Nephrological abnormalities in patients with transaldolase deficiency

Yvette G. T. Loeffen¹, Nathalie Biebuyck², Mirjam M. C. Wamelink³, Cornelis Jakobs³, Margot F. Mulder⁴, Anna Tylik-Szymańska⁵, Cheuk-Wing Fung⁶, Vassili Valayannopoulos⁷ and Arend Bökenkamp⁸

¹Department of Pediatric Nephrology, VU University Medical Center, Amsterdam, The Netherlands, ²Department of Pediatric Nephrology, Necker-Enfants Malades Hospital, Paris Descartes University, Paris, France, ³Department of Clinical Chemistry, VU University Medical Center, Amsterdam, The Netherlands, ⁴Department of Pediatrics, VU University Medical Center, Amsterdam, The Netherlands, ⁵Clinic of Metabolic Diseases, Endocrinology and Diabetology, The Children’s Memorial Health Institute, Warsaw, Poland, ⁶Division of Child Neurology, Queen Mary Hospital, Hong Kong, China and ⁷Reference Center for Inherited Metabolic Disorders, Necker-Enfants Malades Hospital, Paris Descartes University, Paris, France

Correspondence and offprint requests to: Arend Bökenkamp; E-mail: a.boekenkamp@vumc.nl

Abstract

Background. Transaldolase deficiency (OMIM 606003) is a multisystem disorder first described in 2001. Transaldolase is an enzyme of the reversible part of the pentose phosphate pathway. Affected patients have abnormal polyol concentrations in body fluids, mostly in urine. The clinical presentation is variable. The leading symptoms are coagulopathy, thrombocytopenia, hepatosplenomegaly, hepatic fibrosis and dysmorphic features. The objective of our study was to attempt to characterize the renal phenotype of patients with transaldolase deficiency.

Methods. Clinical and laboratory data of all nine patients with transaldolase deficiency presently known were gathered by retrospective chart analysis.

Results. Nephrological abnormalities were present in seven of the nine patients. The most common findings were low molecular weight (LMW) proteinuria and hypercalciuria. The two oldest patients had moderate chronic kidney failure. In two patients, generalized aminoaciduria was found, two patients had renal phosphate wasting and three patients had hyperchloremic metabolic acidosis. Three patients had anatomical abnormalities.

Conclusions. Renal tubular dysfunction is present in the majority of patients with transaldolase deficiency and may lead to chronic renal failure. The combination of unexplained liver dysfunction with LMW proteinuria should prompt metabolic screening for transaldolase deficiency by measuring urinary polyols. In patients with transaldolase deficiency, monitoring of kidney function is mandatory.

Keywords: hypercalciuria; metabolic disease; proteinuria; renal failure; tubular dysfunction

Introduction

Transaldolase deficiency (OMIM 606003) is an inherited metabolic disorder first described in 2001 in a patient presenting with neonatal liver dysfunction and disturbed coagulation tests [1]. Transaldolase is an enzyme of the reversible part of the pentose phosphate pathway, which is shown in Figure 1. Until now, nine patients (10 including a fetus) with transaldolase deficiency have been described in the literature and the clinical phenotype has expanded [1–7].

Affected patients have abnormal polyol concentrations in body fluids, mostly in urine. Sedoheptulose—a seven-carbon chain carbohydrate—is a specific biomarker for transaldolase deficiency [8]. The clinical presentation of transaldolase deficiency is variable. All patients described to date presented with severe symptoms in the neonatal period, with some of them already presenting prenatally. The leading symptoms were coagulopathy and thrombocytopenia, hepatosplenomegaly, hepatic fibrosis and dysmorphic features. In several children, renal dysfunction was noted. We therefore sought to characterize the renal phenotype of patients with transaldolase deficiency.

Materials and methods

Clinical and laboratory data of the nine patients with transaldolase deficiency presently known were gathered by retrospective chart analysis. The need for institutional review board approval was waived. Renal failure was defined as a glomerular filtration rate (GFR) < 90 mL/min/1.73m², i.e. chronic kidney disease Stage 2 in children > 1 year. GFR was estimated using the Schwartz equation [9] in all but one case. In the oldest patient (I.1), a single injection inulin clearance was performed. Low molecular weight (LMW) proteinuria was defined as an increased excretion of α1-microglobulin or β2-microglobulin or a tubular pattern of proteinuria by urine sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE), which was defined as excretion of proteins with a molecular weight < 30 kDa. Calcium excretion exceeding 0.1 mmol/kg/day was classified as hypercalciuria, as was an elevated calcium-creatinine ratio in spot urine samples using age appropriate reference data [10, 11]. Glucosuria was defined by the presence of glucose in the urine during euglycemia, measured either quantitatively or semi-quantitatively by urine dipstick (two patients). Renal tubular acidosis was indirectly assessed by plasma bicarbonate values and the need for bicarbonate supplementation in the absence of a high anion gap. Potassium wasting was defined as hypokalemia < 3.2 mmol/L on several occasions necessitating potassium supplementation, phosphate wasting as persistent...
hypophosphatemia in the presence of a decreased tubular maximum for phosphate reabsorption (TmP/GFR) using age appropriate reference values [12]. Nephrocalcinosis/nephrolithiasis was assessed by ultrasound.

**Results**

**Patient characteristics**

The study population consists of nine children (three females and six males) with transaldolase deficiency from six families (I–VI). In all patients, the diagnosis was confirmed by biochemical (n = 9) and/or mutation analysis of the TALDO1 gene (n = 7). Individual patient characteristics and clinical course are summarized in Table 1. All the patients were born from consanguineous parents. Two children (I.1 and V.1) were born small for gestational age. The main problems seen in the neonatal period were dysmorphic features, coagulopathy, anemia and thrombocytopenia, hepatosplenomegaly with liver dysfunction and cardiac anomalies. Three of the nine patients died. Patient II.1 died from respiratory failure at the age of 18 days, Fig. 1.

![Pentose phosphate pathway](image_url)

**Table 1. Patient characteristics**

<table>
<thead>
<tr>
<th>Patient (family, child)</th>
<th>I.1</th>
<th>II.1</th>
<th>III.1</th>
<th>III.2</th>
<th>III.3</th>
<th>IV.1</th>
<th>V.1</th>
<th>VI.1</th>
<th>VI.2</th>
</tr>
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<tbody>
<tr>
<td>Reference #</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>5</td>
<td>4</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Gender</td>
<td>Female</td>
<td>Female</td>
<td>Female</td>
<td>Male</td>
<td>Male</td>
<td>Male</td>
<td>Male</td>
<td>Male</td>
<td>Male</td>
</tr>
<tr>
<td>Amino acid exchange</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>IUGR</td>
<td>HELPP syndrome</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Oligohydramnion</td>
<td>IUGR</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Neonatal dysmorphisms</td>
<td>–</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Cardiac anomaly</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Hematological problems</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Hepatopathy</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Liver cirrhosis</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Outcome (psychomotor development)</td>
<td>17 Years</td>
<td>18 Days</td>
<td>5 Months</td>
<td>Normal</td>
<td>Normal</td>
<td>Not known</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>

*aSummary of history and extrarenal manifestations as published previously (approximately respective reference #). Hepatopathy: hepatosplenomegaly, liver fibrosis or abnormal liver function. Hematological problems, anemia and thrombocytopenia.*

*bPatients died during the study.*
whereas Patients III.1 and I.1 from internal bleeding complicating liver failure at the age of 5 months and 17 years, respectively.

Nephrological findings

The nephrological findings are summarized in Table 2. GFR ranged from 41 to 110 mL/min/1.73m². As illustrated in Figure 2, GFR was normal in the younger children, whereas the two oldest patients (I.1 and III.2) had moderate chronic kidney failure at the age of 17 and 9 years, respectively.

Six patients had tubular, Patient II.1 had glomerular proteinuria. In three patients, generalized aminoaciduria was found. One patient had glucosuria, renal phosphate wasting was noted in two. Two patients had transient hyperchloremic metabolic acidosis, Patient III.2 is still using sodium bicarbonate supplementation. Of note, no patient had the complete renal Fanconi’s syndrome.

Six children had hypercalciuria, with a maximum calcium-creatinine ratio of 6.67 mmol/mmol found in Patient II.1. Only one of these had nephrocalcinosis. Transient arterial hypertension was noted in Patient III.3 at 4 months of age. Renal ultrasound including Doppler studies and plasma renin and aldosterone were normal.

Imaging studies

Renal ultrasound was performed in all patients. Patient III.1 was the only patient with nephrocalcinosis. Patient VI.1 had renomegaly (kidney length 9 and 10 cm at the age of 3.5 years) with increased echogenicity of pyramids and renal parenchyma. Patient III.2 had right kidney hypoplasia, a dysplastic left kidney and bilateral vesicoureteral reflux, diagnosed at birth.

Discussion

Our study identified renal abnormalities in all but two patients with transaldolase deficiency. The most common findings were tubular proteinuria and hypercalciuria. The two oldest patients developed chronic kidney failure at the age of 17 and 9 years raising the possibility that transaldolase deficiency may lead to progressive renal damage. Patient III.2 had renal hypoplasia/dysplasia from birth, which may have contributed to chronic kidney failure. Yet the rapid decline in GFR in the absence of urinary tract infection is suggestive of a superimposed effect of transaldolase deficiency.

The combination of LMW proteinuria and hypercalciuria is also seen in Dent’s disease and Lowe syndrome [13, 14]. Both diseases may lead to chronic renal failure. The underlying genes (CLCN5 and OCRL1) are involved in the endocytic reabsorption of albumin and LMW proteins in the proximal tubule.

Many metabolic diseases are complicated by renal disease, mostly tubular dysfunction. In the most severe cases, a generalized proximal tubulopathy, the renal Fanconi-deToni-Debré syndrome may develop. Metabolic disease may also lead to chronic kidney failure. Examples are accumulation of intralyosomal cystine in

<table>
<thead>
<tr>
<th>Table 2. Nephrological findings²</th>
<th>I.1</th>
<th>II.1</th>
<th>III.1</th>
<th>III.2</th>
<th>IV.1</th>
<th>V.1</th>
<th>VI.1</th>
<th>VI.2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at last evaluation (years)</td>
<td>3</td>
<td>18</td>
<td>0.5</td>
<td>9</td>
<td>4.8</td>
<td>2</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Proteinuria Tubular: α1-m</td>
<td>39.9 (&lt;4)</td>
<td>30.4 (&lt;0.3)</td>
<td>10.6 (&lt;3)</td>
<td>n.a.</td>
<td>n.a.</td>
<td>1.1 (0.05–1.1)</td>
<td>1.47 (0.05–1.1)</td>
<td></td>
</tr>
<tr>
<td>Proteinuria Glomerular (SDS-PAGE)</td>
<td>n.a.</td>
<td>0.37</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td>Proteinuria Tubular: β2-m</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td>Concentration LMWP, mg/L (reference range)</td>
<td>0.30 (0.75–1.64)</td>
<td>0.30 (0.75–1.64)</td>
<td>0.30 (0.75–1.64)</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td>Transient arterial hypertension</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Nephrocalcinosis</td>
<td>−−−</td>
<td>−−−</td>
<td>−−−</td>
<td>−−−</td>
<td>−−−</td>
<td>−−−</td>
<td>−−−</td>
<td>−−−</td>
</tr>
<tr>
<td>Renal ultrasound</td>
<td>Normal</td>
<td>Normal</td>
<td>Nephrocalcinosis</td>
<td>Hypoplastic right kidney, dysplastic left kidney, bilateral VUR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

² α1-m, alpha-1 microglobulin; β2-m, beta-2 microglobulin; LMWP, low-molecular-weight proteinuria; SDS-PAGE, SDS-polyacrylamide gel electrophoresis; n.a., not analyzed; + , present; −, absent; VUR, vesicoureteral reflux.
nephropathic cystinosis causing increased apoptosis of the cystine-laden renal proximal tubular cell leading to tubular dysfunction, tubulointerstitial damage and ultimately end-stage renal failure [15].

Examples for defective energy metabolism leading to renal dysfunction are mitochondrial diseases and galactosemia. In the liver of TALDO knockout mice, Hanczko et al. [16] found low NADPH, low glutathione and low ATP/ADP ratio and accumulation of lipid hydroperoxides. In the urine of patients with TALDO deficiency, increased citric acid cycle intermediates were detected by nuclear magnetic resonance [17] raising the possibility that disturbed mitochondrial metabolism might play a role in the pathogenesis of the nephropathy, but this may also reflect proximal tubular dysfunction per se.

As a third mechanism, accumulation of toxic metabolites such as galactose-1-phosphate and perhaps galactitol in galactosemia and succinylacetone in tyrosinemia may cause renal damage. In transaldolase deficiency, there is accumulation of polyols, sugars and sugar phosphates [6]. It is tempting to speculate that accumulation of these metabolites is toxic to the proximal tubulus, causing tubular dysfunction and eventually chronic kidney failure from tubulointerstitial damage.

Our study has several limitations: data acquisition was by retrospective chart analysis and the data set was not complete in all cases. Also, the data only allowed for a cross-sectional analysis. The effect of age on GFR was not considered, and the data set was not complete for all cases. In the oldest patients clearly calls for prospective serial monitoring of renal function in these patients. Calculation of GFR from inulin clearance was only 47 mL/min/1.73m2. Therefore, our study may have underestimated the prevalence of renal failure in children with transaldolase deficiency.

Conclusions

Renal tubular dysfunction is present in the majority of patients with transaldolase deficiency and may lead to chronic renal failure. The earliest and most prevalent finding is LMW proteinuria. The combination of unexplained liver dysfunction with LMW proteinuria should prompt metabolic screening for transaldolase deficiency by measuring urinary polyols. In patients with transaldolase deficiency, monitoring of kidney function is mandatory.

Conflict of interest statement. None declared.

References


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