In Vivo MRI/MRS of PTEN-null Mice - an Animal Model of Hypermyelination

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Introduction

Phosphatase and tensin homolog on chromosome ten (PTEN) is a tumor suppressor gene. Its selective inactivation predominantly in oligodendrocytes results in macrocephaly and hypermyelination in the CNS accompanied with increases of the axon diameters and myelination of thinner, normally unmyelinated axons. At the same time the structure of the thickened myelin sheaths is disturbed. The purpose of this pilot study was to investigate this animal model of hypermyelination by T1- and T2-weighted MRI, magnetization transverse ratio (MTR), and diffusion tensor imaging (DTI) as well as by localized proton MRS in vivo.

Methods

Two PTEN null mutants and two controls (at the age of about 90 days) underwent T1-weighted (3D FLASH, TR/TE=17/7.6 ms, α =25) and T2-weighted MRI (3D FSE, TR/TE = 3000/61 ms, 8 echoes, inter-echo spacing = 14.4 ms). MTR maps were based on a spin density-weighted FLASH sequence with and without off-resonance irradiation [1]. MRI was performed at 2.35 T (Bruker Biospin GmbH, Germany) with an isotropic resolution of 117 µm. In addition, one mouse per group underwent DTI (half Fourier DW STEAM, b=10/1000 s/mm^2, resolution 125×125×500 µm) and localized proton MRS in vivo (TR/TE/TM=8000/10/10 ms, 64 averages) at 9.4 T (Bruker Biospin GmbH, Germany). The volume-of-interest (VOI) was placed in a mid-sagittal location including parts of the corpus callosum (2.5×1.2×2.0 mm^3). After MRI/MRS animals were prepared for histology including light and electron microscopy.

Results and discussion

MRI –The PTEN null mutants showed a dramatic contrast enhancement on T2-weighed images (**Fig.1**). Apart from a volume increase of white matter structures such as corpus callosum, external and internal capsule, and fimbria of hippocampus (arrows), structures rarely detectable in normal controls such as optic tract and stria medularis became clearly visible (arrowheads). In comparison to T2, the T1 contrast enhancement was less pronounced, while the increased white matter volume was also observable. Furthermore, PTEN null mutants showed an enhanced white matter contrast on magnetization transfer and proton density weighted images (**Fig.2**). In the corpus callosum the MTR increased from about 50 in controls to about 58 in mutants. These results suggest that the white matter contrast is mainly determined by the degree of hypermyelination rather than by structural irregularities of the enlarged myelin.

DTI – Preliminary DTI measurements revealed no differences in axial and radial diffusivity between normal and mutant mice. It may be assumed that the effects due to increased axon diameter and enlarged myelin thickness counterbalance each other.

MRS – Localized proton MR spectra of a mutant and a control mouse in vivo exhibited major metabolite resonances (**Fig.3**). Although preliminary, MRS revealed a marked increase of choline-containing compounds (Cho). This metabolite abnormality is in full agreement with the histologically confirmed increased number of oligodendrocytes and the degree of hypermyelination. The slightly decreased *N*-acetylaspartate (NAA) in the mutant may reflect a reduced number of axons per VOI. Noteworthy, despite the high lactate/lipid resonance in the mutant, the mouse survived without conspicuous disturbances.

Conclusion

Hypermyelination presented with strong MRI contrast enhancements which were most pronounced in T2-weighted images. Preliminary proton MRS revealed elevated Cho levels which match the increased number of oligodendrocytes and the enhanced myelin content. In general, PTEN null mutants turn out as a useful animal model to study myelin-related contrast mechanisms. Further MRI/MRS investigations with additional PTEN null mutants are in preparation.

References

1. Natt et al., Magn Reson Imaging 21:1113-20, 2003

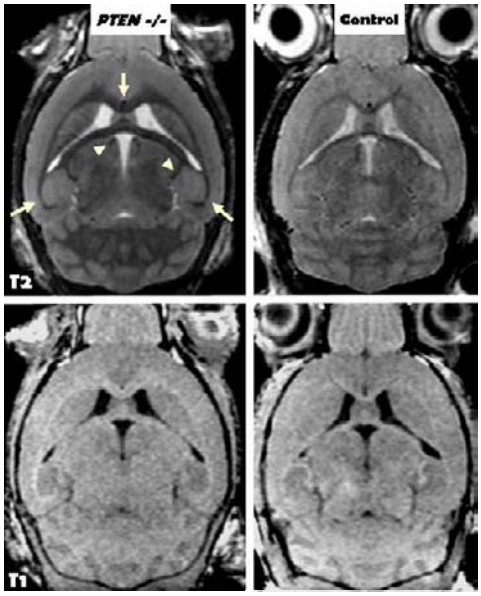

Fig. 1: T1- and T2-weighted images of a PTEN null mutant and a control mouse. Arrows indicate contrast enhancement of white matter structures.

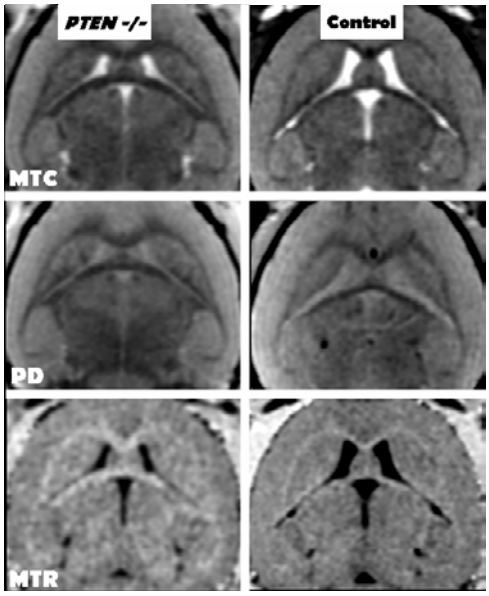

Fig. 2: Magnetization transfer contrast (MTC), proton density weighted images (PD), and maps of magnetization transfer ratio (MTR) of a PTEN null mutant and a control mouse.

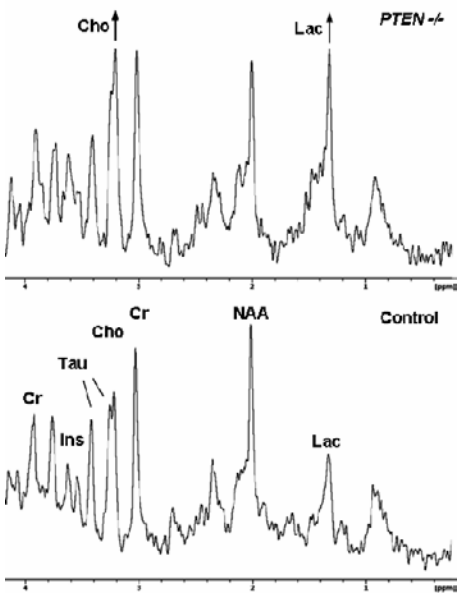

Fig. 3: Localized proton MR spectra of mouse brain in vivo including corpus callosum. Spectra are scaled to total creatine and exhibit resonances of lactate (Lac), N-acetylaspartate (NAA), total creatine (Cr), choline-containing compounds (Cho), taurine (Tau), and myo-inositol (Ins).