

The Clinico-Radiological Paradox in TMEV Induced Murine Models of MS

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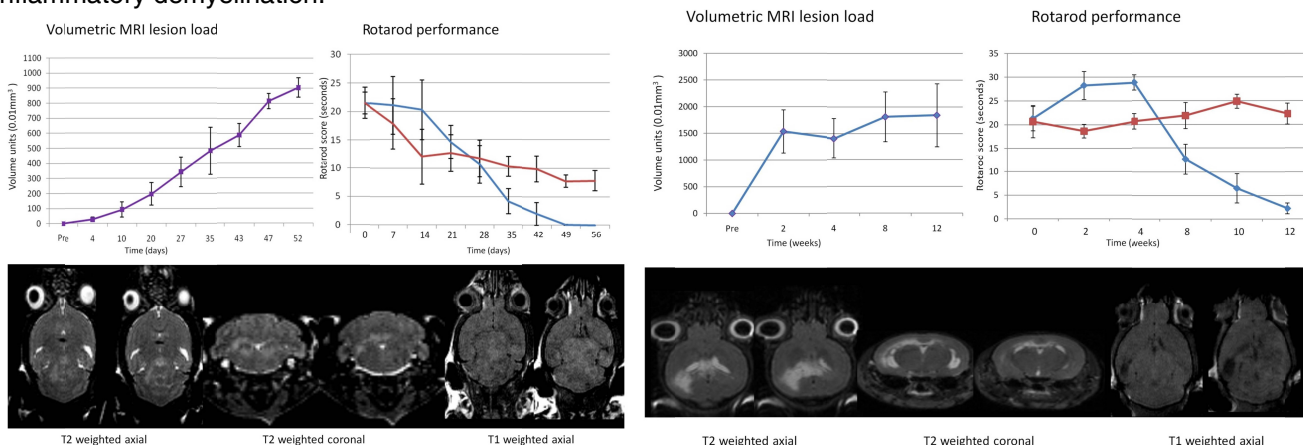
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INTRODUCTION: The clinic-radiological paradox in MS refers to the fact that T2 weighted lesion load shows only mild to moderate correlation with disability¹. A common characteristic of most MS murine models, including the majority of EAE and TMEV-based models is the relative paucity of brain compared to spinal cord lesions. Intracerebral Theiler's Murine Encephalitis Virus (TMEV) infection results in chronic-progressive demyelination in susceptible mouse strain. MS-related MRI findings in this model include brain atrophy², spinal cord atrophy, lesional T1 hypointensity³ and deep gray matter T2 hypointensity in TMEV induced MS models.⁴ Our objective was to establish animal models of MS-related brain lesion formation that allow for investigations of the clinico-radiological paradox. As a first step in accomplishing this, we characterized patterns of lesion formation and volumetric MRI-disability correlations in two TMEV-based MS models with substantial brain lesion load.

METHODS: Seven INF- γ receptor deficient TMEV infected mice of 129 (A) or C57BL6/J (B) background and 3 strain identical uninfected controls were followed until mortality (8 or 12 weeks, respectively) with serial volumetric 7 Tesla MRI (Bruker Avance II, Billerica, MA and Ettlingen, Germany) and rotarod studies. The rotarod assay enables objective characterization of murine disability without the need for a potentially subjective scoring system. MRI studies included volume acquisition T2 and T1 weighted studies with and without gadolinium. Volumetric analysis was conducted in Analyze 10.0 (Mayo Clinic BIR, Rochester, MN)⁵ via a combination of thresholding and seed growing in the 3D ROI tool. Datasets were analyzed by 2 investigators, their kappa statistics demonstrating excellent intra- and inter-rater reliability (>95%).

RESULTS: All animals developed T2 hyperintense / chronic T1 hypointense brain lesions. We observed different patterns of lesion formation: in model (A), the development of lesion load was close to linear with strong disability correlation ($r=-0.96$, $p=0.00002$) throughout the disease course. In model (B), biphasic lesion development was demonstrated: early (< 4 weeks) and unusually large "tumefactive" periventricular lesion formation was followed by lesion development similar to the pattern seen in model (A), and only beyond week 4 was a strong MRI-disability correlation observed in this model ($r=-0.92$, $p=0.02$).

DISCUSSION & CONCLUSIONS: These models demonstrate different patterns of lesion formation and correlation with disability. Model (A) provides an environment with very strong correlation between T2 and T1 lesion load and disability. Features of model (B) include lesions resembling that of tumefactive MS with poor lesion load-disability correlation at that stage, followed by strong correlation in later stages of the model, when more classic-looking lesions develop. These models are complimentary and allow for investigations of the clinico-radiological paradox including NAWM and NAGM studies, and pave the way to a better understanding of the pathomechanism of tumefactive lesions and of disability overall in inflammatory demyelination.



Lesion load, rotarod performance and examples for lesion formation in model A (left panel) and model B (right panel). Note the presence of posterior fossa lesions in (A) and large lesions resembling tumefactive presentation in (B). Red curves: rotarod performance in strain, age and gender matched control cohort.

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