ACUTE RENAL FAILURE IN AN INFANT WITH PARTIAL DEFICIENCY OF HYPOXANTHINE-GUANINE PHOSPHORIBOSYLTANSFERASE

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Summary

A three week old boy presented with pneumonia, weight loss, metabolic acidosis and renal failure (serum creatinine 3.1mg/100ml, uric acid 11.5mg/100ml). Renal biopsy revealed severe crystal nephropathy. Low activity of hypoxanthine-guanine phosphoribosyltransferase (HPRT) in erythrocytes and fibroblasts suggested a partial deficiency of the enzyme. A family study proved the mother to be heterozygous and the maternal grandfather to be hemizygous for HPRT deficiency. The grandfather developed gouty nephropathy and uraemia. The propositus was treated with allopurinol and kept on low purine diet and high fluid intake with sodium bicarbonate. Thereafter GFR gradually improved. At the age of two and a half years, growth and psychomotor development were normal, but ultrasound examination still revealed a dense renal parenchyma. Partial HPRT deficiency is a newly recognised treatable form of renal failure in the newborn.

Introduction

In the early postnatal period transient hyperuricaemia and hyperuricosuria are described especially following asphyxia and dehydration [1] and in autopsies of newborns up to 19.3 per cent incidence of uric acid ‘infarctions’ in kidneys is reported [2]. However, this overload of uric acid is usually not suspected to be the cause of kidney dysfunction. Even in patients with hereditary deficiency of HPRT, which is characterised by overproduction of uric acid since birth, renal complications usually do not occur before late childhood [3]. The following patient demonstrates that partial HPRT deficiency may lead to renal failure even in infancy.

Case Report

A full term male infant, weighing 3980g (S.Z., born 8/3/82) was delivered to a primipara without complications. Seven days after birth an upper respiratory
tract infection and feeding difficulties were noted. At two weeks of age a diagnosis of bronchopneumonia was made and the baby was treated orally by ampicillin and cloxacillin followed additionally by gentamicin i.m. (4.5mg/kg/day) from day 19 to day 25. Because the general condition deteriorated he was admitted to the hospital at day 21. He appeared critically ill; weight 3350g, height 52cm. Laboratory studies: serum sodium 126mmol/L, potassium 7.6mmol/L, capillary blood: pH 7.02, bicarbonate 6mmol/L, base excess -23mmol/L, urinalysis: 31 erythrocytes/mm³, 62 leucocytes/mm³, pH 5.5, culture sterile. The infant received glucose/saline containing sodium bicarbonate intravenously (170ml/kg/day). At the age of 25 days BUN was 37mg/100ml, creatinine 3.1mg/100ml, uric acid 11.5mg/100ml, creatinine clearance 6.2ml/min/1.73m², urine volume 335ml/24hr. Abdominal ultrasound examination showed that both kidneys were of normal size, parenchyma was bright with a patchy pattern. Subsequently antibiotic therapy was stopped while the infusion therapy was continued.

Surgical renal biopsy at the age of 65 days demonstrated no glomerular changes, but at the corticomedullary junction many tubules were obstructed by crystalline needle-shaped material. Crystals were positive with De Galantha stain in alcohol fixed specimen. Some tubular epithelial cells were transformed to multinucleated giant cells. The interstitium showed diffuse fibrosis and focal infiltration by mononuclear cells.

Following kidney biopsy and a detailed family history enzyme studies were performed. HPRT activity in lysed erythrocytes on day 78, 11 days after transfusion, was 31.6nmol/mg protein/hr, but ranged between 0.2 and 1.1 when the test was repeated on seven other occasions. HPRT activity in lysed skin fibroblasts obtained from a skin biopsy was 1.2 per cent of normal. In intact erythrocytes it was considerably higher (Table I) [4].

**TABLE I. HPRT activities in the propositus and his family.** The values given are the mean of activities observed on different occasions, respectively in different subcultures of fibroblasts [4].

<table>
<thead>
<tr>
<th></th>
<th>Age at testing</th>
<th>HPRT nmol/mg protein/hr, lysed erythrocytes</th>
<th>HPRT nmol/ml packed cells/hr intact erythrocytes</th>
<th>HPRT nmol/mg protein/hr lysed fibroblasts</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Propositus</strong></td>
<td>7 weeks</td>
<td>31.6</td>
<td>6.4</td>
<td>0.6</td>
</tr>
<tr>
<td></td>
<td>7 months</td>
<td>0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Maternal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Grandfather</strong></td>
<td>53 years</td>
<td>24.0</td>
<td>12.2</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>Mother</strong></td>
<td>26 years</td>
<td>69.0</td>
<td>41.8</td>
<td>23.3</td>
</tr>
<tr>
<td><strong>Father</strong></td>
<td>26 years</td>
<td>79.7</td>
<td></td>
<td>43.0</td>
</tr>
<tr>
<td><strong>Normal</strong></td>
<td>adults</td>
<td>100.0</td>
<td>57.4</td>
<td>59.1</td>
</tr>
<tr>
<td></td>
<td>(70–150)</td>
<td>(48–63)</td>
<td>(42–82)</td>
<td></td>
</tr>
</tbody>
</table>
Figure 1. Course of disease. Abscissa age in months; ordinate: lower part: • GFR in ml/min/m², calculated from serum creatinine (mg/100ml) and body length (cm) [10], ◊ endogenous creatinine clearance and © ⁵¹Cr-EDTA single injection clearance (ml/min/1.73m²); upper part: serum uric acid (mg/100ml/ and allopurinol dosage (mg/kg body weight)
Clinical course

The boy recovered slowly. On day 75 after birth, weight was 4480g, serum creatinine 1.4mg/100ml, creatinine clearance 21ml/min/1.73m², serum uric acid 11.0mg/100ml and urinary uric acid excretion was increased (203mg/24hr, i.e. 1351mg/1.73m²). At the age of 78 days the treatment with allopurinol was started. The dose was adjusted to serum uric acid and oxypurinol values. In addition sodium bicarbonate was given orally to keep the urinary pH between six and seven. Fluid intake was forced by adding tea to the low purine diet (total fluid 150ml/kg/day). Renal function improved gradually (Figure 1). GFR measured by ⁵¹Cr-EDTA single injection clearance was 110ml/min/1.73m² at the age of two years. Serum creatinine showed some fluctuations suggesting periods of transient reduction of GFR. At the age of two years and four months the boy was 91cm in height and weighed 12.9kg (50th centile). Psychomotor development was excellent and neurological signs were absent. Serum creatinine was 0.83mg/100ml. In the renal ultrasound examinations the kidney size was found to grow at the lower normal limit but the renal parenchyma still appeared dense.

Family study (Table 1)

The father had a typical attack of gouty arthritis at the age of 17 years. At 26 years he appeared to be healthy despite a serum uric acid of 8.0mg/100ml. Urinary uric acid excretions as well as HPRT activities were within normal limits. The mother was healthy with a normal serum uric acid; her HPRT activity was normal in lysed and intact erythrocytes but reduced in fibroblasts. The maternal grandfather experienced his first attack of gouty arthritis and kidney stones at the age of 24 years followed by development of gouty nephropathy. He has been treated by dialysis for the past 11 years. Since 1979 he is known to have partial HPRT deficiency and he has been already reported [5]. Unfortunately this finding was unknown to the authors when the propositus presented.

Discussion

Renal failure in the newborn is usually due to factors related to perinatal stress. In the case presented here it was first attributed to dehydration and to a toxic reaction to amingoglycoside. Serum uric acid was high but could be interpreted as a consequence of severe renal failure. However, hyperuricaemia did not return to normal in spite of partial recovery of kidney function and urate excretion was high. Primary hyperuricaemia as a cause of renal failure is exceptional in infancy. Only three such cases with proven HPRT deficiency have been reported, one with Lesch Nyhan syndrome [6] and two with partial deficiency of the enzyme [3,7]. In all the three cases dehydration and acidosis appear to have contributed to the development of renal failure as in our patient.

In the propositus HPRT activity in lysed erythrocytes was initially raised probably because of the recent blood transfusion. But five months later repeated analyses of lysed erythrocytes and fibroblasts demonstrated an enzyme activity
in the same low range as found in the Lesch Nyhan syndrome, a progressive neurological disorder with hyperuricaemia and related complications [8]. However neurological manifestations were never observed in our patient and psychomotor development was normal. We therefore assume that HPRT in our patient is an unstable mutant enzyme with higher activity in vivo than in the lysed cells, which prevents an expression of the disease outside the kidney. This view is supported by the finding that HPRT activity in intact erythrocytes of the propositus was much higher than in lysed cells.

Partial HPRT deficiency is coded by mutational changes of the structural gene, which is located on the long arm of the X-chromosome. Hemizygotes of a given family have the same variant enzyme presenting with defined characteristics regarding activity, kinetic properties and thermolability [8]. Unexpectedly, HPRT activity of lysed red cells was much lower in our patient compared to that estimated in the grandfather (0.5% vs 24% of normal). However, enzyme activity in fibroblasts as well as metabolic properties and thermolability were similar in both [4]. The higher enzyme activity in the grandfather was due to transfusions. This suggests that the two relatives bear in fact the same mutant enzyme and that this is stabilised by factors probably related to terminal uraemia, which preserves a higher activity in the in vitro tests.

The prognosis of renal function in partial HPRT deficiency is still debated. Since about 25 per cent of older patients with this metabolic defect do not develop nephrolithiasis and 50 per cent of them have normal renal function, the disorder is not necessarily progressive [8]. This suggests that complications like those seen in the propositus may be avoided by very early diagnosis and therapy. Following institution of adequate treatment renal function recovered gradually in our patient. Similar post treatment improvement in the three infants who all had severe kidney failure due to partial or complete deficiency of HPRT has been reported [3,6,7]. However, a complete recovery appears to be doubtful in view of the experimental findings in pigs which showed scars and chronic inflammation in the kidney as long as one year after a brief period of intratubular crystal deposition [9].

References


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