Nuclear magnetic resonance spectroscopy in glutaryl-CoA dehydrogenase deficiency

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Summary: Nuclear magnetic resonance (NMR) spectroscopy is a safe, noninvasive method that is the preferred technique for in vivo analysis of specific chemical compounds in localized brain regions. Besides quantification of compounds, NMR spectroscopy allows the detailed analysis of neurotransmitter, glucose and lactate metabolism following peripheral infusions of stable isotopically labelled precursors. The latter has been successfully applied to patients with different neurological disease states not including glutaryl-CoA dehydrogenase (GCDH) deficiency. In contrast, single patients with GCDH deficiency who were neurologically unremarkable have been studied with conflicting results. One patient was shown to have an increase in intracerebral creatine and phosphocreatine concentrations, while the second studied had unremarkable levels. In a 15-year-old patient, we were able to demonstrate elevated levels of intracerebral lactate and elevated choline/N-acetylaspartate ratios, indicating potentially increased myelin turnover and reduced neuronal integrity in periventricular white matter. Interestingly, spectra in basal ganglia were within normal limits. Systematic studies to address well-defined questions in GCDH deficiency are urgently needed. In particular, analysis of in vivo neurotransmitter metabolism following administration of isotopically labelled precursors in patients with GCDH deficiency, both when metabolically stable and when unstable, may help to advance our understanding of the pathophysiology of GCDH deficiency.

Nuclear magnetic resonance (NMR) spectroscopy of the brain involves the absorption of radiofrequency radiation by atomic nuclei including 1H (hydrogen), 13C (carbon), 31P (phosphorus) and 15N (nitrogen) in an applied magnetic field (Gruber et al. 2003b; Gruetter et al 2003; Novotny et al. 2003). For a molecule of interest containing such nuclei, the resulting NMR spectrum reflects the chemical properties, the positions of nuclei within a molecule and the biochemical environment (Gruber et al. 2003b). Combination of NMR spectroscopy with conventional MR imaging of the brain allows
correlation of specific biochemical information with anatomical structures, which is preferred in clinical applications. Limiting factors for the widespread use of NMR spectroscopy are limitations in quantifying many chemical compounds at lower concentrations (average detection limit approximately 100 μmol/L), the tolerable total acquisition time for patients and the spatial resolution (Gruber et al 2003b).

The spatial resolution in NMR spectroscopy is approximately 20 mm³ or more, compared to 1 mm³ or less that is achievable by conventional MR imaging of the brain. However, it has recently been shown that, owing to an increased homogeneity in smaller voxels, sufficient signal-to-noise ratio can be obtained using a nominal resolution <0.5 cm³ at 3 tesla (3 T), enabling development of anatomically and pathologically matched voxels (amv) after measurement (Gruber et al 2003b).

Typically NMR-visible compounds include myo-inositol (breakdown product of myelin), creatine and phosphocreatine (markers of glial cell density and intracellular energy), choline (marker for myelin turnover), N-acetyl aspartate (NAA, marker of neuronal integrity), glutamate (excitatory neurotransmitter), and lactate (marker for abnormal oxidative metabolism). Glutamate and glutamine signals may not be readily separated at magnetic field strengths below 2.0 T owing to interference with neighbouring signals and interference with unknown factors (Novotny et al 2003). Additional compounds including γ-aminobutyric acid (GABA), glycine, taurine, phenylalanine, glycogen, purine nucleotides and galactitol may only be detected in pathological disease states (e.g. at high concentrations), when special NMR spectroscopy protocols are used as in the case of GABA analysis, or when isotopically labelled precursors are given exogenously (Gruetter et al 1994; Novotny et al 2003; Pouwels et al 1999). Owing to limitations in sensitivity, certain neurotransmitters such as dopamine, serotonin and acetylcholine cannot as yet be measured using NMR spectroscopy (Novotny et al 1998).

To date, NMR spectroscopy has been applied only to single patients with glutaryl-CoA dehydrogenase (GCDH) deficiency using 31P MR spectroscopy in investigating markers of cerebral energy status (Möller et al 2003). One of the two patients studied had an increased concentration of intracerebral phosphomonooesters, while the other showed unremarkable spectra. In particular, there was no decrease in intracerebellar creatine and phosphocreatine levels both within brain lesions and in healthy brain, while there was limited information on choline, NAA and myo-inositol concentrations (Möller et al 2003).

Here we report the results of a preliminary NMR spectroscopy study in a 15-year-old patient with GCDH deficiency in comparison to his 14-year-old healthy brother, using advanced NMR spectroscopy at 3.0 T.

SUBJECTS AND METHODS

Patient: We studied a 15-year-old boy with late-onset GCDH deficiency who was the first child born to healthy nonconsanguineous caucasian parents. Following an unremarkable pregnancy, he was born at full term with borderline macrocephaly (90th centile). Head circumference increased significantly by 3 months of age and