The functional response to furosemide in a case of de Toni-Debre-Fanconi disease

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Abstract

The case of a 13-year-old boy with the advanced clinical picture of the idiopathic De Toni-Debré-Fanconi syndrome is described, on whom acute studies of proximal tubular functions and of the effect of furosemide thereon were performed. Sodium bicarbonate loading corrected the hyperchloremic acidosis, but induced an increase of urinary bicarbonate loss of over 20% of the filtered amount. Furosemide corrected bicarbonate reabsorption in spite of the presence of metabolic alkalosis. The urinary excretion of alpha-amino nitrogen, glucose, and phosphates decreased and tubular reabsorption of the two latter increased under furosemide. On a chronic treatment with furosemide and dietary sodium chloride restriction, correction of hyperchloremic acidosis, hypophosphatemia and rickets was achieved.

Introduction

Gluco-amino-phosphate diabetes, universally known by the eponym De Toni-Debré-Fanconi syndrome, is a multiple etiology global disorder of the proximal tubular function, manifested by massive urinary wasting of bicarbonate, inorganic phosphates, amino acids, glucose, and other substances (Illig & Prader, 1961). Its main clinical features are severe stunting, chronic hyperchloremic acidosis, and rickets. The pure or idiopathic variety is a precise nosological entity, whose treatment has so far been restricted to the piecemeal correction of selected biochemical signs of the disease.

This report concerns a 13-year-old boy, who was studied for the first time in 1968.* In the course of a 2.5-year long stay in the hospital, the effect of induced contraction and expansion of extracellular volume on urinary solute excretion was investigated.

Description of the case

The second child of non-related parents, within an otherwise healthy sibship of six, this boy exhibited a slow physical growth and retarded development since early childhood. He sat up aged one and did not try to walk until four years of age. Mental and dental development had apparently been normal. At the age of five, professional advice was sought for progressive bending of the limbs and a notorious deformity of the chest. Medical treatment and various attempts or surgical correction of the deformities were unsuccessful. Because of non-healing spontaneous fractures and generalized pain, the child soon became permanently bedridden and never did attend school. Progressive malaise, anorexia and paleness ensued.

When 12.8 years old, the boy was admitted to the Hospital de Pediatría. General inspection disclosed a recumbent, extremely dwarfed, dramatically deformed youngster, in acute distress because of severe asthenia, moderate dyspnea and generalized pain upon mobilization. He was barely able to sit up, but not to stand nor to walk. Body length was 95 cm and weight, 13.5 kg.

* In that year, the patient was shown to professors Guido Fanconi and Andrea Prader. Up to the time of the recent telluric catastrophe and the consequent demolition of the main hospitals of the Centro Médico Nacional, no similar case had been admitted to the Hospital de Pediatría.
Besides grotesque bending of the humeri and clavicles, bilateral coxa vara and genu recurvatum, as well as signs of active rickets, such as enlargement of wrists and ankles and beading of the costo-chondral junctions, the thorax was bell-shaped, with a deep Harrison's sulcus, lateral grooves, flaring of the costal edges, scoliosis and kyphosis. There was some cranial bossing; the teeth did not exhibit major enamel defects, but numerous caries; permanent canine teeth had not yet erupted. The liver edge was felt 6 cm below the costal margin; the lower pole of the spleen was barely palpable.

No corneal cystine deposits were found under repeated slit-lamp examinations. Because of the presence of bilateral congenital cataracts, a presumptive diagnosis of Lowe's syndrome was at first entertained.

Radiological findings. Besides the severe deformities and widespread epiphyseal metaphyseal cupping and fraying, the skeletal demineralization was so severe that the cortical outline of several long bones and of the vertebral bodies was barely visible. At least 20 old and recent fractures could be identified, including several Looser-Milkman pseudofractures. Due to the advanced bone rarefaction, assessment of bone age was extremely difficult. There was a severe Caffey's "pneumonia" with secondary lung infiltration.

Laboratory data.*. A persistent hyperchloremic decompensated metabolic acidosis, an elevated "alkaline" phosphatase, low serum phosphate, and an extremely high urinary excretion of phosphates, calcium, glucose, and amino acids, characterized the first two months of hospitalization.

Serum phosphates ranged from 1.24 to 3.14 mg/dl, with a median of 1.68; alkaline phosphatase, from 38.6 to 69.8 Bodansky units; total calcium remained mostly within low normal values, while serum albumin was 34–37 g/l. Total CO₂ ranged from 11.7 to 15.2 mm/l and standard bicarbonate, from 16.1 to 17.5 meq/l; pH from 7.35 to 7.37 and pCO₂, from 22.5 to 25.8 mmHg (Astrup method).** Serum chloride averaged 114, and sodium 136 meq/l; with the exception of a few episodes of hypokalemia, potassium concentration averaged 4.4 meq/l.

Urinary alpha-amino nitrogen values ranged from 23.9 to 93.0 mg/kg/day (normal maximum: 1.6–4.0) with an average of 50.8 ± 11.6. The predominant alpha-amino acids were leucine, isoleucine, valine, methionine, tryptophan, threonine, lysine, cystine, cysteine, serine, histidine, glycine, glutamic and aspartic acids, tyrosine, alanine, and occasionally hydroxyproline and 3-methylhistidine; taurine and glutamine were also regularly found.

Phosphaturia varied widely, but was generally in the order of 300–400 mg/kg/d (normal maximum: 20); calciuria amounted to 9–15 mg/kg/day (normal maximum: 6), and glycosuria, to 1.5 to 3.0 g/l. Two creatinine clearances were normal (67 and 63 ml/min/m²); phosphate/creatinine clearances ratio was extremely high, with an average value of 0.52. Stool fat was normal, as well as the result of a 125I-triolein test.

Clinical course

Treatment was started with 1.25 mg daily of vitamin D₂ per os and neutral phosphate solution. In view of the persistent acidosis, treatment with sodium bicarbonate was started.

* In order to prevent possible mistakes in the recalculation of the host of original data, these are expressed in conventional rather than in SI units.

** Normal values for the city of México (2240 m above sea level) are: standard bicarbonate, 16.5–19.5 meq/l; pH, 7.38–7.44; pCO₂, 24–31 mmHg (Rangel-Carri-lo & Bañuelos, 1976).
The overall condition of the patient improved once the initial bronchopneumonic process had disappeared. Appetite returned, but weight increase was slow. After two months, active as well as passive limb mobilization was no longer painful. All fractures had healed at the time of the fourth month of hospitalization, although the general radiological appearance of the skeleton, with the exception of some metaphyseal recalcification lines, had not changed appreciably. Neither did the chemical abnormalities, which fluctuated widely despite progressive increases in the dosage of vitamin D2, alkali and neutral phosphates.

Although a low CO2 was a common finding, there was no clinically apparent hyperventilation. Spirometry (corrected for the theoretical height in terms of the upper body segment), revealed a very high minute volume, as well as a normal ratio between total ventilation and dead space ventilation, thus indicating a state of "hidden" hyperventilation, despite a normal respiratory rate.

Encouraged by the report of Rampini et al. (1968), treatment with chlorothiazide was started in the sixth month of hospital stay. With a dosage of 125 mg/d, a remarkable improvement of acid-base status took place at once. Unfortunately, a severe hypokalemia with metabolic alkalosis and bouts of latent tetany, even when chlorothiazide dosage was reduced, led to the search for an alternative treatment after 45 days.

**Metabolic studies**

One typical experiment out of several studies is described. Most of these investigations were performed at a time at which basal serum CO2 was below 16 mmol/l.

**Methods.** Urine collection was started under basal conditions and continued during the remainder of the study. Blood samples were taken at the start and six times thereafter, at 20 to 40 minute intervals. After 30 minutes, 4% sodium bicarbonate in 5% glucose solution was injected intravenously at a rate of 1.2 ml/min, during 215 minutes. At minute 120, a rapid intravenous bolus of 20 mg of furosemide was administered.

Glomerular filtration rate was measured with 51Cr EDTA (Garnett et al. 1967). In blood serum as well as in urine there were measured: pH, bicarbonate, sodium, potassium, chloride, phosphates and glucose; ammonium, titratable acidity and alpha-amino nitrogen were measured in 30-minute samples of urine. Conventional laboratory procedures were used throughout.

**Results.** Before the start of bicarbonate infusion, there prevailed a decompensated metabolic acidosis with an urinary pH of 5.20; excretion of bicarbonate was 2.0, that of ammonium 20 and titratable acidity 35 ueq/min/m2 body surface. During bicarbonate load the acidosis was corrected, but bicarbonaturia increased to values above 20% of filtered bicarbonate, while phosphaturia decreased. After furosemide injection, urinary volume and sodium excretion increased, as well as the rate of bicarbonate reabsorption (Fig. 1), despite the decompensated metabolic alkalosis achieved by the bicarbonate load; there was a further fall in phosphate excretion (Fig. 2), a notorious decrease in aminoaciduria (Fig. 3) and an increase in the tubular reabsorption of glucose (Fig. 4).

**Further clinical progress**

In view of these findings, treatment with furosemide, at a dosage of 20 to 40 mg/d, was started. Acid-base balance improved notoriously in a similar way as with chlorothiazide, and serum phosphate concentration started a trend towards normalization. There still was a persistent moderate polyuria, but maximal urine concentration capacity was repeatedly above 1200 mosm/l. The urinary wasting of calcium increased sometimes to 30 mg/kg/d, while phosphate excretion decreased to 50-56 mg/kg/d and alpha-amino nitrogen remained between 35 and 55 mg/kg/d, with a
similar amino acid patterns as initially; glycosuria varied between 2.5 and 3 g/l. A new spirometry gave normal results.

There were no rachitic metaphyseal lesions nor any new fracture. Bone density, as judged visually from radiographic images, had increased considerably, and the cortical outline was clearly visible. Nine months after the initial admission, the patient started to walk. Nevertheless, plasma "alkaline" phosphatase activity was still abnormally high, albeit less so than initially. Lineal growth had been minimal, i.e. 2 cm in one year, while weight had increased 3 kg. Bone age which could now be assessed, was 8-9 years, at a chronological age of 14 years.

Eventually, furosemide dosage was increased to 40 to 80 mg/d and complemented with a 8 MJ/d hyposodic diet, containing 1.5 g salt per day. Although appetite for this diet was poor and weight declined, an almost complete repair of metabolic acidosis and of hypophosphatemia was achieved under this regime. There were no further episodes of hypokaliemia. Glycosuria persisted unaltered, while alpha-amino nitrogen excretion exhibited a striking reduction to roughly one third of previous values.

For psychological reasons, at an age of 15.3 years, the patient was discharged on this only medication, with an apparent length of 99 cm and a weight of 19 kg. The boy attended the out-patient clinic for physical medicine and rehabilitation in a regular way. He felt physically well, but manifested disenchantment because of his dwarfism, and finally deserted. Since his home address could not be localized, the subsequent clinical course of the patient is unknown.

Fig. 1. Renal bicarbonate reabsorption and serum bicarbonate concentration during sodium bicarbonate and furosemide injection.

Fig. 2. Same experiment. Phosphate excretion.
Discussion

Idiopathic De Toni-Debré-Fanconi syndrome, one of its less frequent forms, appears to be equally distributed among children and adults (Illig & Prader, 1961). It remains to be found out whether different ages of onset indicate genetic variants of the disease. The severity of the biochemical and clinical signs covers a wide range. In the present case, dwarfism, acidosis and bone pathology resulting from chronic urinary wasting of bicarbonate, phosphate and amino acids, were of an extreme degree, possibly due to the exceptionally long delay of a rational treatment.

As expected, renal functional derangements were restricted to the proximal tubule. Indeed, glomerular filtration rate, urine-concentrating capacity and sodium excretion remained within normal limits. On the other hand, the threshold for bicarbonate excretion was less than 12 meq/l, while the capacities to decrease urine pH and for excretion of ammonium and titrable acidity were normal, in the presence of a severe metabolic acidosis.

Although its intimate nature is still under question (Roth et al. 1981), the defective solute transport apparently responds in a normal way to the modulatory effects of extracellular fluid volume upon tubular reabsorption. Under physiological conditions, extracellular space expansion leads to a decreased fractional reabsorption rate of bicarbonate (Kurtzman, 1970) and phosphate (Steele, 1970); extracellular volume contraction has the opposite effect (Vander, 1980). In the same way, vigorous replacement of urinary losses in cases of Lowe (Van Biervliet et al. 1975) and Lignac-Fanconi (Arant et al. 1976) syndrome, by causing expansion of extracellular volume, increases bicarbonate and phosphate wasting, while extracellular space contraction, achieved in those patients by means of chronic dietary salt and/or water restriction, or hydrochlorotiazide (Rampini et al. 1968; Oetliker & Rossi, 1969; Callis et al. 1970; Donckerwolcke et al. 1970), resulted in correction of the urinary excretion patterns and of the metabolic acidosis, as well as in improvement or actual healing of the rickets. The increase in serum phosphate concentration and the anticalciuric action of hydrochlorotiazide explain bone remineralization, although several cases were maintained on moderate doses of vitamin D.
In the present case, treatment with chlorotiazide met with comparable results, but had to be interrupted because of severe hypokaliemia. For this reason, the response to furosemide was investigated.

The effect of an intravenous load of this drug was clearly noticeable a few minutes after the start of water and sodium diuresis. The observed enhancement of the tubular reabsorption of bicarbonate, phosphate, amino acids and glucose can therefore be attributed to contraction of the extracellular space. Under chronic treatment with furosemide plus a hyposodic diet, the improvement in the metabolic status could be maintained for a prolonged time, although neither glucosuria nor aminoaciduria decreased significantly, nor, as a possible consequence of the latter, was lineal growth restored. On the other hand, despite the hypercalcuriar effect of furosemide, serum calcium concentration remained within normal limits and rickets did not recur. The residual phosphate excretion may have been due in part to secondary hyperparathyroidism.

References


