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Multiple Sclerosis Severity Scale and Whole-Brain *N*-acetylaspartate Concentration for Patients' Assessment

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Abstract

BACKGROUND—Predicting multiple sclerosis (MS) course is highly desirable but lacking.

OBJECTIVE—To test whether the MS Severity Scale (MSSS) and global neuronal viability, assessed through the quantification of the whole-brain *N*-acetylaspartate concentration, (WBNA) concur or complement the assessment of individual patient's disease course.

METHODS—The MSSS and average WBNA loss rate (Δ WBNA, extrapolated based on one current measurement and assumption that at disease onset neural sparing was similar to healthy controls, obtained with proton magnetic resonance (MR) spectroscopy and MRI) from 61 MS patients (18 male and 43 female) with long (15 years or more) disease duration were retrospectively examined. Twenty seven patients exhibited a “benign” disease course, characterized by an Expanded Disability Status Scale score (EDSS) of less than 3.0; and 34 were “non-benign:” EDSS score higher than 3.0.

RESULTS—The two cohorts were indistinguishable in age and disease duration. Benign patients' EDSS and MSSS (2.1 ± 0.7 , 1.15 ± 0.60) were significantly lower than non-benign (4.6 ± 1.0 , 3.6 ± 1.2 ; both $p < 10^{-4}$). Their respective average Δ WBNA, 0.10 ± 0.16 and 0.11 ± 0.12 mM/year, however, were not significantly different ($p > 0.7$). While MSSS is both sensitive to (92.6%) and specific for (97.0%) benign MS, Δ WBNA is only sensitive (92.6%) but not specific (2.9%).

CONCLUSION—Since the WBNA loss rate is similar in both phenotypes, the only difference between them is their clinical classification, characterized by MSSS and EDSS. This may indicate that “benign” MS probably reflects fortuitous sparing of clinically eloquent brain regions and better utilization of brain plasticity.

Keywords

multiple sclerosis (MS); *N*-acetylaspartate (NAA); proton MR spectroscopy (¹H-MRS); whole brain NAA (WBNA); MS Severity Scale (MSSS)

INTRODUCTION

Multiple sclerosis (MS) is the most prevalent autoimmune disorder of the central nervous system (CNS), affecting more than two million worldwide (1). Its relapsing-remitting (RR)

form, characterized by cycles of relapses of varying severity and length separated by remissions of different duration (2), is the most common, ~85%, subtype (3). Since MS is chronic and given its late twenties average age of onset (4), some of its patients require years of treatment and assistance. Consequently, and due to its variable course and cost of treatment: (5, 6), it may be helpful to ascertain severity of course early in the disease (7, 8). Several demographic, clinical and magnetic resonance (MR) imaging methods for monitoring the disease have been used with variable success, but there is still no universal assessment gold standard (2, 9–13).

The Expanded Disability Status Scale (EDSS) is the most common scoring system for clinical progression of MS (14). Unfortunately, it is susceptible several limitations, primarily: *i*) interrater subjectivity; *ii*) nonlinearity; insensitivities to *iii*) cognitive impairment; and *iv*) disease duration; and *v*) sensitivity to focal pathologies that cause lasting deficits without compromising overall neural integrity, *e.g.*, in the cord (15). The MS Severity Scale (MSSS) that uses a probabilistic method to assign a disease severity score on the basis of EDSS score adjusted for disease duration comes to address the nonlinearity issue as well as yield, by multiplying a patient's MSSS score by ten, the prevalence of an EDSS subgroup within a population (16).

It has already been established that neural damage is the primary cause of irreversible disability in MS (17). Moreover, regional declines in their MR marker, the amino acid-derivative *N*-acetylaspartate (NAA) have correlated better with clinical disability than other imaging metrics (18–22). Since MS pathology is diffuse throughout the CNS (23) it is perhaps not surprising that the global whole-brain NAA concentration (WBNA), a marker for global neuronal integrity (24), has also shown substantial deficits in RR MS patients relative to matched controls (25–27) that correlated with disease duration (28).

The variable course of MS, its duration, cost of medications and their side effects make early characterization of disease status and course desirable (7, 8, 29). This motivated us to test if the WBNA and the MSSS that reflects clinical disability accumulation rate (16), yield similar predictive (or complementary) power *and* assessment. To test this hypothesis we compare the MSSS and its WBNA analog – annual loss rate (Δ WBNA), in a cohort of benign (defined as EDSS $\leq$ 3.0 after 15 or more years (3, 30, 31)) and non-benign MS patients of similar disease duration. Such cohorts were chosen since long disease durations retrospectively characterize their courses.

MATERIALS AND METHODS

I. Human Subjects

This is a retrospective study of 27 benign MS patients: 4 male, 23 female, 50.3 $\pm$ 10.1 years old (mean $\pm$ standard deviation) of 22.9 $\pm$ 6.8 year's disease duration from first symptom and EDSS score of 3.0 or less (median 2.0, range: 0–3.0). To this cohort we matched (in terms of gender, age and disease duration) a group of 34 “non-benign” MS patients: 14 male, 20 female, 53.4 $\pm$ 8.9 years old of 23.4 $\pm$ 7.1 year's disease duration and EDSS score of more than 3.0 (median 4.5, range: 3.5 – 7.0). All benign patients exhibited a RR course. Of the non-benign patients 16 exhibited a RR course, 11 were secondary progressive, 5 progressive-relapsing and 2 were primary-progressive. The rationale for this enrollment was that given the variable course of the disease, there exists a (retrospective) clinical gold standard for these two cohorts: Patients who are currently “benign” very likely have always been so. Conversely, all other patients became “non-benign” when their EDSS score exceeded 3.0 and they were deemed to have had such course in the preceding years as well. All patients had been relapse- and steroid-free for at least three months before their scan and clinical evaluation that included EDSS rating administered by the same neurologist. Seventeen

healthy controls: 8 male, 9 female, 34.0 ± 6.0 years old were also scanned. All participants gave an Institutional Review Board approved written consent.

II. MRI – Brain volume, V_B

All experiments were done in a 3 T Allegra head-only MRI scanner (Siemens AG, Erlangen, Germany) using a transmit-receive head-coil. After placing each subject into the scanner, its field homogeneity was adjusted over the head using our chemical shift imaging based automatic shim procedure (32) to yield consistent 27 ± 4 Hz water linewidth in under 5 minutes. It was followed by sagittal T_1 -weighted Magnetization Prepared Rapid Gradient Echo (MP-RAGE) [TE/TR/TI: 3.49/2150/1000 ms, 7° flip angle, 144 slices 1.1 mm thick, 256×224 matrix and 256×256 mm² field-of-view (FOV)] MRI for brain volumetry; and axial dual echo proton density (PD) / T_2 -weighted turbo spin echo (TR/TE1/TE2= 3980/14/108 ms, “turbo factor” of 7, 250×250 mm² FOV, 256×256 matrix, 40 slices, 4 mm thick each, aligned along the inferior border of the corpus callosum) MRI for lesion volumetry. Imaging ended with an axial post-contrast 2D T_1 -weighted sequence of 3 mm slice thickness (co-aligned with the preceding PD and T_2) MRI.

Subjects' brain parenchyma volume, V_B , was segmented from the MP-RAGE images with our FireVoxel package (33). It starts by placing a “seed” region in periventricular WM to obtain its average signal intensity, I_{WM} . Following selection of all pixels at or above 55% of I_{WM} (but below 135% to exclude fat), a brain mask is constructed for each slice in three consecutive steps: (i) morphological erosion, (ii) recursive region growth retaining pixels connected to the “seed” and (iii) morphological inflation to reverse the effect of erosion. Pixels of intensity under 55% of I_{WM} were defined as cerebrospinal fluid. Masks were truncated at the foramen magnum to include the brain stem and cerebellum but not the cord. Finally, V_B was the pixel volume $\times$ their number in the masks. The precision of this approach was recently established at 3.4% (33), on par with other commercially available brain volume segmentation methods (34–36). Lesion volumes were outlined on the PD and post-contrast T_1 -weighted MRI using a semi-automatic thresholding contour software AMIRA 3.1.1 (Mercury Computer Systems Inc).

III. Intracranial volume - V_{IC}

Intracranial volumes, V_{IC} , were obtained from the MP-RAGE images using MRicro, a free downloadable software package: <http://www.mricro.com> (37). It employs the brain extraction tool to skull-strip the intracranial surface using a deformable model (38). The process estimates the threshold between the brain and CSF, determines the head's center of gravity C , constructs a small tessellated surface F (initially a sphere) centered at C and incrementally adjusts the vertices of F to balance its smoothness and the desired signal intensity criteria. A volume-of-interest masking the extracted brain (see Fig. 1) was then used to calculate the intracranial volume, V_{IC} . The fractional brain parenchyma volume, fBPV (in %) was then defined as $V_B / V_{IC} \times 100$.

IV. WBNA quantification

The global brain NAA amount, Q_{NAA} , was obtained with a non-localizing, $TE/TI/TR=0/940/10^4$ ms ^1H -MRS sequence (39). Its long, $TR \gg T_1$ and short $TE \approx 0$ ensure insensitivity to possible T_1 and T_2 variations, which are typically unknown, especially in pathologies. Absolute quantification was done against a reference 3 L sphere of 1.5×10^{-2} mole NAA in water as (39):

$$Q_{NA} = 1.5 \times 10^{-2} \cdot \frac{\bar{S}_S}{\bar{S}_R} \cdot \frac{V_S^{180^\circ}}{V_R^{180^\circ}} \text{ moles,} \quad (1)$$

where $V_R^{180^\circ}$ and $V_S^{180^\circ}$ are the transmitter voltages for a non-selective 1 ms long 180° inversion pulses on the reference and subject, reflecting by reciprocity their relative coil sensitivity.

The subject and reference NAA peak areas, $\bar{S}_S$ and $\bar{S}_R$, were obtained by averaging the results from manual phasing and selection of the NAA peak limits of integration (as shown in Fig. 1) by four blinded operators. A result more than two average standard deviations (for the four readers' over all 61 patients, ~8%) from the mean for that patient, from any of the readers was rejected. If more than one result was rejected that entire set was excluded.

Note that although other metabolites, *e.g.*, macromolecules and other *N*-acetyl bearing species may also resonate about 2.01 ppm (40, 41), their contribution to the peak area is estimated at less than 10% (41). Finally, while several other metabolites are also visible in the whole-head ^1H MR spectrum, as shown in Fig. 1, since the sequence is non-localizing, only the NAA is implicitly localized by its biochemistry to only the brain whereas the others are present in all tissue types.

To normalize for differences in brain size among subjects, Q_{NAA} was divided by the brain parenchyma volume, V_B , (*vide supra*) to yield the whole-brain NAA concentration:

$$\text{WBNA} = Q_{NAA} / V_B \text{ mM,} \quad (2)$$

a specific, brain size-independent metric. Its *inter*- and *intra*-subject variability in younger healthy individuals has been shown to be better than $\pm 8\%$ (42).

Since the MSSS takes into account disease duration, it is related to the *rate* of EDSS change. Consequently, it is appropriate to compare it with an analogous NAA rate metric, *e.g.*, the average annual whole-brain NAA loss. Even though only one WBNA point was acquired per patient in this study, the average annual projected *rate* of global change (analogous to the MSSS the rate of EDSS change) in the *i*-th patient can still be estimated assuming that: (a) at first symptom their WBNA_i was similar to the average of healthy contemporaries, $\bar{\text{WBNA}} = 12.2 \text{ mM}$ reported previously (42), as well as in this study; and that therefore, (b) the time elapsed since, ΔT_i , is a good approximation of disease duration; and (c) WBNA decline is monotonic at a constant rate given by (43),

$$\Delta \text{WBNA}_i = \frac{\bar{\text{WBNA}} - \text{WBNA}_i}{\Delta T_i} \text{ mM/year.} \quad (3)$$

It is also appropriate to consider an analogous tissue fraction rate metric, estimated subject to the assumption that annual brain atrophy due to normal aging is linear and any excess over the reported rate of 0.33%/year for healthy individuals (44), is MS-related. This excess annual atrophy, ΔfBPV , was calculated based upon the controls' average, $\bar{\text{fBPV}}$ of 87.1% at 34 years as:

$$\Delta fBPV_i = \frac{\overline{fBPV} - (\text{age}_i - 34) \cdot 0.33 - fBPV_i}{\Delta T_i} \quad \%/year, \quad (4)$$

where age_i is the i -th patient age in years and $fBPV_i$ their fractional brain parenchymal volume.

V. Statistics

The patients' EDSS, MSSS, Δ WBNA, fBPV, Δ fBPV T_1 - and T_2 -lesion loads were summarized as means $\pm$ standard deviation. Comparisons between the groups were made using at Mann-Whitney test and confirmed with an unequal variance t -test. The set of results found to be significant by Mann-Whitney were exactly the same as those found significant by the t -test.

RESULTS

Age and disease duration did not differ between the benign and non-benign groups. None of the WBNA data sets had to be rejected due to poor quality. Representative MP-RAGE T_1 -weighted MRI of benign and non benign patients, are shown in Fig. 1 with their corresponding whole-head ^1H spectra. Demographic, clinical and raw MR data for each patient is included in Table 1. Dot plots of their EDSS, MSSS, Δ WBNA and Δ fBPV, are shown in Fig. 2. The average 2.1 ± 0.7 EDSS and 1.2 ± 0.6 MSSS in the benign group was highly significantly lower than the respective 4.6 ± 1.0 and 3.6 ± 1.2 of the non-benign MS patients (both $p < 0.001$). The benign patients' 10.2 ± 3.4 mM and the non-benigns' 9.8 ± 2.4 mM WBNA were both significantly lower than the controls' 12.2 ± 2.4 mM ($p < 0.03$ for both), but not different from each other ($p > 0.5$). Similarly, the 0.10 ± 0.16 mM/year Δ WBNA for the benign and 0.11 ± 0.12 mM/year in the non-benign, are not significantly different from each other ($p > 0.7$).

Each patient's Δ WBNA is plotted against their MSSS in Fig. 3. Based on Δ WBNA statistics from the 27 benign patients, we define a cutoff of 0.42 mM/year (the mean of 0.10 mM/year decline rate plus two 0.16 mM/year standard deviations). Any Δ WBNA below this cutoff, indicates "benign," whereas above it is "non-benign." Likewise an MSSS to the left of the 2.0 cutoff, corresponding to its accepted 20% prevalence (31, 45), indicates "benign" and to its right, "non-benign." Fig. 3 shows the MSSS to be both very sensitive to (25/27 patients = 92.6%) and specific for (33/34 patients = 97.0%) benign MS. Conversely, although Δ WBNA has high sensitivity (25/27 patients = 92.6%) to benign MS, it has very low (1 of 34 = 2.9%) specificity.

Each patient's Δ fBPV is plotted against their MSSS in Fig. 3. The fBPV, an index of brain atrophy, was significantly higher in controls, 87.1 ± 4.5 , than in both patient groups ($p < 0.001$), but *not*-significantly different between the benign and non-benign ($77.2 \pm 7.4\%$, $76.6 \pm 8.8\%$, $p > 0.7$). There was no significant difference between the benign patients' Δ fBPV of $0.22 \pm 0.35\%/year$ and the non-benigns' $0.20 \pm 0.44\%/year$ ($p > 0.8$). In analogy to the Δ WBNA, we define a Δ fBPV threshold of 0.92%/year (0.22%/year of the benign patients plus two 0.35%/year standard deviations), below which a patients is deemed "benign," as shown in Figs. 2 and 3. Here too, even though Δ fBPV exhibits 100% sensitivity to benign MS, it has very low (~3%) specificity.

Although the two patient groups differed significantly in their T_1 -hypointense lesion loads, 2.2 ± 2.2 cm³ in the benign versus 4.4 ± 5.5 cm³ in the non-benign ($p = 0.029$), their respective T_2 -hyperintense lesion loads: 6.4 ± 5.4 cm³ and 8.5 ± 7.9 cm³, were not different ($p > 0.1$).

DISCUSSION

Though important for improving the efficacy of care, there remains no prospective metric for early prognosis of MS course (8). Therefore, we chose our cohort to comprise of patients who have gone through a long (15+ years) of disease duration rendering their current clinical status a retrospective gold standard for their overall past course: either benign or non-benign. Since neural damage is the major cause of permanent disability in MS patients (18, 46–48) and because benign MS is characterized by a mild clinical course, it is likely therefore, that markers sensitive to each would provide similar clinical assessments. Unfortunately, the data *does not* support the hypothesis, as reflected by disparate sensitivity and specificity characteristics.

There may be several explanations for the difference between clinical disability and WBNA deficits. First, benign may have more effective compensatory mechanisms than non-benign patients. Second, they may have had lesions evolving in clinically silent brain regions. Third, the classification system to differentiate benign from non-benign has a sharp cutoff at 3.0 rendering a patient with an EDSS of 3.5 “non-benign.” The classification depends on 0.5 EDSS unit difference that comprises the distinction between “mild disability in three or four functional system” versus “more than minimal disability in several others” (14). Indeed, as seen in Fig. 2a, 13 out of 61 (21%) patients have an EDSS score between 3.0 and 3.5. Although the same neurologist evaluated all these patients, another clinician or the same one at a different time may return a different score, potentially switching a “borderline” patient's classification. The composition of the cohort presents another potential confounding variable in that the RR-MS benign patients are being compared to non-benign patients of several different phenotypes. There was, however, no difference between the non-benign sub-groups in terms of their EDSS, MSSS Δ WBNA or fBPV. (Although this may be attributable to the relatively small number, 16 or less, of patients in each of these non-benign subgroups).

That benign and non-benign patients' Δ WBNA were not significantly different may indicate that, on average, individuals suffer the same amount of diffuse neurodegeneration in either clinical classification. That their raw fBPVs and Δ fBPVs, shown in Fig.3, are similar is non-specific and can be from any of the processes of which brain atrophy is the end stage. These results also highlight the MS paradoxes using other MR metrics including higher lesion loads (49) and contradicting brain atrophy (50–52) in benign than in more disabled patients.

The lack of longitudinal studies of benign MS translates to vague long-term outcomes. To date, the longest, a 21 year study of 47 originally benign patients (by a similar definition), showed that only seven (15%) were still benign, ten (21%) had died with significant MS-related disability and eight (17%) died of non-MS related causes. The remaining 22 all required ambulatory assistance (53). The significant neuroaxonal injury in both benign and non-benign MS reflected by Δ WBNA in this study is consistent with that conclusion. Moreover, although Δ WBNA implicitly assumes that the loss is linear throughout the disease duration, it is likely a good approximation despite possible fluctuations or individual disease course heterogeneity. While measurable axonal damage has been shown to occur already at first symptom (26) (the starting point here), overall WBNA loss in benign have been similar to those extrapolated from non-benign patients of a much shorter disease durations (54). This linear extrapolation indicates that there is no dominant NAA loss either very early or very late in the disease course.

Although the MSSS may be more sensitive than EDSS to differences in disease progression, more studies are needed to establish its stability over time. In a small study the MSSS scores

were reported to be stable in nine out of ten patients over time (16). However, the EDSS in that study was assessed using a standardized protocol that may have reduced fluctuations in these scores leading to an apparently stable MSSS. Although a study aiming at replicating these findings in a large cohort is currently underway (55), its results are not yet disseminated.

The study is not without some limitations, however. First, the VOI of the WBNA method is essentially the whole head for reasons of spatial coverage (sensitive to global diffuse neurodegeneration) and speed (~2.5 minutes/scan). Consequently, global NAA changes smaller than 6–8%, are beneath its detection threshold and, therefore, regional NAA differences, *e.g.* in T_1 -hypointense lesions, are “averaged out,” or lost to partial volume averaging. Using alternative multi-slice 3D multi-voxel ^1H -MRS methods may overcome this problem at the expense of less than 70% brain coverage versus greater than 90% for WBNA (56, 57). Second, since this is a cross-sectional study of patients diagnosed retrospectively, NAA loss rates are only estimates contingent on the veracity of the underlying assumptions – primarily those of known date of onset and a monotonic decline thereafter. It is noteworthy, however, that the need for a decade and a half of follow-up to just establish a retrospective benign/non-benign course may render a longitudinal study both difficult and costly. Third, we do not have additional cognitive measures on any of the patients in either patient cohort, despite the fact that these metrics are gaining in acceptance as necessary to better define the various MS phenotypes (8). Finally, we do not account for (possible) effects of treatment, its type, dose, length or changes in its regimen in these patients, due in part to their long disease duration.

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Fig. 1.

Top: Representative axial T_1 -weighted MP-RAGE brain slices of a 53 year old benign (left); and a 53 year old non-benign MS patients (right), both female. Note the similar atrophy and higher T_1 -lesions load of the non-benign compared with the benign patient.

Bottom: The corresponding whole-head ^1H -MRS on common intensity and frequency scales. Note the NAA peak at 2 ppm, lipids suppression and that of the other metabolites peaks [most notably the glutamate (Glu), total creatine (Cr) and total choline (Cho)] only NAA is implicitly localized by its biochemistry to just the brain. Subjects' NAA peak area, S_5 (hatched), for Eq. [1] was obtained by integration.

Fig. 2.

Dot plots of the EDSS (a), MSSS (b) Δ WBNA (c) and Δ FBPV (d) of the 27 benign (○, based on the 15+ years of disease duration and EDSS $\leq$ 3.0 definition) and 34 non-benign (●) MS patients studied. An MSSS of 2.0, based on its accepted prevalence, a Δ WBNA of less than 0.42 mM/year Δ FBPV under 0.92%/year, based on the benign cohorts' average +2 standard deviations, are considered benign (arrows). Note that EDSS and MSSS in benign patients are significantly lower than non-benign, but that there is no clear difference in either Δ WBNA or Δ FBPV between the two cohorts.

Fig. 3.

Scatter plot of MESS versus Δ WBNA (top) and Δ fBPV (bottom) of the 27 benign (○) defined based on the 15+ years of disease duration and EDSS $\leq$ 3.0 criterion and 34 non-benign (●) MS patients. Dotted lines represent cutoffs of the confirmed benign patients' statistics: 2.0 for the MESS; 0.42 mM/year for the Δ WBNA and 0.92%/year for Δ fBPV. Note that the MESS is both very sensitive (25/27, 92.3%) to and specific (33/34, 97.0%) for benign MS whereas both Δ WBNA and Δ fBPV, while very sensitive to that phenotype are both of very low specificity.