Imaging optic nerve and spinal cord lesions in myelin antigen TCR transgenic mice with contrast-enhanced MRI

Jordan C Bell[1], Qingwei Liu[2], Qiang Zhao[3], Yong-Jun Wang[4], Fu-Dong Shi[1], and Gregory Harrison Turner[2]

[1]*Neurology, Barrow Neurological Institute, Phoenix, AZ, United States,* [2]*Neuroimaging Research, Barrow Neurological Institute, Phoenix, AZ, United States,* [3]*Neurology, Tianjin Neurological Institute, Tianjin, China,* [4]*Neurology, Capital Medical University, Beijing, China*

Introduction

Neuromyelitis Optica (NMO) is the co-occurrence of optic neuritis and myelitis [1]. NMO has been shown to have inflammatory foci that localize specifically to the optic nerve and spinal cord [1-4]. This is very significant because, unlike in multiple sclerosis (MS), there are little to no lesions in the brain. Often times NMO patients have been diagnosed as multiple sclerosis (MS) patients, current research however, has started to identify NMO as its own specific disease [1,4-5]. An early and correct diagnosis of NMO, often via contrast-enhanced MRI, is imperative due to the poorer prognosis of the disease as compared to MS, and the differences in treatments [4]. Kuchroo's group developed a TCR transgenic mouse ($2D2^{tg}$), with majority of CD4 cells recognizing a myelin antigen myelin oligodendrocyte glycoprotein (MOG) derived from a MS patient, that showed isolated optic neuritis [6]. This model shows promise in helping to understand populations of NMO patients that present with classic NMO symptoms those being inflammatory foci in the spinal cord and and optical nerve. To evaluate how this model replicates the clinical NMO phenotype, lesion progession in the optic nerve and spinal cord of $2D2^{tg}$ mice was examined longitudinally using both contrast-enhanced MRI and histology.

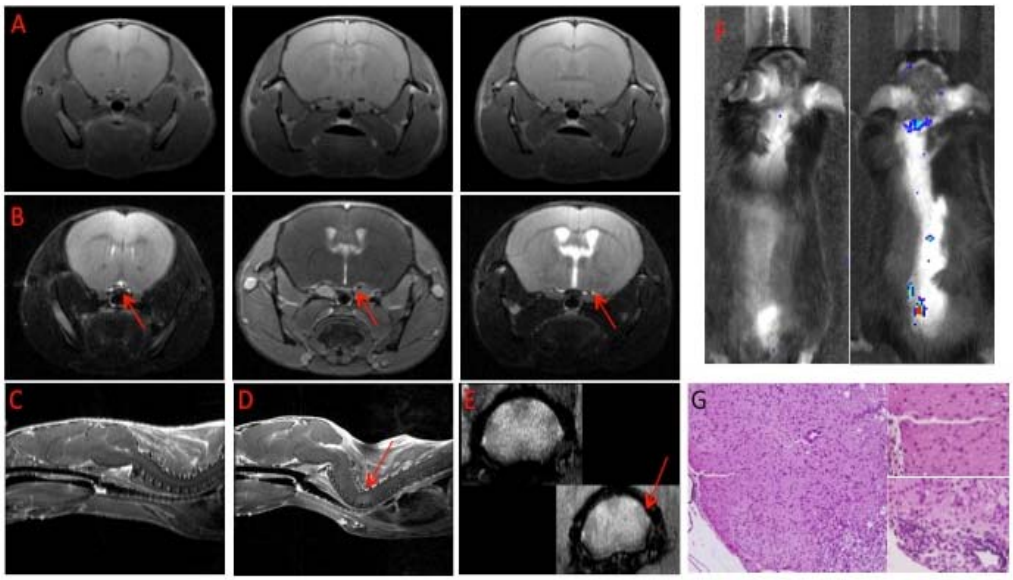
Methods

Mice were separated into 2 groups: Group 1 contained C57BL/6 mice, Group 2 contained $2D2^{tg}$ mice. C57BL/6 mice were purchased from Taconic (Germantown, NY) and $2D2^{tg}$ mice were purchased from The Jackson laboratory (Bar Harbor, ME). In order to get a timeline of progression, mice were scanned every two weeks, starting at four weeks of age until three months of age. At the end of the three month period, the mice were sacrificed for histological staining.

In vivo MRI was performed on a 7 Tesla small-animal scanner (Bruker BioSpin, Billerica, MA). The axial 2D multiple slice T1 weighted image of Brain was acquired, with TR 463ms, TE 10.58ms, 0.5mm slice thickness without slice gap, field of View (FOV) 2.56cmx2.56cm, matrix 256x256, eight averages, 20 slices, total scan time 16 minutes. In addition, the sagittal 2D multiple slice T1 weighted image of spine was acquired, with TR 320ms, TE 10.58ms, 0.5mm slice thickness without slice gap, field of View (FOV) 2.56cmx2.56cm, matrix 256x256, eight averages, 8 slices, total scan time 16 minutes. All the images were acquired after intravenous (i.v.) administration of contrast agent Gd-DTPA (Magnevist, Schering AG, Berlin, Germany), with dosage 0.2mmol/kg bodyweight. For imaging of ROS generation in brain, bioluminescence images in live mice were captured with a 1 min acquisition time using a cooled IVIS imaging system (Xenogen IVIS-200, Alameda, CA) after injection of 27 mg/kg DHE (Molecular Probes, Eugene, OR).

Results

To identify regions in the brain and spinal cord that may be affected in the 2D2tg mice, lesion development was assessed by the presence of Gd-DTPA post-systemic contrast agent application. On MR images, 80% of $2D2^{tg}$ mice showed BBB breakdown. The optical nerve, chiasm and tract were enhanced when comparing $2D2^{tg}$ mice (Fig. 1B) to WT C57BL/6 mice (Fig. 1A). This enhancement indicates BBB breakdown along the optical nerve tract. Because of the importance of spinal cord involvement in NMO we also acquired images of the spinal cords of WT (Fig. 1C) and $2D2^{tg}$ mice (Fig. 1D). 40% of $2D2^{tg}$ mice had enhanced spinal cord lesions after administration of Gd-DTPA (Fig. 1E) Visualization of brain inflammation by in vivo bioluminescence imaging of $2D2^{tg}$ and WT (Fig. 1F) show inflammatory signals that correlate with regions we expect to see in the $2D2^{tg}$ mouse model. There is signal present along regions of the spinal cord, a small signal coming from eye of mouse and in the brain stem. To investigate the enhancement seen in the $2D2^{tg}$ images we compared tissue sections from WT C57BL/6 mice and $2D2^{tg}$ mice. On histological examination, the presence of cellular infiltrates was confirmed for sites of contrast enhancement in the MRI. Fig. 1G is a representation of inflammatory infiltrates of a $2D2^{tg}$ mouse spinal cord.



Conclusion

The principal finding in this study is that the $2D2^{tg}$ mouse model is an ideal NMO animal model. These results indicate that clinical MR imaging, that is imperative in decifering NMO patients from MS patients, is replicated in the $2D2^{tg}$ animal model along with histological correlations. This animal model phenotype is important due to the different disease treatments and prognosis between NMO and MS.

References

1. Cree, B. A. C., et al. (2002). Semin Neurol 22(2): 105-122. **2**. Wingerchuk, D. M., et al. (1999). Neurology 53(5): 1107-1114. **3**. Lucchinetti, C. F., et al. (2002). Brain 125(Pt 7): 1450-1461. **4**. Wingerchuk, D. M. and B. G. Weinshenker (2003). Neurology 60(5): 848-853. **5**. Kinoshita, M., Y. Nakatsuji, et al. (2009). Biochem Biophys Res Commun 386(4): 623-627. **6**. Bettelli, E., M. Pagany, et al. (2003). J Exp Med 197(9): 1073-1081.