# Brain abnormalities in Phenylketonuria: evaluation with a 3 T MR system

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## INTRODUCTION

Phenylketonuria (PKU) is a disorder of amino acid metabolism, caused by an inborn error in the phenylalanine (Phe) hydroxylase gene, which heavily reduces hepatic hydroxylation of phenylalanine to tyrosine. Although the neonatal screening and diagnosis have radically modified the prognosis of this disorder, some clinical and neuroradiological alterations have been found in early treated subjects.

PKU has been studied under numerous aspects. It is known the existence on MRI of hyperintesities on T2 weighted images involving white matter and optic chiasm and Phillips et al. (2001) showed in three patients affected by PKU with classical hyperintesities of the white matter, alterations overlapping to DW images, compatible with a restricted diffusion. Beside, proton magnetic resonance spectroscopy is a valuable tool for measuring noninvasively the concentration of several brain metabolites in vivo (Kreis 1997). Several groups have demonstrated that it is possible to detect and quantify brain Phe concentrations in PKU patients by means of 1H MRS on a clinical 1.5 T MR scanner (Kreis et al 1995; Leuzzi et al. 2000; Moats et al 2000). However, there are still limitations to detect Phe in brain. Despite continuing progress in 1HMRS acquisition methodology on clinical 1.5 T scanners, and despite increasingly sophisticated quantification routines, the measurement of brain Phe concentrations is still quite noisy. In fact, the very large volume of interest necessarily used (more then 30 cc) affects the detection of Phe signal, due to the concurrent line-broadening effects on the resonance and the presence of macromolecular contributions (MM) at 7.3 ppm (Pietz et al. 2003).

In this study we report the 1H MRS data, acquired in addition to MRI and DWI images, of 32 cases with PKU. In particular, we analysed how the use of high-field magnets increase signal-to-noise ratio and lower detection thresholds of brain PHE concentration and if the use of 3 T system can characterize the pathogenic role of WM MRI signal abnormalities revealed in PKU patients.

## MATERIALS and METHODS

32 PKU patients, 17 males and 15 females, aged 7 to 34 years (mean 18.9, SD 6.0), early (21) and late (11) detected, were enrolled for the study. All patients underwent to a MR study, performed with a 3 T General Electric scanner (Signa Horizon LX, General Electric Medical System, Milwaukee, WI). WM involvement was assessed on axial FLAIR (fluid attenuated inversion recovery), T1 weighted images and coronal FSE T2 weighted images and sagittal FSPGR T1 weighted images. Alterations of WM were analyzed both qualitatively, with reference to signal intensity in the pulse sequences used, and quantitatively with reference to their anatomical location and extension. DTI was performed on axial plane, using an echo planar modified spin-echo sequence with a b-value of 1000 sec/mm$^2$ and with the diffusion gradient applied along 25 different directions. Then ADC and FA maps have been calculated. Single-voxel $^1$H MRS was performed using a short TE PRESS sequence (TE=35 ms). Voxel volume was just 8 cc (extremely lower with respect to 32 cc necessary at 1.5 T) and was placed in the periventricular deep white matter. Results of amplitude of Phe at 7.36 ppm were computed as relative values with respect to Cr/PCr peak at 3.05 ppm, considered as internal reference. All the other metabolites (NAA, Cho, Cr/PCr, mI) have been analyzed by means LCmodel routines.

## RESULTS and CONCLUSIONS

WM alterations was found in 93.7% of all PKU patients and there was no significant difference in the severity of WM involvement between early and late detected patients, demonstrating absence of correlation with factors influencing the prognosis or denoting the clinical condition in deficient subjects; as a possible causal factor, the length of the exposure of the brain to high Phe values seems to influence the severity of WM alterations WM alteration does not reflect a derangement in the normal organization of cerebral myelin pathways detect by means the evaluation of DTI indices. In fact the analysis of DTI revealed decreased ADC values in the hyperintense areas but normal FA indices in the most part of the myelinic fibres. In particular, the fibres system that has ontogenetically an older origin, as optic radiations, appeared normally represented.

H$^1$MRS revealed abnormal elevation of the signal at 7.36 ppm, associated to normal values of the principal metabolites (NAA, Cho, Cr/PCr, mI ) The relative amplitude of the signal at 7.38 ppm with respect to Cr/PCr signal increases linearly with blood Phe values, until values of 1200 microM, were the dispersion of brain Phe values rises, suggesting a more marked inter-individual variability, probably due to the saturation of the specific Phe transport system at level of BBB. With respect to other studies conducted with 1.5 T systems, Phe signal is easily detectable and analytically valuable for the increase of signal-to-noise ratio and the better spectral resolution. In fact the use of a smaller VOI reduced the line-broadening effects and the presence of macromolecular contributions (MM) at 7.3 ppm. Furthermore no correlation was found between the degree of WM involvement and the concurrent concentration of brain Phe, suggestive that brain Phe levels have to be considered as marker to monitor the influx of Phe from blood into brain tissue, especially during therapeutic follow-up studies.