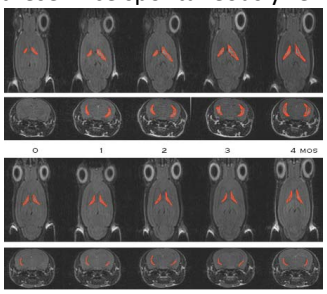
Determinants and Consequences of Brain Atrophy, Disability, Demyelination, Remyelination and Neuronal Loss in an MS Model

Istvan Pirko[1], Jeffrey Gamez[1], Pascal Alihnuii Atanga[1], Stephanie J LaFrance[2], Slobodan I Macura[3], and Aaron J Johnson[2]

[1]*Department of Neurology, Mayo Clinic, Rochester, MN, United States,* [2]*Department of Immunology, Mayo Clinic, Rochester, MN, United States,* [3]*NMR Core Facility, Mayo Clinic, Rochester, MN, United States*

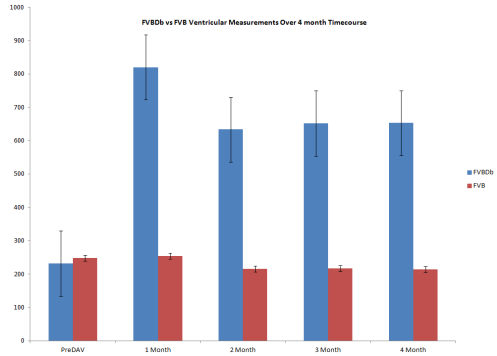
Target Audience: neuroradiologists, neuroscientist and neurologists.

Purpose: Brain atrophy is present from the earliest stages of MS, becoming especially prominent in secondary progressive disease. Unlike classic lesion-derived measures (lesion load, lesion count), atrophy shows moderate to strong correlation with disability[1]. While much has been learned about atrophy over the last decade; however, its pathomechanism remains unclear. Theiler's Murine Encephalitis Virus (TMEV) infection of mice is an accepted model of progressive MS[2]. Brain atrophy was demonstrated in TMEV infected SJL/J mice, with strong disability correlations[3]. It has been established that class I haplotype is a key determinant of disease development, but its effects on atrophy have never been studied. Our hypothesis was that class I haplotype has a major influence on atrophy development, which may shed light on the pathogenesis of atrophy, on CNS cell types "lost" during atrophy, and on the correlation between demyelination, remyelination, disability and atrophy. We chose FVB mice and transgenic FVB/D(b) mice, which are genetically identical, with the only difference being their class I haplotype. FVB mice represent a unique strain, as these mice spontaneously remyelinate, and typically only develop minimal and reversible disability[4].



T2 weighted serial MRI-s in a FVB/D(b) mouse (top half) and in a FVB mouse (lower half). Note atrophy development over 4 months in the FVB/D(b) mouse, resulting in ventricle enlargement

Methods: Fourteen FVB and fourteen FVB/D(b) mice were intracerebrally injected with 10^6 PFU of TMEV, and monitored for 4 months via monthly volumetric brain MRI using a 7 Tesla vertical bore Bruker Avance scanner at 125µm isometric resolution. Rotarod assay was used to assess neurologic function. Image analysis was performed using Analyze 11.0 with a semi-automated seed growing method[3]. Lateral ventricle volumes were used for determination of atrophy. We studied brain-infiltrating lymphocytes with FACS, and viral load via RT-PCT; statistical analysis was performed in SigmaPlot11.



Serial lateral ventricle volumetric measurements in FVB/D(b) (blue) and FVB (red) mice. Y axis: volume in units of 0.01 cubic mm.

Results: Significant and early development brain atrophy was demonstrated in FVB/D(b) mice, but not in the parental FVB strain. At 1 month, a 3.5-fold ventricle volume difference was demonstrated between the two strains (p=0.0018), and the increase within the FVB/D(b) group from pre-infection to one month was 3.6-fold (p=0.00047). The atrophy in FVB/D(b) mice reached its peak by 1 month, and persisted throughout the observation period. Neither strains have developed significant disability per rotarod measures. Viral load studies demonstrated persistent viral infection in the FVB strain, but not in FVB/D(b). Brain infiltrating CD8 T-cell analysis via FACS using tetramer technology demonstrated that the majority (>80%) of CD8 T-cells recognize the immunodominant VP2 peptide in FVB/D(b) mice, suggesting that the very efficient viral clearance in this strain is mediated by epitope specific CD8 T-cells.

Discussion: Strains trains that efficiently clear the virus (including FVB/D(b)) fully eliminate the infection by the end of the first month. Viral clearance is mediated by CD8 T-cells, and includes the removal of infected neurons. Given that the development of atrophy coincides with elimination of infected neurons, the same immune mechanism is likely responsible for both processes, and it is the loss of neurons (and their axons) that results in tissue loss. Unlike SJL/J or B10Q mice that develop early and significant brain atrophy that correlates with disability[3], FVB mice don't develop significant brain atrophy, and also don't display persistent disability (i.e., the lack of atrophy correlates with lack of disability). Therefore, *in mice with persistent viral infection (and consequential demyelination), there is a strong correlation between atrophy and disability.* Since FVB mice efficiently remyelinate, and myelin possesses axonal protective properties, the lack of atrophy and disability in these mice is likely related to axonal preservation. However, *in mice resistant to demyelination due to efficient viral clearance (FVB/D(b)-s) there is no correlation between atrophy and disability*: atrophy does develop due to the loss of virally infected neurons, but in lack of persistent demyelination of the spinal cord, there is no disability.

Conclusions: Atrophy and disability are independent from each other in strains that don't demyelinate, but strongly correlate when chronic demyelination is present. Brain atrophy development is overall unrelated to demyelination, and is the consequence of axonal/neuronal loss. Remyelination results in axonal preservation, preserved disability, and lack of brain atrophy in this model.

References:

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