A Case of Renal Tubular Acidosis with Secondary Hyperparathyroidism, Lipemia and Aminoaciduria with Review of Japanese Literature

FUMIO ETO, TAKUO FUJITA, GOSUKE INOUE
AND MASAKI YOSHIKAWA

*Department of Geriatrics, University of Tokyo Faculty of Medicine,
Bunkyo-ku, Tokyo 113*

Synopsis

A 44 year old female with renal tubular acidosis, osteomalacia, lipemia and aminoaciduria is reported. Mild hypocalcemia, marked hypophosphatemia and elevated serum alkaline phosphatase were associated with high serum immunoreactive parathyroid hormone level, which was promptly suppressed by intravenous calcium infusion, indicating secondary hyperparathyroidism. Among 56 cases of renal tubular acidosis so far reported in Japan, patients in the first decade predominated and the male to female ratio was 1 to 3. Osteomalacia was found in 19 and hypergammaglobulinemia in 11 but aminoaciduria was seen only in 2. Marked lipemia was the most unusual aspect in the present case.

Among a spectrum of renal tubular dysfunction leading to disturbance of calcium and phosphorus metabolism and osteomalacia, renal tubular acidosis is one of the most common varieties (Wrong *et al.*, 1959; Elkinton 1960; Elkinton *et al.*, 1960), and a considerable number of cases have already been reported in Japan. Combination of primary renal tubular acidosis with aminoaciduria and lipemia, however, is rather unusual, and the role of parathyroid hormone in this syndrome still remains controversial (Reiss *et al.*, 1973). We have recently experienced such a case, which is the subject of the present report, along with the review of Japanese literature.

Case Report

K. T., a 44 year old housewife, was admitted to the Department of Geriatrics, University of Tokyo Hospital, on May 7, 1973 with chief complaints of thirst, polyuria, arthritis and lumbago.

Family History was non-contributory ex-

cept for her father who died of apoplexy at the age of 58 and her sisters with teeth extremely susceptible to carious changes. No consanguinity is known.

Past History indicated the birth at term following normal gestation, followed by a rather slow but usual growth through infancy and childhood. Despite irregular eating habits and somewhat unbalanced diet, her nutritional conditions remained satisfactory. Her teeth were so susceptible to carious change that she became edentulous already in her twenties. At the age of 8, she suffered from peritonitis of probably tuberculous nature and recovered without complications. Menarche was at 18 and menopause as early as 39. Since her marriage at 27, no pregnancy ever occurred. She had average intelligence and school achievement.

The present illness apparently started with thirst and polyuria in her teens. Her gait became unstable due to acute left coxitis at the age of 19, followed by fracture of the left femoral neck without remarkable trauma. After application of the plaster of Paris cast for 3 months, her left hip became ankylosed.

At 28, she experienced high fever with pain in the extremities and lumbago repeatedly. Since the age of 35 she developed excessive appetite and gained weight. After the detection of hypertension of 220/110 was at age 42, she was referred to us under the suspicion of renal tubular acidosis at 44.

Physical examination revealed a well developed, well nourished woman, 150 cm in height and 47 kg in weight, with blood pressure of 180/110 and mild arteriosclerotic changes of ocular fundi. Skin was free of xanthelasma or edema. Pelvis, femora and tibiae were tender to compression. The range of movement was reduced markedly in the left hip and moderately in the left ankle.

Laboratory tests revealed BSR 12 mm/hr, CRP 3+, ASLO less than 100, negative Wasserman reaction and rheumatoid factor. Hemoglobin was 14.6 g/100 ml, RBC 491×10^4 , platelet 16.5×10^4 and WBC 3,900/mm³ with normal differential count. Urinalysis revealed pH 6.5, specific gravity 1.013, 1+ protein, and negative sugar with 1–5 RBC and 10–20 WBC per HPF. Feces was of normal color and consistency without detectable fat droplets. Serum uric acid was 9.8 mg, cholesterol 295 mg/100 ml, triglycerides 258 mg/100 ml, free fatty acids 1028 μ Eq/L, and total lipids 1,032 mg/100 ml. Serum lipoproteins on paper electrophoresis revealed elevated pre- β -lipoprotein, elevated and narrow β -lipoprotein in the absence of chylomicron peak, indicating type II hyperlipoproteinemia. EKG revealed ST segment depressions in leads II, aVL and V3 through V6, suggesting myocardial damage. Arterial blood gas studies revealed pH 7.33, pO₂ 88 mmHg, O₂ saturation 96%, pCO₂ 32 mmHg, buffer base 41.5 mEq/L, standard bicarbonate 16.5 mEq/L, actual bicarbonate 16.5 mEq/L and total CO₂ 17.4 mEq/L. PSP excretion was 25% in 15 minutes and 73% in 2 hr and Fishberg's concentration test revealed the highest urinary specific gravity of 1.016, and osmotic pressure 450 m Osm/kg H₂O. GFR was 77 ml, and RPF 213 ml/min, with

filtration fraction of 0.36. BMR was -6%, PBI 3.22 μ g/100 ml, urinary 17OHCS 2.7–3.6 mg/24 hr, and 17 KS 3.2–3.6 mg/24 hr. Blood sugar and serum immunoreactive insulin (IRI) before and 30, 60, 90, 120 and 180 min after oral load of 100 gram glucose was 80, 145, 196, 188, 158 and 116 mg/100 ml and 21.7, 106.5, 107.9, 119.1, 149.3 and 112.5 μ U/ml, respectively. Despite oral loading of 0.1 g/kg ammonium chloride, pH of urine stayed above 5.7, when blood pH was as low as 7.26, as shown in Fig. 1. Analysis of amino acid content of urine revealed a definite increase of cystine and lysine, with a slight increase of threonine, methionine and alanine but other amino acids in normal concentrations, as shown in Table 1.

Serum Ca was 8.35 and inorganic P 1.91 mg/dl, alkaline phosphatase 17.8 and 24.3 King-Armstrong units and %TRP 60%. On the day of intravenous infusion of 15 mg Ca/kg according to the method of Haas (1966)

Table 1. Amino acid in urine, μ mole/24 hours

Amino Acid	March 1973	May 1973	Dec 1973
Taurine	770		
Aspartic Acid	28		128
Threonine		<u>450</u>	<u>434</u>
	227		
Asparagine			
Glutamine			
Serine	452	496	503
Glutamic Acid	26	+	98
Proline	64	low	+
Citrulline	22		low
Glycine	782	640	1618
Alanine	<u>302</u>	<u>340</u>	<u>266</u>
Valine	39	34	49
Cystine	<u>239</u>	<u>270</u>	<u>276</u>
Methionine	low	92	+
Isoleucine	16	+	39
Leucine	34	50	49
Tyrosine	41	+	69
Phenylalanine	29	+	59
β -AIBA	950		
Lysine	<u>832</u>	<u>690</u>	<u>440</u>
Histidine	697	916	+
Arginine	32	+	69

Underlined values were consistently supernormal.

Fig. 1. Ammonium chloride loading test. In the long test, 0.1 g/kg/day of NH_4Cl was orally administered for 3 days and urine pH was measured on day 2 and 3. In the short test, 0.1 g/kg NH_4Cl was administered and pH of hourly urine specimen was measured. In none of these specimen, pH went down below 5.7. Since at least one specimen should give pH below 5.4, diagnosis of renal tubular acidosis was made.

urinary calcium excretion showed only a slight increase from the level on the control day, indicating retention of 90% of the infused Ca, or a marked avidity of the skeleton for the calcium. Serum immunoreactive parathyroid hormone measured by the method of Fujita *et al.* (1972) 2.9 ng/ml (normal level, 0–0.6 ng/ml) and definitely suppressed by calcium infusion as shown in Fig. 2, indicating secondary hyperparathyroidism. Bone X-ray picture revealed a general decrease of density, calcification or ossification of ligaments surrounding joints, periosteal thickening of the upper left humerus, pseudofracture of the left pubic arch and right femur (Fig. 3) and ankylosis of the left hip and sacroiliac joint. Intravenous pyelography and aortography revealed hypoplastic left kidney with irregular

contour but without stenosis of the renal artery.

Under the diagnosis of primary renal tubular acidosis of distal type, treatment with 50,000 units of Vitamin D_2 and 30 ml of Shohl's solution, sodium citrate and citric acid mixture, was given daily. After 2 weeks, arterial blood pH rose to 7.38, pCO_2 40 mmHg, and actual bicarbonate 23.4 mEq/L, with gradual improvement of pains in bones and joints.

Discussion

Systemic acidosis with persistently alkaline urine even after ammonium chloride loading definitely places the present case in the group

Fig. 2. Calcium loading test. Serum immunoreactive PTH was definitely elevated before infusion of Ca-gluconate containing 15 mg Ca and became undetectable during induced hypercalcemia, again rising 24 hrs later.

of renal tubular acidosis, of which numerous studies are already available with attempts of classification and elucidation of pathophysiological mechanism. After the first description by Butler *et al.* (1936) of acidosis in children with diffuse nephrosclerosis, Albright (1942) described a group of patients with osteomalacia, nephrocalcinosis and metabolic acidosis and called this disease tubular insufficiency without glomerular insufficiency. Pines and Madge (1951) introduced the currently used term renal tubular acidosis.

Tsuda *et al.* (1962) was apparently the first to describe this syndrome as such in Japan, though many cases had no doubt escaped proper description and report before this time. Fifty-six cases of renal tubular acidosis, with defects in urinary acidification due to distal tubular insufficiency without overt renal failure have so far been reported in Japanese literature. The age distribution indicates a

Table 2. Age and sex distribution of cases of tubular acidosis in Japan

Age in Years	Male	Female	Total
0-9	7	12	19
10-19	2	5	7
20-29	0	6	6
30-39	0	8	8
40-49	4	7	11
50-59	0	4	4
60-	0	0	0
Adult	1	0	1
Total	14	42	56

preponderance in the first decade, and the disease occurred in the first year of life in 2 cases (Table 2). Male to female ratio was 1:3. Urinary tract infection was described in 11 and nephrocalcinosis in 26, probably facilitated by alkaline urine. Hypergammaglobulinemia was found in 11 and Sögren syndrome in 4, suggesting an autoimmune mechanism

Fig. 3. Pseudofracture of the right femur.

(Morris *et al.*, 1968). Distal tubular involvement leading to urinary concentration and polyuria in Sögren syndrome was found in 8 cases collected by Kahn *et al.* (1962). Serum was normal in 23 and low in 2, serum inorganic phosphorus low in 21 and normal in 6, and serum alkaline phosphatase high in 17 and low in 5 among cases with such measurement. Aminoaciduria was seen in 4 and data on quantitative analysis are available in 2.

One is a 20 year old female excreting excessive amount of histidine, serine, tyrosine, threonine and glutamine and the other is the present case with excessive amount of cystine, lysine, threonine, and alanine in urine. Glycosuria was seen in none of these 4 cases. Muldowney *et al.* (1968) pointed out the role of secondary hyperparathyroidism in the development of aminoaciduria in osteomalacia, based on the reversibility in response to treatment. Amino-

aciduria persisted after 6 months of treatment and correction of acidosis and hypocalcemia in the present case. Osteomalacia or rickets were found in 19 of 56 cases. The present case apparently occupies a rather unique position, representing 1 of the 2 cases with amino-aciduria and the only case with definite lipemia among 56 cases of primary renal tubular acidosis so far reported in Japan. These complications may represent separate familial or genetic abnormality along with the distal tubular problem.

References

- Albright, F., C. H. Burnett, P. F. Smith and W. Parson (1942). *Endocrinology* **30**, 922.
- Butler, A. M., J. L. Wilson and S. Farber (1936). *J. Pediatrics*, **8**, 489.
- Elkinton, J. R. (1960). *Amer. J. Med.* **28**, 165.
- Elkinton, J. R., E. J. Huth, G. D. Webster, Jr. and R. A. McCance (1960). *Amer. J. Med.* **29**, 554.
- Fujita, T., H. Orimo, K. Okano and M. Yoshikawa (1972). *J. Bone and Joint Surg.* **54**, 181.
- Haas, H. G. (1966). *Knochenstoffwechsel und Parathyreoidea Erkrankungen*, Thieme.
- Kahn, M., A. D. Meritt, M. J. Wahl and J. Orloff (1962). *Ann. Intern. Med.* **56**, 883.
- Morris, R. C., Jr., A. Sebastian and E. Morris (1968). *J. Clin. Invest.* **47**, 70a.
- Muldowney, F. P., Frearey, R. and D. McGeeney (1968). *Quart. J. Med.* **148**, 517.
- Pines, K. L. and A. H. Mudge (1951). *Amer. J. Med.* **11**, 302.
- Reiss, E. and J. M. Canterbury (1973). *Ann. Rev. Med.* **24**, 217.
- Tsuda, J., F. Takiguchi, M. Konno and T. Togo (1962). *Shonika Rinsho* (In Japanese) **15**, 1256.
- Wrong, O. and H. E. F. Davies (1959). *Quart. J. Med.* **28**, 259.