Two-year Serial Whole-Brain N-Acetylaspartate in Relapsing Remitting Multiple Sclerosis Patients

Daniel Rigotti[1], Matilde Inglese[1], Ivan Kirov[1], Nissa Perry[1], Joseph Herbert[2], Robert I Grossman[1], and Oded Gonen[1]
[1]*Radiology, New York University School of Medicine, New York, NY, United States,* [2]*Neurology, New York University School of Medicine, New York, NY, United States*

Introduction:

Multiple sclerosis (MS) is the most prevalent demyelinating neurological disorder and the primary cause of non-traumatic disability in young and middle-aged adults. Its irreversible effects of MS are widely accepted to be chiefly caused by neuronal loss such that surrogate markers specific for the viability and concentration of these cells correlate better with clinical disability and might predict a more accurate outcome. The CNS-metabolite *N*-acetylaspartate (NAA) is considered a good marker for their concentration and health. Previous studies measuring its whole-brain) concentration (WBNAA) cross-sectionally have shown it to be a biomarker that can sensitively detect diffuse neuronal loss and dysfunction. Moreover, WBNAA has been shown to be stable in young healthy controls both at multiple sites (1) over a period of four years (2). Since MS is a chronic and heterogeneous, it is important to test whether WBNAA can more accurately and sensitively detect temporal changes in neural integrity than other MR (localized) or clinical metrics. To address this issue, we report results from a serial study of the WBNAA concentration in newly diagnosed MS patients.

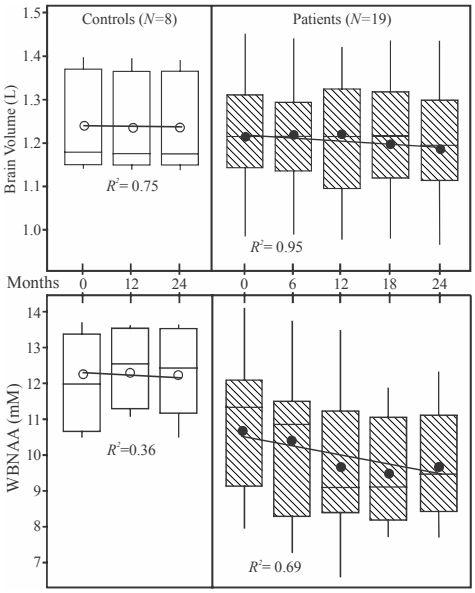

Fig. 1. Box plots showing the first, second (median) and third quartiles (*box*) and ±95% (*whiskers*) of WBNAA and V_B distributions at baseline and each subsequent scan. Note the degenerative nature of MS reflected in the decreasing WBNAA.

Methods:

Absolute whole-brain NAA amount was obtained with non-localizing proton MR spectroscopy (3) at 6-month intervals from 19 newly diagnosed (disease duration 47±28 months) relapsing-remitting MS subjects (5 men, 14 women) 33.5±5.0 years old and 8 (2 men, 6 women) age-matched controls. The absolute whole-brain NAA amount was converted into WBNAA concentration by dividing by their brain's parenchymal volume obtained from MRI image segmentation. All subjects gave written IRB approved informed consent.

Results:

Box plots of WBNAA and V_B for all patients and controls are shown in Fig.1. Patients' baseline WBNAA, 10.5±1.7mM and declined to 10.3±1.8, 9.9±1.8, 9.5±1.5 and 9.8±1.5 mM at 6, 12, 18 and 24 months, all significantly lower than the controls' 12.3±1.3, 12.3±1.0, and 12.2±1.1 mM at 0, 12 and 24 months (p=0.001 for all). Patients' WBNAA also declined significantly (5%/year, p‹0.002) versus the controls who did not (0.4%/year, p›0.7). Similarly, patients' semiannual V_B's also declined from 1217 cm^3 at baseline declined to 1213, 1210, 1205 and 1205 cm^3 and were significantly different from the controls' annual 1240, 1235 and 1235 cm^3 at baseline. Patients' overall V_B declined significantly (0.5%/year, p‹0.0001, R^2=0.95), but the controls' did not (0.2%/year, p=0.08, R^2=0.75). The difference between the two groups' mean V_B annual decline rate was also significant (p‹0.003). Mean lesion loads (Fig.2) increased significantly (p=0.001) from 3.0 to 3.7, 3.8, 3.6 and 3.9 cm^3. These volumes represent less than 0.5% of the entire parenchymal volume.

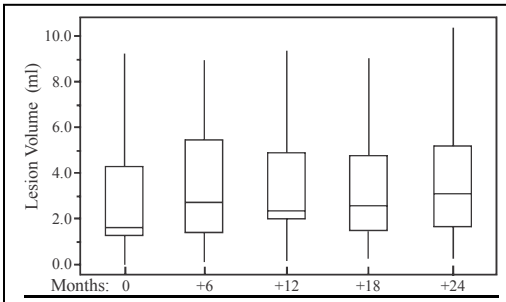

Fig 2. Box plots depicting lesion load distributions of MS patients. Note despite the significant increase, such small volumes do not fully cover the disparity between patient and control V_B's, indicating granular neurodegeneration undetected by MRI.

Discussion:

This is the first time that quantifiable changes that reflect ongoing pathogeneses have been measured in MS patients using the WBNAA methodology. Significant changes in WBNAA, and, therefore, overall neural health, were observed on the group and individual level in two year. While the specific cause and mechanism of NAA loss remains uncertain, it is clear that it is a result of ongoing disease activity, resulting in neuronal loss and/or dysfunction. Since this decline is quantifiable in a much shorter period of time compared to discernable clinical changes (measured by EDSS, etc.) which can take much longer to manifest clinically, the outcome of this study may indicate that WBNAA avails the neurologist a more sensitive feedback mechanism for the efficacy of treatment and the course of individual patients.

References: (1) Benedetti, *et.al. AJNR*, 28:72. (2) Rigotti, *et.al. AJNR,* 28:1650. (3) Gonen, *et.al. Neurology*, 11:54