Long-term follow up of a new case of hawkinsinuria*

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Abstract  Hawkinsinuria is a rarely diagnosed autosomal dominantly transmitted inborn error of tyrosine metabolism with impaired conversion of 4-hydroxyphenylpyruvate to homogentisate. As a consequence of the defective 4-hydroxyphenylpyruvate dioxigenase activity, large amounts of the unusual, ninhydrin-positive amino acid hawkinsin and later on 4-hydroxycyclohexylacetic acid are formed and excreted. Clinically the disease is characterised mainly by chronic metabolic acidosis and severe growth retardation as a result of protein overload. As the ability to form 4-hydroxycyclohexylacetic acid and thereby to cope with the still not very well defined reactive and toxic intermediates increases, clinical symptoms vanish. We report here a new patient with hawkinsinuria having experienced a series of admissions because of unclear hepatopathy, growth retardation, and renal tubular acidosis.

Conclusion  Prolonged tyrosyluria in the newborn and young baby should cause the clinical chemist not only to exclude tyrosinaemia, galactosaemia, and fructose intolerance but also to look carefully for hawkinsin in the aminoacid chromatogram.

Key words  Hawkinsinuria · 4-hydroxycyclohexylacetic acid · Tyrosyluria · Chronic metabolic acidosis · Growth retardation

Introduction

Hawkinsinuria is an infrequently observed disorder of tyrosine metabolism transmitted as an autosomal dominant trait with variable clinical expression. The defect is located at the 4-hydroxyphenylpyruvate dioxigenase enzyme (EC 1.13.11.27) converting 4-hydroxyphenylpyruvate to homogentisate. It is thought that a highly reactive epoxide intermediate, formed during the complex transformation, reacts with cysteine or glutathione and hydride anions to give ninhydrin-positive (2-L-cystein-S-yl-1.4-dihydroxycyclohex-5-en-1-yl)-acetic acid, called hawkinsin [6], and 4-hydroxycyclohexylacetic acid [7, 8] respectively. Whereas hawkinsin is excreted early in life, the ability to form and excrete the latter compound develops gradually and is observed not before the 11th month of age [1].

Clinically the patients present with metabolic acidosis and failure to thrive following weaning from breast milk or they become symptomatic at once under standard formula feeding. Since the description of the first case [3], only three additional symptomatic patients and several biochemically affected but clinically asymptomatic patients have been described.

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atic family members have been detected so far [1, 4, 10]. We describe here a new case of hawkinsinuria who was first misdiagnosed as having fructose intolerance.

Materials and methods

Aminoacidopathies were screened for by high voltage electrophoresis on paper sheets, the electropherograms being routinely stained with ninhydrin. Special staining to detect sulfur-containing compounds was done with the iodoplatinate reagent [2]. Quantitation of amino acids was performed with an autoanalyzer following the standard procedure of Spackman et al. [9]. Desulphuration of urinary sulfur-containing compounds was accomplished by reaction with freshly prepared Raney-nickel essentially as described by Niederwiser [6]. Organic acids were investigated as methyl esters by gas chromatography-mass spectrometry [5]. For $^1$H-NMR-spectrometric measurements, urine was centrifuged for 30 min at 3000 g. To 500 μl of urine, 50 μl of trimethylsilyl-2,2,3,3-tetradeuteropropionic acid (TSP; 20.2 mmol/l D$_2$O) was added as an internal standard, pH was adjusted to 2.5 ± 0.05 with concentrated hydrochloric acid. Measurements were performed with a Bruker DRX-600 spectrometer (Bruker Analytische Messtechnik, Karlsruhe, Germany) using 128 60°-rf-pulses with an acquisition time of 6 ms and a sweep width of 6605 Hz. The chemical shift of TSP was set at zero. Interpretation of the spectra was enhanced by ACD/Chem Sketch and ACD/HNMR software (Advanced Chemistry Development, Toronto, Canada).

Case report

The boy was the third child of a nonconsanguineous healthy Austrian couple. Both older sisters are healthy and not affected. Pregnancy, delivery and development during the first 3 months of life were normal. After weaning from breast milk at the age of 3 months recurrent vomiting, inappetence, and failure to thrive occurred. At the age of 9 months the child was admitted to a peripheral hospital for the first time because of developmental delay (height and weight < 3rd percentile), haemorrhage, urinary tract infection, and suspected renal tubular acidosis. Symptoms ceased under treatment with sulphametrol/trimethoprim and bicarbonate. During the following 3 months three additional admissions became necessary because of unclear hepatopathy, clotting disturbances, enteritis, chicken-pox, severe growth retardation and renal tubular acidosis. Amino acid analysis revealed an unknown compound at that time attributed to medication. Because of diarrhoea and recurrent vomiting and for further clarification of his severe growth retardation (Fig. 1) which included also head circumference (documented to be well below the 3rd percentile between the age of 10 and 15 months), the patient was admitted to the Gottfried von Preyer’s Children’s Hospital in Vienna at the age of 13 months. Renal tubular acidosis was confirmed but had to be designated as idiopathic since no causing conditions were found despite numerous investigations. There were no other pathological internal and neurological findings. Amino acid analysis revealed an unknown peak. Investigation of organic acids showed severe tyrosyluria (4-hydroxyphenylpyruvic and 4-hydroxyphenyllactic acid), elevated excretion of lactic and pyroglycemic acid. Tyrosinemia, galactosemia, fructose intolerance or a liver disease of unknown origin were suspected. For clinical reasons (recurrent vomiting, seen often following ingestion of fruits and a tendency toward hypoglycemia), liver biopsy was performed at the age of 2 years and 4 months to exclude fructose intolerance as well as a glycosogenosis. Enzymatic studies revealed reduced activities of fructose-1.6-bis-phosphatase and fructose-1-phosphate aldolase. Despite of the not fully convincing results, a diet low in fructose was introduced. Vomiting ceased gradually, the child gained weight and started growing. Even renal acidosis improved so that bicarbonate therapy could be stopped at the age of 3 years. A second liver biopsy at 3 years and 8 months showed normal values. Therefore the diet was discontinued. A now initiated further screening for inborn errors of metabolism revealed excretion of high amounts of 4-hydroxycyclohexylacetic acid (Table 1) thus giving the clue to the diagnosis hawkinsinuria. Today, at the age of 10.5 years, the boy is completely normal. Somatic growth parameters normalised (Fig. 1) including head circumference. His psychomotor development had never been affected. He continues to excrete hawkinsin and increasing amounts of 4-hydroxycyclohexylacetic acid (Table 1).

Table 1 Excretion of metabolites in hawkinsinuria during different stages of the disease as measured by $^1$H-NMR spectroscopy (+ detected, n.d. not detected)

<table>
<thead>
<tr>
<th>Age (years/months)</th>
<th>Lactate</th>
<th>Pyroglutamate</th>
<th>Tyrosyluria</th>
<th>4-Hydroxy-cyclohexyl-acetate [mmol/mol creatinine]</th>
<th>Hawkinsin [mmol/mol creatinine]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/1</td>
<td>++</td>
<td>++</td>
<td>+++</td>
<td>n.d.</td>
<td>2150</td>
</tr>
<tr>
<td>3/8</td>
<td>normal</td>
<td>n.d.</td>
<td>normal</td>
<td>230</td>
<td>470</td>
</tr>
<tr>
<td>3/9</td>
<td>normal</td>
<td>n.d.</td>
<td>n.d.</td>
<td>1100</td>
<td>400</td>
</tr>
<tr>
<td>10/7</td>
<td>normal</td>
<td>n.d.</td>
<td>n.d.</td>
<td>800</td>
<td>200</td>
</tr>
</tbody>
</table>