Similar Global N-acetylaspartate in Benign and Non-Benign Multiple Sclerosis

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Introduction:

Approximately 20% of relapsing-remitting multiple sclerosis (RR MS) patients exhibit a benign course defined as full functionality (Expanded Disability Status Scale [EDSS] ≤ 3.0) after at least 15 years of disease duration [1]. Unfortunatley, this diagnosis is only retrospective. Considering the high costs and side effects of MS treatment and its variable course, an early determination of individualized treatment is needed but lacking. Existing metrics, such as lesion load, have not adequately met this challenge; yet regional declines in the neuronal marker *N*-acetylaspartate (NAA) have correlated promisingly with clinical disability [2]. Our goal, therefore, is to test whether clinically benign MS patients retain higher global concentrations of NAA (WBNAA) than their more profoundly disabled contemporaries.

Methods:

Lesion loads (both T_1 and T_2) and fractional brain parenchymal volume, a marker of atrophy (fBPV) were obtained from MR imaging and WBNAA from proton MR spectroscopy [3] in *(i)* 24 benign MS patients: 23.1±7.2 years disease duration, median EDSS score of 2.0, *(ii)* 16 non-benign patients: 21.0±4.0 years disease duration, median EDSS of 4.0 and *(iii)* 17 healthy, age-matched controls.

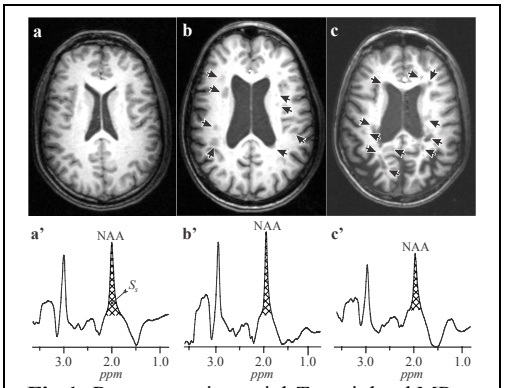

Fig.1: Representative axial T_1-weighted MP-RAGE brain slices and WBNAA spectra from age and gender matched individuals of the control (**a**), benign (**b**) and non-benign (**c**) groups. Note the relatively similar atrophy of both patients compared to the control and the higher lesion load of the non-benign group. Also note that though other metabolites are present, only NAA is biochemically exclusive to the brain.

Results:

Sample MP-RAGE images and spectra from each subject group (control: **a**, benign: **b**, non-benign: **c**) are shown in Fig.1. They illustrate the relative similarity between the two phenotypes in terms of atrophy (which is much higher than in controls), and T_1 hypointense lesion. Indeed, the controls' fBPV, 86.2±3.3%, was significantly higher than either patient group (benign: 76.4±6.7%, non-benign: 76.8±9.1%, $p<0.01$), as shown in Fig.2. Also displayed in Fig.2 is that the non-benign group had higher T_1 hypointense lesion load (4.5±5.8 vs. 2.1±2.2 cm^3 (p=0.031)), but indistinguishable T_2 hyperintense lesion volumes from the benign group (9.8±7.4 vs. 6.2±5.5 cm^3, ($p>0.05$)). The controls' 12.2±2.3 mM WBNAA was higher than the benigns' 10.5±2.4 mM, and non-benigns' 10.1±2.3 mM, ($p<0.04$ for both), yet, as shown in Fig.3, there was no difference between patient groups ($p>0.7$).

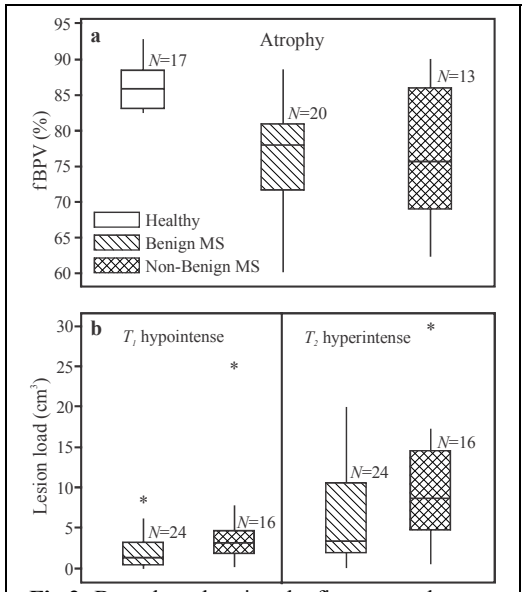

Fig.2: Box plots showing the first, second (median) and third quartiles (box), ±95% (whiskers) and outliers (*) of fBPV (**a**); and T_1-hypo- and T_2-hyper-intense lesion loads (**b**) of each group. Note that the benign and non-benign patients' fBPV distributions are *both* significantly lower than the controls but not statistically different from each other; and that the non-benign have a significantly higher T_1 hypointense lesion load than the benign but similar their T_2 hyperintense loads.

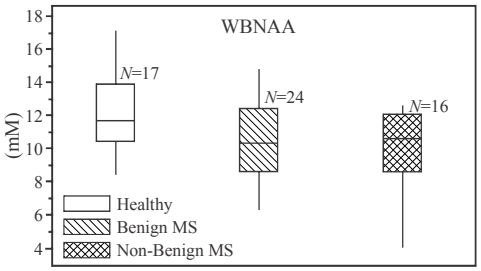

Fig. 3: Box plots of the WBNAA distributions of the three groups. Note that both patient cohorts' WBNAA is significantly lower than the controls', but similar to each other.

Discussion:

Aside from a higher T_1 hypointense lesion load, the non-benign group was indistinguishable from the benigns in every other metric studied. The disconnect between clinical definition and MR-derived measures is likely due to a combination of insufficient boundaries of the clinical phenotype, variations in brain plasticity and the distribution of lesions and neurodegeneration in brain areas of disparate eloquence.

References:

1. Ramsaransing and DeKeyser, *Acta Neirol Scand,* 113:359.
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3. Gonen, *et.al. Neurology*, 11:54.