A CASE OF TRANSIENT RENAL TUBULAR ACIDOSIS TYPE 1,4 HYBRID RTA: A STUDY OF THE PATHOPHYSIOLOGIC CHARACTERISTICS OF THE ACIDIFICATION DEFECT.

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Summary

The diagnosis of transient renal tubular acidosis was made in a 16 months old boy. Bicarbonate titration studies revealed that the acidification defect consisted of an association of proximal and distal tubular acidosis. The effect of experimentally induced potassium depletion revealed that hyperkalemia contributed to the acidification defect. After correction of the acidification disorder a defect in urinary concentration was still present.

Speculation

The different tubular defects of transient renal tubular acidosis are due to reversible (toxic) damage of the tubular membrane. Assessment of distal tubular H^+ secretion by measurement of $(U-B)pCO_2$ after oral $NaHCO_3$ administration is impossible in patients with decreased urinary concentration capacity. The incidence of transient renal tubular acidosis (R.T.A.) reached a peak between 1948 and 1953. This condition was first called idiopathic renal acidosis in infancy and subsequently transient R.T.A. (12). The clinical picture and biochemical disorder as well as longterm prognosis have been studied in great detail (2,3,4,13). However accurate biochemical micro-methods for clinical use allowing a detailed study of the pathophysiological characteristics of the acidification defect were lacking at that time. In recent years few cases of transient R.T.A. have been published (7,11,14,15). We report a case of transient R.T.A. in which a detailed analysis of the acidification defect was made.

CASE REPORT

S.L., a white boy, was 16 months old on hospital admission. He was the first child of non-consanguineous parents. His younger sister was in good health and had normal levels of bicarbonate in serum. The child was admitted because of apathy, vomiting, anorexia and fretfulness. He received no medications before admission. Height was 83.5 cm (P50) and weight 8.9 kg (P10). Physical examination revealed slight hypotonia but no other abnormalities. Bloodpressure was 90/70 mmHg. Blood data: Hb 8.0 mmol/l, Hematocrit (CV) 42%, Blood pH 7.21 and base-excess -14.5 mmol/l, plasma electrolytes: Na^+ 141, K^+ 5.1 to 6.1, Cl^- 117, Ca^{2+} 2.44 and P_i 1.82 mmol/l. Serum creatinine was 27 μ mol/l, urea 5.0 mmol/l and alkaline phosphatase 300 U (normal), Parathyroid hormone was 0.23 μ g aeq PTH/l (normal). The serum immunoglobulins were normal (IgM 1.6, IgG 4.7, IgA 0.88 g/l and IgD 26 μ mol/l). No plasma immune complexes were demonstrated using anti IgG and IgM. G-6PD was 14.1 U/g Hb (normal). The urine production was 1280-1557 ml/24 hr $\times$ 1.73 m^2 . The urine showed no abnormalities and the urine culture was negative. Urine pH was consistently above 7.0. All values of glomerular filtration rate estimated by inulin and by endogenous creatinine clearance were within normal limits (inulin 102-130, creatinine 118-135 ml/min $\times$ 1.73 m^2). Tubular reabsorption of phosphate was normal (90%). The pattern of urinary aminoacid excretion was normal. No glucosuria was present. The maximal urinary osmolality after thirsting was 604 mOsm. Urinary calcium excretion during acidosis showed high normal values (4.6 - 5.0 mg/kgBW $\times$ 24 hr). Bone X-ray showed no abnormalities of the skeleton, intravenous pyelography was normal, there was no evidence of nephrocalcinosis. The diagnosis of renal tubular acidosis was established, the acidosis required for its sustained correction alkali therapy in amounts of 15 mmol/kgBW daily (fig.3). Blood pH and serum HCO_3^- remained between normal limits throughout treatment. At the age of 24 months the child was readmitted for reevaluation of alkali requirement. Acidosis did not reappear after therapy was discontinued. On admission height was 89 cm (P50) and weight 11.9 kg (P50). Blooddata: Hb 6.6 mmol/l, CV 34%. Blood pH was 7.43 and base-excess +1 mmol/l. Plasma electrolytes were Na^+ 135 and K^+ 5.0 mmol/l. Radiological examination did not show bone abnormalities or any calcification in the kidneys.

INVESTIGATION OF RENAL ACID-BASE REGULATION

To evaluate the characteristics of the renal acidification defect net acid excretion was assessed after oral ammonium chloride loading and tubular reabsorption of bicarbonate was determined during intravenous administration of bicarbonate both according to the procedures described by Edelmann et al (5). During the bicarbonate titration study sodium bicarbonate (0.5 mmol/l) was infused at an hourly rate of 1.1 - 2.7 mmol/kg. Before the test ammonium chloride was administered to decrease serum bicarbonate concentration below 12 mmol/l. Urinary excretion of hydrogen ion was assessed after oral administration of 100 mEq per m^2 of body surface of ammonium chloride. Water was administered throughout the test at the rate of 50 ml per hour. Bloodsamples were obtained through an indwelling needle placed in a superficial vein. Urine was collected through and indwelling urethral catheter by a disposable syringe and examined immediately. To assess the H^+ secreting capacity of the distal tubule the difference between urine and blood pCO_2 [(U-B) pCO_2] was assessed following the method described by Halperin et al (6), which was adapted to children by Hutcheon et al (8). These studies were done on first admission and after complete recovery. It must be mentioned that in all studies the concentration of bicarbonate in plasma [(HCO₃)_p] and in urine [(HCO₃)_u] were obtained by direct measurement of total carbon dioxide (TCO₂) according to a method described earlier (17). Plasma bicarbonate was calculated from (TCO₂)_p by subtraction of the dissolved carbon dioxide ($\alpha \times pCO_2$, where α is 0.0304 mmol/mHg). For the calculation of the urinary bicarbonate concentration the solubility coefficient (α) of physiological saline at 37° C. was used (0.0326 mmol/mHg). During the first admission maximal acid excretion after an acute ammonium chloride load was also investigated after potassium depletion induced by a low potassium diet in combination with a potassium binding resin (Kayexalate). Plasma renin activity and aldosterone and 24 hours urinary excretion of aldosterone were measured during correction of acidosis, during administration of Kayexalate and after Na^+ depletion by chlorothiazide treatment.

RESULTS

- Experiment no.1 (performed during the acidotic phase): During acute NH_4Cl loading urinary pH did not decrease below 7.23 (table I and fig.1). Excretion of titratable acid (T.A.) and ammonium (NH_4^+) were low during severe acidosis, the net acid excretion (N.A.E.) being negative. During the bicarbonate infusion test the excretion of bicarbonate was relatively fixed and less than 4% of filtered bicarbonate at (HCO₃)_p values ranging from 11 to 18 mmol/l. When the (HCO₃)_p was further increased above 18 mmol/l the fractional excretion of filtered bicarbonate rose to 15% at normal (HCO₃)_p (fig.2). Intravenous administration of 100 mg acetazolamide resulted in a marked inhibition

of bicarbonate reabsorption ($^{14}C\text{HCO}_3^-/C_{in} \times 100 = 52.40\%$). Following oral administration in one single dose of 3 mmol/kgBW of sodiumbicarbonate maximal alkaline urine pH values were reached (pH 7.8) and (HCO₃)_u concentration exceeded 100 mmol/l. The corresponding (U-B) pCO_2 values ranged from 16 to 27 mmHg (table II).

- Low K^+ experiment (performed during the acidotic phase): Due to Kayexalate administration plasma K^+ decreased to a level less than 4.5 mmol/l (fig.3). During administration of 15 g Kayexalate per day blood pH normalised in combination with a small deficit of base (BE -4 mmol/l). After termination of Kayexalate treatment and potassium supplementation acidosis reappeared (fig.3). Acute NH_4Cl administration during this treatment resulted in normal TA + NH_4^+ (13) μ Eq/min $\times$ 1.73 m^2 excretion mainly due to an considerable increase of NH_4^+ excretion. Bicarbonate excretion remained unaltered (93 μ mol/min $\times$ 1.73 m^2), however N.A.E. became positive (table I). Urine pH did not decrease below 7.0. - Experiment no. II (after recovery of acidosis): After NH_4Cl loading urinary pH decreased to 4.71 and excretion of T.A., ammonium and N.A.E. were within normal limits (table I). During the bicarbonate infusion test (fig.2) bicarbonate was completely reabsorbed at (HCO₃)_p levels less than 18 mmol/l, when the (HCO₃)_p levels were further increased negligible amounts of bicarbonate were excreted ($^{14}C\text{HCO}_3^-/C_{in} \times 100$ less than 1%). Only at (HCO₃)_p above 25 mmol/l significant bicarbonaturia was found. The (U-B) pCO_2 measured after oral bicarbonate loading revealed values less than 20 mmHg. The ability to concentrate urine after thirsting was still impaired (644 mOsm). (table II).

DISCUSSION

Lightwood and colleagues described a transient type of renal tubular acidosis in infants (13). The pathophysiology of the acidosis in these infants was unknown. Latner and Burnard (10) presented evidence for a defect in bicarbonate reabsorption but other studies also showed that in those patients there was an inability to acidify the urine adequately (13). Therefore Lightwood's syndrome was defined as a form of distal renal tubular acidosis often associated with bicarbonate wasting. Leumann and Steinman (10) and Hirschman et al (7) identified a patient with transient tubular acidosis and bicarbonate wasting. The bicarbonate titration studies did not allow to implicate a defect in the reabsorption of bicarbonate in the proximal tubule. Hyperkalemia was not reported in these patients. Mc.Sherry et al reported the occurrence of transient renal tubular acidosis and hyperkalemia in infants. The urine of these patients was acidic during spontaneously occurring acidosis and the reabsorption of filtered bicarbonate was subnormal at normal plasma bicarbonate concentrations (14). Our data suggest that in our patient both proximal and distal acidification mechanisms are involved in the disease process. The finding of a high urinary pH and impaired acid excretion in the presence of severe metabolic acidosis indicates that impairment of renal acid excretion (distal R.T.A.) is at least in part responsible for the metabolic acidosis. For its sustained correction the acidosis required alkali therapy in amounts of 15 mmol/kg BW daily (fig.3). The difference in alkali requirement with endogenous produced non volatile acids (less than 3 mmol/kg BW $\times$ day) reflects the magnitude of HCO_3^- wasting at normal (HCO₃)_p values (HCO₃ wasting R.T.A.). The bicarbonate titration curve showed a trivial (less than 4%) and relatively fixed fractional excretion of filtered bicarbonate ($^{14}C\text{HCO}_3^-/C_{in}$) over (HCO₃)_p values ranging from 12 to 18 mmol/l as found in patients with classic distal tubular acidosis, but when the (HCO₃)_p was increased above 18 mmol/l, HCO_3^- wasting was dependent on the filtered load and increased to values as high as 15% of filtered load, as found in patients with proximal tubular acidosis. Halperin et al (6) have argued that after administration of large amounts of bicarbonate resulting into maximal alkaline urine the inability to increase urinary pCO_2 is indicative for an H^+ secretion rate defect in the distal tubule. They found invariably (U-B) pCO_2 values less than 12 mmHg in patients with distal R.T.A.. During acidosis as well as after recovery we found our patient to have pCO_2 (U-B) values higher than 12 mmHg but lower than reported in normal children and adults (table II). Arruda et al (1) have demonstrated that urinary pCO_2 is critically dependent on (HCO₃)_u values and therefore the ability to concentrate the urine is essential for the formation of high urinary pCO_2 . The persistence of a defective urine concentration capacity in our patient may have contributed to the reduced (U-B) pCO_2 values. Our observation criticizes the usefulness of this test in assessing distal acidification. We obtained more information on the H^+ secretory capacity of renal tubules by inducing potassium depletion. During low K^+ diet and Kayexalate administration in our patient only small amounts of $NaHCO_3$ (2.5 g per day or 3 mmol/kg BW) were sufficient to compensate acidosis. NH_4Cl loading during K^+ -depletion did not decrease urinary pH below 7.0, bicarbonaturia persisted but an important increase in T.A. and NH_4^+ resulting in positive N.A.E. were noticed. In healthy subjects K^+ depletion induced by a potassium binding resin was not associated with any change in blood acid-base parameters. The response to an acute ammoniumchloride load however was altered and showed a moderate increase of urinary pH, unchanged excretion of T.A. and bicarbonate but an 15% increase in ammonium excretion resulting in increased N.A.E. (19). In adults with hyperkalemia, metabolic acidosis and isolated hypoadosteronism, the acidification defect is similar to that observed in patients with proximal R.T.A. but urinary ammonium excretion is greatly reduced even when the urine is highly acidic (16). Administration of potassium-sodium exchange resins in these patients corrects acidosis and urinary ammonium excretion increases manifold (18). In our patient potassium depletion only partly corrected the acidification defect. Persisting hyperkalemia always reflects insufficient tubular secretion of potassium ions and potassium secretion is critically dependent on a normal ability of adrenal gland to secrete aldosterone. Aldosterone secretion was tested in our patient in different clinical conditions and was appropriate (table III). From the data collected in our patient we concluded that beside distal tubular acidosis another defect in renal acidification was present presumably due to a defect in potassium secretion. These findings appear to reflect a hybrid of types I and 4 R.T.A.. After correction of the acidification disorder a defect in urinary concentration was still present without hypokalemia or nephrocalcinosis. We therefore postulate that the different defects are due to reversible (toxic) damage of tubular membrane. The differences in expression of tubular defects in patients with transient tubular acidosis reported in the literature are in accordance with this hypothesis.

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Table I. AMMONIUM CHLORIDE LOADING.

Subjects	Blood			Urine			
	pH	HCO_3^-	K^+	pH	TA	NH_4^+	N.A.E.
		mmol/l			uEq/min/1.73 m ²	HCO_3^-	
Experiment no. I	7.15	9.0	6.2	7.23	13.3	25.85	- 54.24
Experiment no. II	7.31	17.1	5.0	4.71	67.4	80.90	+148.3
normal infants (5)	7.31 ±0.012	17.1 ±0.43		4.87	62 ±4.9	57 ±4.3	119 ±9.2
Experiment low K^+	7.28	14.0	4.2	7.09	31.1	100.6	+ 38.56

N.A.E.: net acid excretion

Table II. Oral $NaHCO_3$ loading: (U-B) pCO_2 .

Subject	Urine			Plasma (U-B)		Maximal urinary osmolality after thirsting mOsm/Kg H ₂ O
	pH	pCO_2 mmHg	TCO_2 mmol/l	pCO_2 mmHg	pCO_2 mmHg	
Exper. no. I	7.71-7.94	48-56	101-105	29-32	16-27	604
Exper. no. II	7.68-7.84	47-57	87-90	36-39	11-19	644
Distal R.T.A. (7)	7.60-7.82	29-47	-	29-36	0-12	
Normal controls (6)	7.20-7.79	65-94	-	30-40	28-58	1089 ± 110

Table III. ALDOSTERONE SECRETION AND EXCRETION ; RENIN SECRETION.

Clinical situation	Aldosterone		Renin
	plasma aldosterone ngr/100 ml	urinary excretion Aldo 18-oxo ug/24 hrs	plasma renin ngr/ml/hr.
K^+ depletion; Na^+ administration	12	-	1.2
$NaHCO_3$ admin.	8.5	1.4	0.1
K^+ administration Na^+ depletion	82	77	1.5

normal values in children 1 - 4 y.: (n = 16)
 plasma aldosterone : mean value : 26.66 S.E.: ± 6.40
 plasma renin : mean value : 4.47 S.E.: ± 0.78
 urinary aldo 18-oxo : mean value : 0.95 S.E.: ± 0.22

Fig. 1. Relation between urinary pH and serum total CO_2 during R.T.A. (exp. no. I) and after recovery (exp. no. II).

Fig. 2. Bicarbonate reabsorption and excretion during R.T.A. (exp. no. I) and after recovery (exp. no. II). Data on normal controls extracted from reference 5.

Fig. 3. Response of acidosis to respectively $NaHCO_3$ and Kayexalate administration.