urine chemistries, or any effect on symptoms or growth pattern. Serum potassium remained at less than 3.0 mEq/liter. The substitution of KCl for K citrate did not affect the clinical or biochemical status. An open renal biopsy in 1961 again did not reveal juxtaglomerular hyperplasia in more than 50 glomeruli examined. Adrenal histology was essentially normal.

At 4 yr of age, sodium supplements were added. The additional electrolyte supplements amounted to potassium 10 mEq/kg/day, chloride 30 mEq/kg/day, and sodium 20 mEq/kg/day. A growth spurt occurred within a month. Subsequently that year, the height and weight increased to 10th–25th percentile. Hypokalemic alkalosis continued.

At 10 yr of age, in spite of low serum potassium levels, total body potassium was normal as measured by the ^{40}K technique. Peripheral renin activity in the upright position was 4000 units/ml/hr (bioassay method of Skeggs *et al.* (35)). The electrolyte supplements were maintained. Weight was at the 50th percentile, the height at the 25th percentile.

At 20 yr of age, hypokalemic alkalosis continued in spite of the supplements of KCl and NaCl. Weight was at the 90th percentile and height at the 10th percentile. Blood pressure and mental status remained normal. Peripheral renin activity in the upright position was 13.7 ng/ml/hr (RIA). Plasma aldosterone was 10 ng/dl (RIA) and plasma cortisol level was 9 mcg/day (RIA). Twenty-four-hr urine aldosterone was 12 mcg/day (RIA), 24-hr-urine 17 ketosteroids, and 17 ketogenic steroids were normal.

Table 1. *Peak effects of diuretics on urinary flow (U) in ml/min, bicarbonate, sodium, potassium, and chloride excretion (mEq/min)*

Subjects	Acetazolamide					Mercuhydrin					Hydrochlorothiazide				
	V	HCO_3	Na	K	Cl	V	HCO_3	Na	K	Cl	V	HCO_3	Na	K	Cl
R.S.															
Pre	0.67	0.03	0.06	0.04	0.03	0.30	0.01	0.03	0.04	0.05	0.73	0.01	0.05	0.09	0.08
Post	1.53	0.16	0.11	0.08	0.10	1.97	0.03	0.21	0.08	0.24	0.68	0.01	0.06	0.08	0.09
N.S.															
Pre	0.18	0.00	0.04	0.02	0.04	0.15	0.00	0.01	0.01	0.02	0.23	0.00	0.02	0.02	0.04
Post	0.28	0.06	0.05	0.04	0.01	0.25	0.00	0.03	0.01	0.03	0.32	0.00	0.05	0.03	0.08
A.C.															
Pre	0.60	0.01	0.06	0.02	0.03	0.12	0.01	0.03	0.01	0.01	ND[1]				
Post	0.70	0.06	0.12	0.03	0.02	0.78	0.01	0.17	0.01	0.14		ND[1]			

[1] ND, not done.

METHODS

At 3 yr of age, studies were performed to delineate the renal defect in this patient. Studies were performed while on an intake of 10 mEq/K/kg/day, sodium 2 mEq/kg/day, chloride 12 mEq/kg/day. The authors studied the effects of diuretics which are known to exert their actions at different nephron sites. Acetazolamide (5 mg/kg iv) was used as an agent which inhibits proximal tubule HCO_3 and sodium reabsorption (32). The distal tubule (5, 28) was examined using mercuhydrin (0.5 ml/kg, subcutaneously) and also by the oral administration of hydrochlorothiazide (2.5 mg/kg). Urine was collected before administration of the diuretic and hourly thereafter for 3–6 consecutive hr. The response after mercuhydrin was examined after the 1st hr after administration of the drug in order to observe the effect of mercurial after any theophyllin activity has disappeared. The aldosterone sensitive portion of the tubule was tested by the administration of spironolactone (by mouth) at 40 mg/kg/day. Twenty-four-hr urine collections were performed before and for at least 7 days after the start of spironolactone administration. Sodium, chloride, and potassium intake was kept constant as noted above. Glomerular filtration rate was determined by the clearance of inulin and creatinine. Sodium and potassium were measured by flame photometry, serum CO_2 content by the method of Van Slyke and Cullen (37), chloride by the method of Sendroy as modified by Van Slyke and Sendroy (38). Studies were also performed in a normal age-sex matched control (sodium intake was 2 mEq/kg/day, chloride 4 mEq/kg/day, potassium 2 mEq/kg/day) and a similarly matched child was made alkalotic by the administration of $NaCHO_3$ given at 3 mEq/kg/day for at least 3 days. These studies were performed in 1961.

RESULTS

The results are shown in Table 1. Before the administration of the different drugs, the urine flow, sodium, bicarbonate, potassium, and chloride excretions were greater in R.S. than the normal control. However, these parameters were similar in R.S. and the alkalotic control.

After acetazolamide, the peak increase in urine flow, bicarbonate, sodium, and chloride excretion in the normal and alkalotic controls were similar to those obtained by Walker and Cumming in 7 normal infants (39). The response noted in R.S. was greater.

Mercuhydrin administration resulted in peak increases in urine flow, bicarbonate, sodium, potassium, and chloride excretions in the normal and alkalotic control similar to those reported by Walker and Cumming (39). The effect was again greater in R.S.

Hydrochlorothiazide resulted in a slight increase in urine flow, bicarbonate, sodium, and chloride excretions in the normal control comparable in magnitude to those previously reported with this dosage of hydrochlorothiazide in infants (39). However, no effect was seen in R.S.

Spironolactone resulted in a slight increase in urine flow from 0.37–0.58 ml/min. Before the administration of spironolactone bicarbonate, sodium, potassium, and chloride excretions were 0.01, 0.03, 0.06, and 0.07 mEq/hour, respectively. After 7 days of spironolactone administration, the corresponding values were 0.50, 0.02, 0.02, and 0.02 mEq/hr.

DISCUSSION

In 1960, Pronove *et al.* (29) reported a 5-yr-old boy who had idiopathic hypokalemic alkalosis. Subsequently, additional features were noted, including hyperaldosteronism, hyperreninemia, normal blood pressure, and hyperplasia of the juxtaglomerular apparatus (2). From the time of the original publication, more than 100 cases of similar patients have been reported (30). When no cause can be identified such as diarrhea, cystic fibrosis, brain disease, abuse of laxatives and diuretics, these patients are designated as having Bartter's syndrome.

Recently Gullner *et al.* (19) described a familial disorder with hypokalemic metabolic alkalosis, hyperreninemia, and aldosteronism, but without juxtaglomerular hyperplasia (19). They suggested that this family had a condition other than Bartter's syndrome.

The present report details the followup from infancy to adulthood of a patient with hypokalemic metabolic alkalosis, salt wasting, and hyperreninemia, but with normal aldosterone levels and without juxtaglomerular hyperplasia. It is unlikely that the latter finding is due to sampling error, because the renal biopsy was performed twice with total glomerular samples of over 100 (2 yr 7 months and 3 yr 9 months). The increase in height to the 10th and 25th percentile and weight to greater than the 50th percentile after electrolyte supplementation also distinguished this patient from those with Bartter's syndrome (33, 34). In the latter condition, catchup growth in patients not treated with prostaglandin synthetase inhibitors did not occur until after adolescence (33, 34). Thus, several pieces of evidence suggest that like those reported by Gullner *et al.* (19), this patient does not have Bartter's syndrome. It is suggested that this new condition be termed renal alkalosis (9). Such a distinction is important because therapies of hypokalemic metabolic alkalosis of the Bartter's type are not without untoward side effects (8).

The authors attempted to determine the site of the renal tubular lesion in our patient by examining the response to various diuretic agents (32). Whereas clearance methods could have been employed, inferential studies of transport in various segments of the nephron are difficult under the best of circumstances and especially so when comparisons are made between normal patients and those with Bartter's syndrome (11). Because the state of hydration and acid base balance are known to modify the effects of diuretic agents (10), studies were performed at a time when the patient was clinically in a euvolemic state and an alkalotic control was also used for comparison. Acetazolamide produced a greater increase in urine flow, bicarbonate, sodium, potassium, and chloride excretion in this patient than in controls, suggesting that the proximal tubule is intact in this patient and that the areas distal to the site of action of acetazolamide did not increase their resorptive rates in a comparable fashion (32). Similarly, the greater increase in the response of this patient to the effects of mercuhydrin indicates that the thick ascending limb of Henle is functionally intact (5). The administration of hydrochlorothiazide in this patient had no significant effect on urine flow or electrolyte

excretion. The dose used has been shown to result in significant changes in urine flow and electrolyte excretion as was shown in one normal control and in the patients reported by Walker and Cummings (39). Thus, these studies suggest that the distal tubular reabsorptive capacity (25) was defective in this patient.

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