Pre-symptomatic Cerebellar Lesions and Ventricle Enlargement in an EAE Mouse Model revealed by Microscopic MRI

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Introduction

Microscopic MRI (µMRI) enables the acquisition of highly resolved images in a reasonable scan time, thereby providing the possibility to perform *in vivo* longitudinal studies in animal models. Neurodegenerative diseases such as Multiple Sclerosis (MS) require highly sensitive imaging methods that allow an early diagnosis and initiation of therapy that aims at slowing or even preventing further disease progression. Using an animal model of MS, Experimental Autoimmune Encephalomyelitis (EAE), and the qualities of µMRI, this study explored the temporal and spatial distribution of pre-symptomatic brain modifications associated with encephalomyelitis.

Methods

EAE was induced in 10 female SJL/J mice (8-10 weeks old) as previously described [1]. On a daily basis, mice were weighed and assessed for neurological symptoms using defined scoring methods [1]. A baseline anatomy scan was performed in all animals prior to disease induction. Pre-symptomatic daily scans (starting on day 5 post-immunization) were acquired to monitor possible brain alterations prior to disease manifestation. µMRI was performed using a Bruker Biospec 9.4T system and a cryogenically-cooled quadrature-resonator (Bruker, Ettlingen, Germany). A TurboRARE sequence was used for high resolution T_2-weighted (T2W) images (horizontal: 16 slices 35x35x400µm; coronal: 22 slices 35x35x500µm; TR/TE 3000/43ms). T_2 relaxation maps were acquired using a birdcage head volume coil (MSME, 16 slices 100x100x400µm, 8 echoes, TE 10-80ms).

Results

Heterogeneous brain alterations were identified prior to the onset of neurological symptoms. µMRI revealed signal intensity changes in the cerebellum as early as 3 days prior to symptoms. In seven out of 10 animals, T_2-weighted imaging revealed hyper- and hypo-intense lesions in the cerebellum (Fig. 1). Also, an increase in ventricle size, up to 2-3 times larger than in pre-induction period, was detected 2-3 days before disease onset (Fig. 2). The increase in ventricle volume was inversely correlated with animal weight loss (Fig. 3). To determine the water content within the ventricles, we performed T_2 relaxation maps. An increase in CSF T2 relaxation time (+15%) was noticed when comparing animals before and after disease onset (Fig. 4)

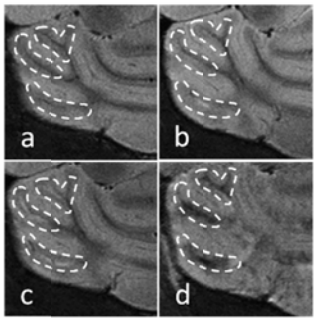

Figure 1 - T2 weighted images of the cerebellum of SJLJ/J mice pre EAE induction (a), four days (b) and three days (c) before symptom manifestation and first day of disease onset (d).

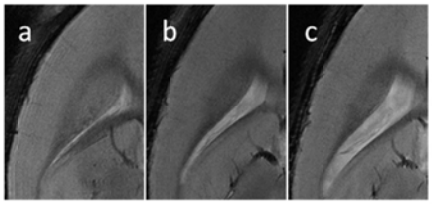

Figure 2 - Increase in ventricle size prior to disease manifestation. Shown is a representative left lateral ventricle before EAE induction (a), two days before clinical symptoms (b) and the first day of disease onset (c).

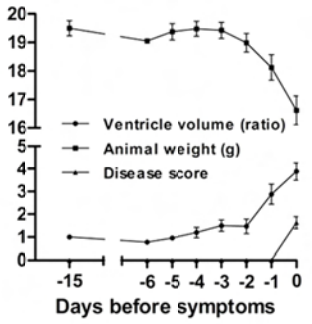

Figure 3 - Inverse correlation between ventricle volume and animal weight and disease score between pre disease induction and disease onset time-points.

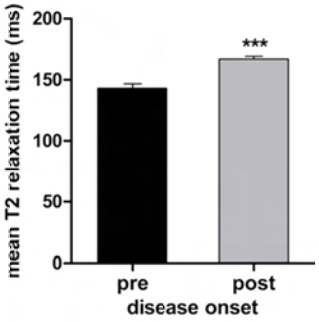

Figure 4 - Ventricle T2 relaxation time in animals before and after disease symptom manifestation (p=0.0003).

Discussion and Conclusions

In this study we detected and tracked early structural changes in brain tissue of EAE mice - most frequently in the cerebellum - prior to neurological symptoms. Also prior to disease onset, we were able to detect a significant enlargement of the ventricles. An increase in the T_2 relaxation time of the cerebrospinal fluid (CSF) after disease onset indicates an increase in water content in the ventricles and is suggestive of a dysregulation in CSF homeostasis. This is in line with microscopic studies showing significant structural changes in the CSF-producing choroid plexus during central nervous system inflammation [2]. In summary, high spatial resolution MRI was useful to identify structural modifications in the CNS, even prior to the appearance of symptoms. Furthermore, T_2 relaxation maps of the CSF indicate a possible alteration in CSF homeostasis. The combination of these MR methods provides the opportunity to better understand the early processes involved in the development of encephalomyelitis, and to provide insight into the clinical scenario.

References

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