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Is liver analysis still required for the diagnosis of primary hyperoxaluria type 2?

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The primary hyperoxalurias (PH) are inherited disorders of glyoxylate metabolism, leading to endogenous oxalate overproduction and the inevitable precipitation of calcium oxalate, leading to renal stones and/or nephrocalcinosis and renal failure. Type 1 PH (PH1) is caused by deficiency of alanine:glyoxylate aminotransferase (AGT), while the type 2 disease (PH2) is due to lack of glyoxylate reductase/hydroxypropyruvate reductase (GRHPR). While AGT is liver-specific, GRHPR is ubiquitously expressed although predominantly in the liver [1,2].

As the presenting symptoms of both the diseases are very similar, but with a slightly better prognosis for PH2, it is important to make a correct diagnosis to enable appropriate management decisions to be made including choice of liver–kidney or kidney-only...
transplantation in the event of end-stage renal failure. PH2 has, up to now, most frequently been diagnosed by the presence of hyperoxaluria and l-glyceric aciduria, although absence of l-glyceric acid cannot exclude the disease [3]. However, few labs can detect l-glycerate, and we have anecdotal evidence of l-glyceric aciduria without PH2. A definitive diagnosis is made by measurement of the activity of the two enzymes AGT and GRHPR in a single liver biopsy. This test is not without a degree of risk to the patient, and the tissue has to be frozen and shipped frozen to a specialist laboratory for analysis. More recently, the identification of the GRHPR gene [4,5] has made DNA analysis feasible, although each new mutation identified should ideally be proven to be pathological. Therefore, a simpler, less invasive test of enzyme activity would be welcome.

The article by Knight and colleagues [6] published in this issue of the journal presents a potential method for the diagnosis of PH2 by measurement of GRHPR activity in blood mononuclear cells (BMCs). The assay measures both the forward (glyoxylate reductase) and reverse (non-physiological) d-glycerate dehydrogenase reactions catalysed by the GRHPR enzyme. The latter is a modification of the leucocyte d-glycerate dehydrogenase assay first described for PH2 [7,8] with the hydroxypyruvate reaction product captured as a hydrazone derivative to increase the sensitivity and high performance liquid chromatography detection to improve specificity. The enzyme activities obtained in three patients with PH2 were undetectable compared with the controls, and there was no GRHPR immuno-reactivity detected, supporting the diagnosis.

However, the recent finding of additional non-mutated GRHPR transcripts in leucocytes from PH2 patients [9] raises questions about the use of blood for PH2 diagnosis. These transcripts may be the product of another, very similar, gene or pseudogene expressed in white blood cells. As yet, we know neither the significance of these transcripts nor their effect on the expressed protein, so it is difficult, at the moment, to be fully confident about the specificity of the proposed method. However, the complete absence of immunoreactive GRHPR protein in the PH2 patient samples would support a non-functional role for the other non-mutated transcripts.

As with all rare diseases, analysis is restricted to a small number of centres with an interest in the disorders. It is therefore unlikely that there will be more than one or two labs worldwide that would be interested in setting up such a service. With that in mind, pre-analytical issues including sample stability and common interferences would need to be addressed as a priority, along with the minimum sample volume to determine whether it can be used for paediatric cases, as this disease can present very early in life. As yet no data have been presented on whether there might be an age-related reference range or on the range of activity seen in heterozygotes for the disease—the latter will be particularly important if trying to make or exclude the diagnosis in other family members. We know from previous studies that heterozygotes may have intermediate levels of enzyme activity [7,8]. These issues will undoubtedly be more fully investigated in the future as will an increasing number of patient samples.

This article presents an interesting development in the PH2 story. However, it will require further evaluation before it can be considered a reliable replacement for the liver enzyme analysis. In the meantime, the assay could prove useful in a research setting, for example to evaluate the true incidence of PH2 in oxalate stone formers.

Conflict of interest statement. The author is consultant scientist in charge of a diagnostic service for primary hyperoxaluria.

(See related article by Knight et al. Nephrol Dial Transplant 2006; 21: 2292–2295.)

References

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