The Contribution of Magnetic Resonance to Explaining Phenylketonuria Brain Lesions

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Introduction

Magnetic resonance makes it possible to observe changes in patients with phenylketonuria (PKU). This study deals with a comparison of different MR techniques in PKU patients and tries to explain the origin of different MR findings.

Methods

A selected group of 14 patients with classical phenylketonuria (mean age 23.3 years) from our group of long-term PKU patients and a control group of 20 age-matched healthy volunteers (mean age 24.0 years) were examined. The examination protocol was approved by the Grant Ethics Committee.

All measurements were performed on a 1.5 T Siemens whole-body Magnetom-Vision MR imager with a standard CP coil. MR imaging included T_2-weighted transversal slices (TR/TE1/TE2=2500/20/80 ms, 6 mm), T_2 measurement using SE sequence with 16 echoes (TE 22.5-360 ms, echo-spacing 22.5 ms, TR=3000 ms, 5 mm), and diffusion weighted (DW) images using SE EPI sequences with a) single bipolar gradient in the *x*, *y* and *z* directions with b=1100 s/mm^2 (TR/TE=4000/121 ms) and b) using "trace" gradient form [1] with b=650 s/mm^2. The apparent diffusion coefficients of water in the *x*, *y* and *z* directions ($ADC_{x,y,z}$) were calculated using images from method a) and compared with *ADC* maps calculated from "trace" images (two points b=65 and 650 s/mm^2). ^{1}H MR spectra were obtained using STEAM sequence (TR/TE/TM=5000/10/15 ms) from a 3.5 ml VOI in periventricular white matter. The measured spectra were evaluated automatically on workstations using the LCModel program [2].

Results

Well-known pathological lesions characterized by symmetrical areas of T_2 enhancement, especially in the posterior parts of the lateral ventricles, were observed in all patients. In the most affected areas the mean value of the relaxation time T_2 was found to be about 220 ms in the group of patients compared to 95 ms in healthy volunteers. Mean *ADC* of water measured in PKU patients decreased by about 30% compared to control data, i.e. $0.5\text{x}10^{-5}$ ($\bar{s}=0.03\text{x}10^{-5}$) vs. $0.7\text{x}10^{-5}$ ($\bar{s}=0.01\text{x}10^{-5}$) cm^2/s. The concentrations of the metabolites NAA and Cr were unchanged in the group of patients compared to the control group (NAA=11.2 mM, Cr=6 mM); a significant difference was found in the concentration of choline compounds (1.8 mM in controls vs. 1.5 mM in patients). The distance that water molecules diffuse between collisions (*R*) in the *x*, *y* and *z* directions can be calculated (assuming the fast exchange of water molecules in a soft tissue) by the equation

$$R = \sqrt{2ADC * T_2}$$

The results showed the mean distance of *R* in the *x*, *y* and *z* directions in PKU lesions to be 14, 15 and 13 μm vs. 12 μm in controls. The tortuosity λ in the lesion can be calculated as

$$\lambda = \sqrt{D_w / ADC}$$

where D_w is the free water diffusion coefficient $D_w=2.2*10^{-5}$ cm^2/s. Tortuosity in the *x*, *y* and *z* directions is increased in PKU patients by about 20% compared to controls. (2.2, 2.1, 2.3 vs. 1.8, 1.8, 1.8, respectively).

Discussion and conclusion

Results of T_2 relaxometry, diffusion measurements and ^{1}H spectroscopy can be used for the formulation of a hypothesis that explains the changes in MR images of patients with phenylalaninaemia: the increase of T_2 in a patient is controlled by raising the concentration of free water molecules in the lesion. Molecules of water in the lesion also have better mobility as described by *R*, which is higher in the lesion than in the VOI of the controls. The increase in water mobility might be explained by changes in the myelin sheaths, which, presumably, have different geometry in PKU patients than in controls, and thus water molecules can diffuse better between them due to changes in extracellular space volume and geometry[3] [3]. These changes could also result in the observed increase in tortuosity in PKU lesions which tended to show greater anisotropy. The unchanged concentrations of NAA and Cr show that there is probably no change in the total number of cells in the lesion, and also the same concentrations in PKU patients and control groups explain the good clinical state of patients under a suitable diet. The decrease of choline compounds [4] is consistent with the decrease in neurotransmitter levels in the brains of PKU patients [5].

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