Mitochondrial involvement and Erythronic Acid as a Novel Biomarker in Transaldolase Deficiency

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Introduction
The biochemical diagnosis of transaldolase (TALDO) deficiency (OMIM 606003) relies on finding strongly increased concentrations of several polyols in body fluids. Sedoheptulose, arabitol, ribitol and erythritol have been identified as key diagnostic metabolites in TALDO deficiency. The use of LC–MS/MS and GC–MS for this purpose has been reported.

Aim
In this study we investigate the potential use of 1H–NMR spectroscopy to diagnose TALDO deficiency.

Materials and Method
- 6 Patients from 4 families with genetically–confirmed TALDO deficiency were included in this study (Table 1).
- 1H–NMR measurements (1D and 2D COSY) in urine samples were performed on a Bruker 500 MHz spectrometer.

Results
The 1D and 2D COSY 1H–NMR spectra from all TALDO deficient patients showed a characteristic metabolic profile, mainly due to the resonances deriving from erythronic acid and the β-furanose anomer of sedoheptulose (Fig. 1C). GC–MS analysis confirmed the increased erythritol, ribitol and arabitol concentrations in urine of the TALDO deficient patients (Table 1).

| Table 1 | Concentrations (µmol/mmol creatinine) of metabolites found in the urine from patients with TALDO deficiency.
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<tr>
<td>Patient</td>
<td>Age</td>
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<td>Erythritol</td>
<td>Ribitol</td>
<td>Arabitol</td>
<td>Oxoglutaric acid</td>
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*1, year; m, month; 2 Analyzed by 1H-NMR; 3 Analyzed by GC-MS; 4 All data from 2 different families; 5 Reference range; nd, not detected.

Conclusion
We have shown that NMR spectroscopy of urine can be used to diagnose patients with TALDO deficiency. The high urinary concentration of erythronic acid in TALDO patients has not been reported before and may serve as a new diagnostic hallmark of TALDO deficiency. Figure 2 depicts the putative metabolic pathway that may explain the high concentration of erythronic acid in urine of TALDO–deficient patients.

The finding of increased citric acid cycle intermediates hints towards a disturbed mitochondrial metabolism in TALDO deficiency.

Figure 1. 1H–NMR spectra (500 MHz) of urine and model compounds measured at pH 2.50.

A. Erythronic acid
B. Sedoheptulose isolated from sedum spectabile
C. Urine of a patient with transaldolase deficiency (S=sedoheptulose and E=erythronic acid. Subscript numbers refer to the carbon position in the molecule).

Figure 2. Pentose Phosphate Pathway

Transaldolase deficiency (solid black square) results in accumulation of sedoheptulose, erythritol and erythronic acid.