Comparison of MRI with Histopathology in T-cell Clone Mediated Mouse EAE

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Introduction
Although MRI techniques are widely used for a characterization of multiple sclerosis (MS), the histopathological correlates of specific MRI signal alterations in humans are still poorly defined. Experimental autoimmune encephalomyelitis (EAE) induced by the adoptive transfer of a PLP specific T-cell clone in SJL/J mice resulted in a reproducible formation of lesions in the upper brain stem. The purpose of this study was to correlate the MRI contrast alterations observed by T1- and T2-weighted 3D MRI as well as Gd-DTPA enhancement with histopathology.

Method
Ten SJL/J mice underwent MRI measurements during the acute phase of EAE. Three healthy age-matched mice served as controls. T1-weighted (3D FLASH, TR/TE = 17/7.58 ms, α = 25°) and T2-weighted images (3D FSE, TR/TE = 3000/98.25 ms, 16 echoes, inter-echo-spacing = 12.5 ms) were obtained at 2.35 T (Bruker Biospin) with an isotropic resolution of 117 µm. Four animals additionally received an i.v. injection of gadolinium-DTPA (0.5 mmol/kg body weight, Magnevist™, Schering AG). After MRI, the animals were sacrificed and prepared for histology. Quantitative region of interest analyses were based on normalized MRI signal intensity. Cell density, as well as density of myelin fibers and axons were determined in corresponding histological sections using conventional staining including hematoxylin/eosin, luxol fast blue, and Bielschowsky’s silver impregnation as well as immunohistochemistry.

Results and discussion
Twenty-five of a total of 27 lesions identified by histopathology could be also retrieved by MRI. T1- and T2-weighted MRI revealed two different types of EAE brain lesions. As shown in Fig. 1 type A lesions were characterized by a reduction of signal intensity on both T1- and T2-weighted images, whereas type B lesions in Fig. 2 appeared hyperintense on T2-weighted images with slightly reduced or isointense signals on T1-weighted images. Histopathologically, type A lesions showed a significantly higher inflammatory cell density and more myelin loss than type B. No iron deposition was detected. Statistical analyses revealed significant inverse correlation of both cell density and myelin loss with T1 and T2 signal intensities (p<0.05). In contrast to toxic myelin loss [1], demyelination did not cause hyperintense contrast alterations, suggesting that the inflammatory cell densities dominated the observed signal reduction on T2-weighted images. Figure 3 demonstrates Gd-DTPA enhancement to be most prominent in the perilesional area of type A lesions and correlated with immunoglobulin deposition, whereas no Gd-DTPA enhancement was observed in the center of densely infiltrated, granulocyte-dominated lesion.

Conclusions
In the established clonal EAE mouse model two dominant lesion patterns with distinct histopathological findings were identified. High-resolution 3D MRI not only proved useful for the assessment of lesion pathology, but also offers a promising tool to monitor lesion development and novel therapeutic strategies tackling inflammation and promoting remyelination. Further improvements are to be expected for combinations with cellular labeling techniques.

References

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