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Retrospective approach to explain growth retardation and urolithiasis in a child with long-term nutritional acid loading

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Wachstumsverminderung und Harnsteine bei einem Kind mit langwährender alimentärer Säurebelastung, eine retrospektive Betrachtung

Summary: An infant with phenylketonuria unintentionally received a highly acidic low phenylalanine diet for 29 months. Temporary growth retardation and urolithiasis were observed, probably as direct effects of chronic acid loading. Caries at the age of 6 years may be a late consequence. This case report shows that chronic dietary acid load may cause serious side effects.

Zusammenfassung: Ein Säugling mit Phenylketonurie erhielt unbeabsichtigt für insgesamt 29 Monate eine phenylalaninarme Diät mit hoher alimentärer Säurelast. Eine vorübergehende Wachstumsretardierung und die Entwicklung von Harnsteinen dürften direkte Folgen, eine Karies im Alter von 6 Jahren möglicherweise eine langfristige Konsequenz der chronischen Säurebelastung gewesen sein. Das Beispiel dieser Krankengeschichte zeigt, daß eine chronische alimentäre Säurebelastung ernsthafte klinische Folgen haben kann.

Key words: Children; phenylketonuria; low phenylalanine preparations; acidic diet; maximum renal net acid excretion; urolithiasis

Schlüsselwörter: Kleinkind; Phenylketonurie; phenylalaninarme Diätprodukte; alimentäre Säurelast; maximale renale Säureausscheidung; Harnsteine

Introduction

In children and adults, intake and metabolism of a regular mixed European diet results in a surplus of protons, which must be excreted by the kidney (13). In infants and children with normal renal function acute and chronic maximum renal net acid excretion capacity is usually much higher than renal acid load resulting from nutrition and metabolism. However, maximum renal acid stimulation due to chronic dietary acid load was observed in prematures and newborns fed infant formulas (9), in infants and children with parenteral nutrition (5), and in infants and children with phenylketonuria receiving special amounts of low

phenylalanine preparations (2, 12). In one patient of the latter group, who unintentionally received two highly acidic low phenylalanine preparations for 29 months, growth retardation and urolithiasis were observed, probably as a consequence of a marginally tolerated chronic dietary acid load.

Case report

The subject, a girl, was born in August 1968. Birth weight was 3.3 kg, length 52 cm. The father (182 cm) had hyperuricemia with two episodes of urolithiasis. The mother (160 cm) was healthy. Screening on the 4th day of life led to the diagnosis of classical phenylketonuria. Dietary treatment with the unintentionally highly acidic low phenylalanine preparation A (12), a hydrolysate of bovine serum (Albumaid-XP^{P}, Scientific Hospital Suppl., Liverpool, England) was started in the third week (Table 1). Feeding was difficult, e.g., vomiting was common. Growth was insufficient (Fig. 1) (15). At the age of 13 months physiotherapy was started because of psychomotoric retardation. At the age of 17 months the girl received the low phenylalanine amino acid mixture B (P-AM^{R}, Deutsche Maizena Werke, Hamburg, FRG), which later was also shown to result in a high renal acid load (Table 2) (11). Vomiting stopped. However, feeding remained difficult.

Macrohematuria was first observed at the age of 23 months. X-rays showed bilateral nephrolithiasis. In serum, creatinine (84 µmol/l), uric acid

Table 1. Estimation of renal net acid excretion in a child with phenylketonuria (body weight 10 kg, body surface area 0.45 m^2) receiving the low phenylalanine preparation A and supplemental food in 1971.

		Intake			Absorption retention urine		
		Preparation C	Supplemental food	Total			
Chloride	mmol/d	94	24	119	119	3*	116
Phosphorus	1.8 × mmol/d	20	8	28	18	4	14
Sulfur	2 × mmol/d	30	1	31	23	0	23
Organic acids	meq/d						9
Sum of nonmetabolizable anions	mmol/d						162
Sodium	mmol/d	40	25	65	65	2*	63
Potassium	mmol/d	19	17	36	32	2*	30
Calcium	2 × mmol/d	36	4	40	12	7	5
Magnesium	2 × mmol/d	5	4	9	2	0	2
Sum of nonmetabolizable cations	mmol/d						100
Renal net acid excretion	mmol/d						62

* including dermal loss (10)

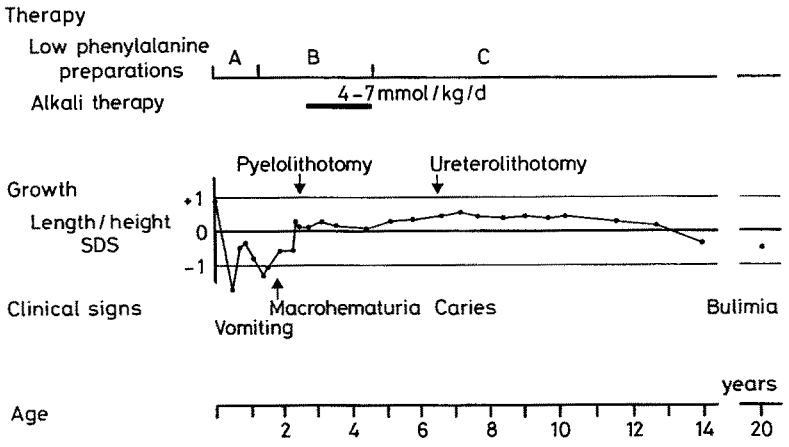

Fig. 1. Growth and clinical signs in a patient with phenylketonuria fed two highly acidic low phenylalanine preparations and one normal low phenylalanine preparation.

(178 μmol/l), and sodium (136 mmol/l) levels were normal, but chloride was elevated (116 mmol/l). Blood phenylalanine levels usually ranged between 60 and 240 μmol/l. Blood acid base status was not determined. In urine, hypercalciuria (max. 0.31 mmol/kg/d, normal: < 0.15 mmol/kg/d) and nor-

Table 2. Estimation of renal net acid excretion in a child with phenylketonuria (body weight 10 kg, body surface area 0.45 m^2) receiving the low phenylalanine preparation B and supplemental food in 1971.

		Intake			Absorption retention urine		
		Preparation C	Supplemental food	Total			
Chloride	mmol/d	31	24	55	55	3*	52
Phosphorus	1.8 × mmol/d	41	8	49	29	4	25
Sulfur	2 × mmol/d	30	1	31	23	0	23
Organic acids	meq/d						9
Sum of nonmetabolizable anions	mmol/d						109
Sodium	mmol/d	0	25	25	25	2*	23
Potassium	mmol/d	0	17	17	15	2*	13
Calcium	2 × mmol/d	46	4	50	13	7	6
Magnesium	2 × mmol/d	1	4	5	0	0	0
Sum of nonmetabolizable cations	mmol/d						42
Renal net acid excretion	mmol/d						67

* including dermal loss (10)

Table 3. Estimation of renal net acid excretion in a child with phenylketonuria (body weight 10 kg, body surface area 0.45 m^2) receiving the low phenylalanine preparation C and supplemental food.

		Intake			Absorption retention urine		
		Preparation C	Supplemental food	Total			
Chloride	mmol/d	18	24	42	42	3*	39
Phosphorus	1.8 × mmol/d	29	8	37	22	4	18
Sulfur	2 × mmol/d	18	1	19	14	0	14
Organic acids	meq/d						9
Sum of nonmetabolizable anions	mmol/d						80
Sodium	mmol/d	47	25	72	72	2*	70
Potassium	mmol/d	18	17	35	31	2*	29
Calcium	2 × mmol/d	26	4	30	11	7	4
Magnesium	2 × mmol/d	5	4	9	2	0	2
Sum of nonmetabolizable cations	mmol/d						105
Renal net acid excretion	mmol/d						–25

* including dermal loss (10)

mal renal excretion of uric acid (595 µmol/d, normal: 790 ± 80 µmol/d), oxalic acid (110 µmol/d, normal: 126 ± 15 µmol/d), and the amino acids were observed (1). The excess of chloride in relation to the sum of sodium and potassium in urine was 3.6 mmol/kg/d. Creatinine clearance ranged between 32 and 55 ml/min/1.73 m^2.

At the age of 29 months, x-rays showed enlargement of the calculi. Pyelolithomy was done on the right side. The calculus was composed of urate (46 %, 2.7 mmol/g), oxalate (18 %, 2.0 mmol/g), calcium (15 %, 3.8 mmol/g), phosphate (12 %, 1.3 mmol/g), and ammonium (4 %, 2.2 mmol/g). Due to constant low urine pH of 5.1–5.3 an alkali therapy was started. Surprisingly, 6 mmol/kg/d were necessary to increase urine pH to the range 6.4–7.0.

Finally, at the age of 54 months the association of the acid diet and the high renal acid load was perceived (12). Therefore, alkali therapy was stopped and a low phenylalanine casein hydrolysate C (Aponti PKU, Aponti GmbH, Köln, FRG) known to result in high urine pH values was given (Table 3); urine pH was above 6.4. The size of the calculus on the left side remained unchanged. Nevertheless, eventually colic ureterlithotomy was done at the age of 6 years. Severe dental caries were present. Up to menarche at the age of 12 years serum parathormone concentrations and urinary calcium excretion were repeatedly slightly elevated.

Final height was 159.5 cm (–0.47 SD) (15). At the age of 17 years the patient had an incidence of bulimia. Her intelligence quotient was 77 %.

She still consumed a low phenylalanine preparation. The serum concentrations of creatinine (71 μmol/l), uric acid (226 μmol/l), calcium, phosphorus, and parathormone, as well as the blood acid-base status were normal. Creatinine clearance ranged between 66 and 91 ml/min/1.73 m^2. Urinary calcium excretion was 0.05 mmol/kg/d.

Estimation of renal net acid excretion

Renal net acid excretion corresponding to the sum of titratable acidity plus ammonium minus bicarbonate was estimated according to our theoretical model (8, 12) in a child with phenylketoniuria, body weight of 10 kg, and body surface area of 0.45 m^2 (Tables 1, 2, 3).

According to the ionogram of the urine, renal net acid excretion corresponds to the difference of the main anions (chloride, phosphate, sulfate, organic acids) and the main cations (sodium, potassium, calcium, phosphorus). Urinary excretion of all ions except organic acids was estimated on the basis of the intake, intestinal absorption, retention, and metabolism data. Intestinal absorption was assumed to be 100 % of the intake for sodium and chloride, 90 % for potassium, and 75 % for organic sulfur (16). Intestinal absorption of calcium, magnesium, and phosphorus was calculated according to the following formulas: calcium absorption = 0.093 × calcium intake + 4.33 in mmol (7); magnesium absorption = 0.39 × magnesium intake − 0.95 in mmol; phosphorus absorption = 0.523 × phosphorus intake + 1.61 in mmol (7). Retention including dermal loss of sodium, potassium, and chloride in a child aged 12 to 24 months was assumed to be 2 mmol/d, 2 mmol/d and 2.4 mmol/d, respectively (3). Calcium retention was estimated to be 3.5 mmol/d, phosphorus 2.3 mmol/d, and magnesium 0.12 mmol/d (3). About 100 % of the absorbed organic sulfur is oxidized to sulfate and excreted in the urine. Organic acid excretion in urine is about 36 meq/d/1.73 m^2 (13).

Discussion

This case report shows that, in infants and children, long-term use of highly acidic diets may cause serious side-effects. In our patient, growth retardation and urolithiasis were observed, probably as direct effects of chronic dietary acid load. Caries may be a late consequence. We do not believe there has been any case report about a child with normal renal function, who stayed, from the age of 3 weeks and for a period of more than 2 years in a borderline situation of acid base metabolism due to a high renal acid load of dietary origin.

Dietary treatment

The two highly acidic, low phenylalanine formulas A and B were used for several years up to 1973 (12). In a prospective study of 22 children with phenylketonuria, who all started with the highly acidic low phenylalanine formula B at an age of more than 1 year, linear growth (12), weight gain,

and serum values of calcium, phosphorus, and alkaline phosphatase were normal in the presence of mild metabolic acidosis and low values of serum potassium and urine pH (2, 12).

The two highly acidic low phenylalanine formulas A and B were also given to some infants. These infants were not included in the prospective study (2). In some of them, introduction of the highly acidic preparations resulted in refusal to eat, vomiting, weight loss, and pronounced metabolic acidosis (2, 12). The patient reported on here was neither in such a stage of well-compensated metabolic acidosis as was our group of children of the prospective study, nor did she deteriorate to decompensated metabolic acidosis, as did some of our infants; she showed either nonspecific clinical signs like vomiting and decreased weight gain, or exceptional findings like urolithiasis. Therefore, the patient reached the age of 54 months before we first suspected that her clinical findings might had been the result of a long-term borderline situation of acid base metabolism.

Acid base metabolism

Unfortunately, blood acid base status was not determined before the start of alkali therapy at the age of 30 months in our patient. There are, however, several indirect arguments pointing to a severe renal acid load in our patient. The serum levels of chloride of 116 mmol/l and sodium of 136 mmol/l are indicative of hyperchloremic metabolic acidosis. In children on a regular diet the urinary excretion of sodium and potassium usually is 1 mmol/kg/d above urinary excretion of chloride (13). An excess of urinary excretion of chloride of 3.6 mmol/kg/d is a typical finding of acid loading with ammonium (14) or arginine chloride. In children, renal net acid excretion is about 1 mmol/kg/d (13). In the patient an oral alkali therapy of 4.5 mmol/kg/d did not increase urinary pH above 5.8. Finally, 6 mmol/kg/d were necessary to increase urine pH to the range of 6.4 to 7.0.

A cross-sectional study in 50 patients with phenylketonuria receiving the low phenylalanine preparations A and B, balance studies in three patients and theoretical calculations documented the high renal acid load in nutrition with these two preparations (12). With intake of preparation A the high renal acid load was primarily caused by a very high content of chloride (Table 1). In addition, there was a high intake of organic sulfur resulting from both a high protein intake and a high ratio of sulfur intake to protein intake of 0.54 mM/g (normal diet 0.25 mM/g) (12).

With intake of preparation B the high renal acid load was the result of an excess of chloride intake, as well as an unusually high intake of phosphorus and organic sulfur (Table 2). We therefore assume that, in the case presented here, the chronic renal acid load was about 7 mmol/kg/d or 280 mmol/d/1.73 m^2. This dosage corresponds to the normal dosage of 260 mmol/1.73 m^2 used in acute acid loading tests in children, and is higher than the acute maximum renal net acid excretion of 181 mmol/d/1.73 m^2 in children (4). All these data point to a high renal acid load over a long period in our patient. In addition, the long-term steady-state of acid base metabolism, even if we assume a borderline situation with chronic metabolic acidosis, indicates no major impairment of renal handling of hydrogen ions in our patient.

Growth retardation

In the presented case the first period of linear growth retardation resembles the clinical course of prematures and term neonates with late metabolic acidosis (8, 9). Late metabolic acidosis is caused by a temporary disproportion between daily acid load and renal capacity for hydrogen ion excretion (9). Three stages may be distinguished: the stage of development of acute maximum renal acid stimulation, the stage of compensated negative acid balance with chronic maximum renal acid stimulation, and the stage of decompensated retention acidosis. Growth retardation and indolent drinking are typical findings of the stage of compensated negative acid balance with chronic maximum renal acid stimulation (8, 9). Late metabolic acidosis is a self-limited disorder in the first week of life due to the rapid postnatal improvement of kidney function. In the first group of patients of Kildeberg (9), mean birth weight was 2.0 ± 0.3 kg ($n = 12$) and mean maximum renal net acid excretion was 3.4 mmol/kg/d ($n = 2$). The patient presented here was probably in a comparable stage of compensated negative acid balance with chronic maximum renal acid stimulation. Of course, she was much older than the patients with late metabolic acidosis of Kildeberg (9), however, the daily acid load also was considerably higher. After a period of catch-up growth, there was a second period of growth retardation. In this period vomiting and refusal to eat was frequently observed like in several of our other children receiving the highly acidic preparations. Thus, the side-effects of acid base metabolism and the unpleasant taste of the preparations might have secondarily resulted in failing appetite, caloric malnutrition, and high urinary osmolality. In prematures it is well known that the combination of acid loading and administration of pitressin considerably decreases maximum renal capacity for hydrogen ion excretion (11). Thus, acid base metabolism might had been deteriorated further by dehydration. Nevertheless, this period ended with a remarkable spontaneous growth spurt that normalized linear growth already before the start of alkali therapy. High fluid intake, a therapeutic measure after the discovery of urolithiasis, might have been the factor that increased maximum renal capacity for proton excretion and induced catch-up growth. The swings between growth retardation and catch-up growth may best be explained by one principal factor, the metabolic acidosis and several modulating factors, such as decreased energy intake and varying maximum renal capacity for net acid excretion due to different amounts of fluid intake.

Urolithiasis

Several factors were involved in the development of urolithiasis: low urine pH and high urinary ammonium concentration due to maximum renal acid stimulation, hypercalciuria due to metabolic acidosis and, probably, high urinary osmolality because of vomiting and dehydration, as well as transient hyperuricosuria during periods of decreased caloric intake (14). Chronic renal acid stimulation was probably the primary factor as there was no further growth of the remaining calculus during alkali therapy. The calculus consisted of ammonium urate and calcium oxalate, a typical finding in children with endemic urolithiasis (10, 14).

In the 19th century, endemic urolithiasis was very common in European children (10). Today, calculi of uric acid are extremely rare in children from this region. Endemic urolithiasis is usually attributed to inadequate nutrition (10, 14). This is a very global concept. Our observation may stress one pathogenic factor, the long-term low urine pH. Recently, uric acid urolithiasis was also observed in children with seizures not controlled by standard anticonvulsive medication (6). The patients received a ketogenic diet consisting, after an initial period of fasting, of 80 % fat and 20 % protein and carbohydrates, as well as a restricted fluid intake. They also showed low urine pH and high urinary osmolality.

After effects of long-term acid loading

Hypercalciuria (> 0.15 mmol/kg/d) and slightly elevated serum levels of parathormone were still repeatedly observed after the correction of acid base metabolism. Therefore, the possibility of tertiary hyperparathyroidism as a long-term consequence of longlasting metabolic acidosis was evaluated. However, after puberty normal calciuria and normal serum parathormone levels were observed. Furthermore, in 1982, a cross-sectional study in 17 of our patients with phenylketonuria (age 12.3 ± 1.4 years), who all received the highly acidic, low pheylalanine preparations before 1973, showed normal calciuria and normal serum parathormone levels. Severe caries at the age of 6 years and possibly bulimia at the age of 17 years may be late effects of decreased dental mineralization and psychological stress during feeding in the first years of life.

Conclusions

In natural foods the range and interrelationship of the content of protein and minerals are limited. Therefore, in children and adults receiving normal foods, renal acid load is much lower than maximum renal acidification capacity. In synthetic diets and parenteral nutrition, high contents of the sulphur containing amino acids, as well as an unbalanced content of the major minerals may result in a very high renal acid load rising above acute or even chronic maximum renal net acid excretion capacity (5, 12).

In several European countries licorice products with 8–10 % ammonium chloride (150–187 mmol/100 g) are freely offered to the public. In children regular consumption of high amounts of this highly acidic confectionary may cause similar side-effects if additional individual risk factors are present. Therefore, highly acidic dietary products should be avoided in dietetics and not be offered to the public without constraints.

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