Primary hyperoxaluria type 1: clinical, genetic and biochemical studies
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Primary hyperoxaluria remains undiagnosed in patients with hyperoxaluria and recurrent urolithiasis

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Primary hyperoxaluria (PH) is a metabolic disorder caused by deficiency of either the liver-specific enzyme alanine:glyoxylate aminotransferase (AGT) for PH type 1 (PH1) or glyoxylate reductase/hydroxypyruvate dehydrogenase (GR/HPR) for PH type 2 (PH2). PH increases endogenous oxalate production, leading to the development of renal stones and nephrocalcinosis, which may result in end-stage renal disease (ESRD) (1). The first step in the diagnostic process involves measurement of urinary oxalate, glycolate, and L-glycerate, followed by enzymatic analysis of AGT (in liver) or GR/HPR (in lymphocytes), or genetic testing of the AGXT gene for PH1 or the GRHPR gene for PH2. Extensive metabolic screening is rarely performed in adults who present with stone disease because PH disease presentation usually occurs in childhood, not in adulthood. Nevertheless, more than one-third of PH1 is diagnosed in adult patients in ESRD (2). Early diagnosis and treatment is of utmost importance in PH, because conservative therapy can prevent renal insufficiency (2), particularly pyridoxine therapy in PH1 (3). If treatment is not initiated in a timely manner, ESRD will ensue in these patients. Therefore, adequate diagnostic measures should be taken after the first clinical signs and symptoms have evolved.

We performed a comprehensive search among all nephrologists in The Netherlands (2) and discovered a relatively high prevalence of PH in The Netherlands. The high number of adult patients who were diagnosed only after the development of ESRD (59% for adults) indicates that our search method may have missed patients with PH and prompted us to design a strategy to identify more patients with PH. During a period of 8 years, in one routine academic hospital laboratory, we traced all patients with hyperoxaluria and performed further metabolic and genetic investigations to diagnose or exclude PH.

Since 1995, urinary oxalate has been measured at the Laboratory for General Clinical Chemistry at the Department of Clinical Chemistry in the Academic Medical Center. Until 2003, results of urinary oxalate screening revealed hyperoxaluria in 32 of 150 patients, according to the reference interval we determined with a 24-h urine collection study.
performed in this laboratory. In 25 of these 32 patients (those we were able to contact) we performed analyses of urinary oxalate, glycolate, and L-glycerate in fresh 24-h urine by ion chromatography (Dionex) and gas chromatography. Hyperoxaluria was detected in six patients (clinical characteristics as listed in TABLE 05.1). One patient had PH1, confirmed by detection of a C.508G>A mutation on the so-called minor allele of the AGXT gene, leading to a Gly170Arg amino acid substitution in the AGT enzyme. The urinary oxalate excretion rate was only mildly increased because this patient used pyridoxine at the time of urinalysis. The other five patients had urinary glycolate and L-glycerate excretion rates that were within the reference intervals and therefore in these five patients the diagnosis of PH was rejected and no further testing was performed. Four of these five patients had developed urinary tract symptoms after the onset of intestinal disease, diagnosed as secondary hyperoxaluria related to malabsorption. The fifth patient did not have evidence of PH or secondary hyperoxaluria and therefore this case was classified as idiopathic hyperoxaluria.

**TABLE 05.1** Characteristics of patients with hyperoxaluria

Reference value: 0-54 mmol/mol creatinine

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age years</th>
<th>Age at first symptoms years</th>
<th>Symptoms</th>
<th>Urinary oxalate mmol/mol creatinine</th>
<th>Co-morbidity</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>59</td>
<td>2</td>
<td>UNI</td>
<td>60</td>
<td></td>
<td>PH1</td>
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<tr>
<td>2</td>
<td>85</td>
<td>34</td>
<td>U</td>
<td>80</td>
<td></td>
<td>IH</td>
</tr>
<tr>
<td>3</td>
<td>55</td>
<td>51</td>
<td>UNR</td>
<td>70</td>
<td>Sb</td>
<td>SH</td>
</tr>
<tr>
<td>4</td>
<td>40</td>
<td>31</td>
<td>UNR</td>
<td>200</td>
<td>Cd</td>
<td>SH</td>
</tr>
<tr>
<td>5</td>
<td>63</td>
<td>48</td>
<td>UI</td>
<td>130</td>
<td>Sb,Cd</td>
<td>SH</td>
</tr>
<tr>
<td>6</td>
<td>69</td>
<td>50</td>
<td>UE</td>
<td>100</td>
<td>Sb</td>
<td>SH</td>
</tr>
</tbody>
</table>

**Abbreviations**

Symptoms: U; urolithiasis, N; nephrocalcinosis, R; renal insufficiency, E; end-stage renal disease

Co-morbidity: Sb; short bowel after intestinal resections, Cd; Crohn's disease

In this study, we searched for PH in a specific patient group in which we suspected that PH may have been underdiagnosed (2). Apparently, our strategy led to the discovery of a patient with previously undiagnosed PH. In view of the very low prevalence of PH in populations studied so far, the finding of a new PH patient in a cohort of 150 patients is remarkable and confirms that PH remains undiagnosed in some adult patients, and that the prevalence of this disease may be higher than...
previously estimated (2). The cases we describe in this report show that PH can be diagnosed only with an immediate and complete diagnostic work-up, a procedure that provides the best opportunity to prevent further renal damage. Therefore, episodes of urolithiasis, nephrocalcinosis, recurrent urinary tract infections, or unexplained decline of renal function require assessment of urinary oxalate to exclude PH. We strongly suggest that performing the same screening strategy in other hospital laboratories will detect more PH patients who may benefit from early recognition and treatment.

As previously reported, hyperoxaluria, dehydration, and other co-morbidities may lead to renal involvement (4). Citrate administration decreases the risk of stone formation (5), but this treatment was not used in three of the cases we investigated, an omission that may have placed them at higher risk for renal involvement. Therefore, all available conservative measures to decrease the risk of stone formation should be taken in patients with any type of hyperoxaluria.

REFERENCES


