Is "Benign Multiple Sclerosis" really benign?

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SUMMARY. Multiple Sclerosis (MS) is the most common demyelinating disease of the central nervous system. Its nonlethal, heterogeneous nature, early onset and lack of cure contribute to an uncertain prognosis and difficult clinical assessment. Approximately 20% of relapsing remitting (RR) MS patients will undergo a benign course, characterized by full functionality after 15 or more years of disease duration. While disease modifying treatments now exist; high cost limits their availability in some countries, prompting neurologists to not administer them to the patients with clinically mild course. Though MR metrics have proven effective in the diagnosis of MS and the monitoring of its evolution, they have produced conflicts and paradoxes that inhibited accurate clinical classification and prognosis. One hypothesis is that the benign course may indicate less overall neuronal damage than other subtypes. This can be specifically addressed with MR proton spectroscopy (^{1}H-MRS)-provided biochemical information of several brain metabolites, especially the N-acetylaspartate (NAA) whose global concentration (WBNAA) is considered a specific marker for overall neuronal integrity. This paper will describe the use of WBNAA to study benign MS and the conclusions that the subtype is likely a fortuitous combination of eloquent brain sparing and effective compensatory mechanisms. Since these may not prevent an eventual precipitous clinical decline, benign patients may, therefore, benefit from the same treatment options offered other RR MS patients with more active disease.
Key words: brain, N-acetylaspartate (NAA), multiple sclerosis (MS), MR spectroscopy (MRS), whole brain NAA (WBNAA).

RESUMEN. La esclerosis múltiple (EM) es la enfermedad desmielinizante más común del sistema nervioso central (SNC). El no ser letal, el ser de naturaleza heterogénea, de comienzo temprano y la inexistencia de tratamiento curativo contribuyen a un pronóstico incierto y a una difícil evaluación clínica. Aproximadamente el 20% de los pacientes con curso remitente-recurrente (EMRR) tiene un curso benigno, caracterizado por una situación funcional normal al cabo de 15 años o más tras el comienzo de la enfermedad. En la actualidad existen tratamientos modificadores de la enfermedad, pero su alto coste limita su disponibilidad en muchos países, lo que impide su utilización por los neurólogos en casos con un curso leve. Aunque las medidas de RM han demostrado su utilidad en el diagnóstico y la monitorización de la evolución de la EM, se han producido paradojas que impiden una clasificación clínica adecuada y el establecimiento del pronóstico con certeza. Hay una hipótesis que sostiene que el curso benigno se asocia con una menor pérdida neuronal que en las otras formas clínicas. Este aspecto puede investigarse de forma directa mediante la espectroscopía de protón por RM (^{1}H-ERM), que facilita información bioquímica de varios metabolitos cerebrales, especialmente del N-acetilaspartato (NAA,) cuya concentración global es considerada un marcador específico para la integridad neuronal total. Este trabajo describe el uso de la determinación del NAACT para estudiar la EM benigna y las conclusiones de que el subtipo de enfermedad es probable sean una combinación fortuita de la no afectación de áreas cerebrales elocuentes y la presencia de mecanismos compensatorios efectivos. Puesto que estas condiciones pueden no prevenir un curso clínico eventualmente catastrófico, los pacientes considerados benignos, por lo tanto, pueden beneficiarse de las mismas opciones terapéuticas ofrecidas a otros pacientes con EMRR con una enfermedad más activa.
Palabras clave: cerebro, N-acetilaspartato (NAA), esclerosis múltiple (EM), Espectroscopía por Resonancia Magnética (ERM), NAA cerebral total (NAACT).

Multiple sclerosis (MS), the most common demyelinating disease of the central nervous system (CNS), affects over 2 million worldwide and is the leading cause of non-traumatic neurological disability in young and middle-aged adults[1]. Roughly 85% of MS patients, two thirds of whom are young women [average age of onset in the US is 27 years[2]], enter the relapsing-remitting (RR) stage at diagnosis. This is characterized by acute episodes lasting days to weeks followed by partial or complete remission for months to years[3]. The cycles continue and most patients enter the secondary-progressive (SP) stage, where disability accumulates from incomplete remissions. Approximately 20% of patients, however, exhibit a clinically benign course, defined retrospectively, as full functionality, reflected by an Expanded Disability Status Scale [EDSS[4]] score of 3.0 or less after 15 or more years of disease duration[5, 6].

Since MS has an insignificant impact on life expectancy[7], it results in many decades of progressively deteriorating quality of life[8, 9]. Though incurable, six drugs are currently FDA-approved for MS in the US as disease-modifying agents that can alter its natural history: The intramuscular β-interferon-la (Avonex), subcutaneous β-interferon-1a (Rebif), subcutaneous β-interferon-1b (Betaseron), glatiramer acetate (Copaxone), and the immunosuppressant Natalizumab (Tysabri), a laboratory-produced monoclonal antibody given by IV infusion. For SP MS the most convincing data favors mitoxantrone (Novantrone)

as most likely to retard progression and delay disability[10-12]. Unfortunately, these are expensive, on average nearly $50,000/year per patient in the US[13]; and nearly €25,000 in Spain[14], exclusive of the cost of ancillary care and productivity loss. If cost limits treatment availability, it is expedient that the patients with the mildest course will be the least likely to be treated. Unfortunately, clinical metrics are unreliable and sometimes even deceptive markers for the full burden of disease.

Previous attempts to predict who will have a benign course had only moderate success[6, 15, 16]. Using imaging metrics for this purpose has so far yielded paradoxes such as higher lesion loads and magnetization transfer ratios in benign than in more disabled MS patients[17, 18], conflicting brain atrophy rates[19-21] and global atrophy similar to SP MS patients of similar disease duration[22, 23]. Various explanations as to why laboratory (in particular, quantitative MR) metrics have fallen short have been reviewed by Rovaris *et al*.[24]. While they provide interesting insights into the nature of the pathological underpinnings of the benign course, they could not identify a reliable diagnostic method that will establish this prognosis[6, 15, 16].

Most MR studies of benign MS have used conventional imaging that is insensitive to diffuse neurodegeneration. A marker sensitive to axonal damage followed by neuronal cell death, the probable cause of permanent neurological deficits in MS[25-28], would presumably be useful for determining subclinical damage to normal appearing brain and lesions. This can be assessed directly by proton MR spectroscopy (^{1}H-MRS) quantification of the neuron-exclusive metabolite N-acetylaspartate (NAA)[29, 30]. Its two key attributes are that its ^{1}H-MRS signal at 2.02 ppm is the most prominent *in vivo*; and with the exception of Canavan disease[31], its concentration is reported to decline in all CNS disorders[32, 33]. Regional declines of NAA in other forms of MS have correlated better with clinical disability than other imaging metrics[34-38].

Surprisingly, only four papers describing ^{1}H-MRS studies of the benign phenotype of MS are published[17, 23, 39, 40]. All are cross-sectional and employ single-voxel ^{1}H-MRS to probe selective small regions of the benign MS brain. Among them they have yielded inconclusive results: The two focusing on chronic lesions showed higher NAA levels than in SP MS patients[39, 40], whereas the other two report no differences between normal-appearing brain tissue or lesions among benign, SP or RR MS patients[17, 23].

The results reported in the previous spectroscopy studies may be attributed to the same problems of most of the numerous ^{1}H-MRS studies to date in other forms of MS. Specifically, that they have used either small (few ml) single-voxels, or larger two- or three-dimensional volumes-of-interest (VOI)[41-43]. These must be placed away from the skull to avoid the lipid contamination shown in Figure 1a, excluding most of the cortex[44]. These VOIs, therefore, must also be MRI-guided to pathologies. Since MS is diffuse throughout the brain, such small VOIs may lead to confounding extrapolation errors[45]. Localized MRS also suffers (i) VOI repositioning errors in serial studies; (ii) long, ~7 min, acquisition for ample signal-to-noise-ratio (SNR); and (iii) the T_1 and T_2 relaxation times in patients and controls are needed for absolute metabolic quantification[46].

❑ The WBNAA method

The above concerns are addressed by WBNAA, a non-echo, i.e., non T_2-weighted, non T_1-weighted, non localizing ^{1}H-MRS sequence that acquires the ^{1}H-MRS signal from the entire head, as shown in Figure 1b[47]. It is a short (~2.5 minutes/scan) and relatively simple sequence that eliminates the lipid contamination (compare Figure 1a and 1c) and avoids the usually unknown, (especially in pathologies) T_1 and T_2-weighting of the NAA that is inherent in other small-voxel studies. Note that although several peaks are seen in the whole-head spectrum (Figure 1c), only the NAA is implicitly localized to the brain. Since the others, e.g., the creatine+phosphocreatine (Cr), Choline+phosphocholine (Cho), glutamine (Glu) and myo-Inositol (mI), are found in all tissue types unlike the NAA, none of them can be ascribed to a specific region[48]. It is also noteworthy that while other metabolites, particularly macromolecules and other N-acetyl-bearing species also resonate at 2.02 ppm[49], their contribution to the peak area is less than 10%[50].

Absolute quantification is done using the phantom-replacement method against a reference 3 L sphere of 1.5×10^{-2} mole NAA in water in the same experimental setup after the patients' exams. Subject and reference NAA peak areas, S_S and S_R, are then obtained by manual phasing and selection of the NAA peak limits of integration, as shown in Figure 3, by four blinded operators. Any result more than two average standard deviations (for the four readers' over all the patients, ~8%) from the mean for that patient, is rejected. If more than one is rejected than that entire set is excluded as "poor quality". The results are then averaged into $\overline{S_S}$ and $\overline{S_R}$ and Q_{NAA} estimated as[51],

$$Q_{\mathrm{NAA}} = 1.5\times10^{-2}\cdot\frac{\overline{S_{\mathrm{S}}}}{\overline{S_{\mathrm{R}}}}\cdot\frac{V_{\mathrm{S}}^{180^\circ}}{V_{\mathrm{R}}^{180^\circ}}\ \text{moles}, \qquad [1]$$

where $V_{\mathrm{R}}^{180^\circ}$ and $V_{\mathrm{S}}^{180^\circ}$ are the transmitter voltages for non-selective 1 ms 180° inversion pulses on the ref-

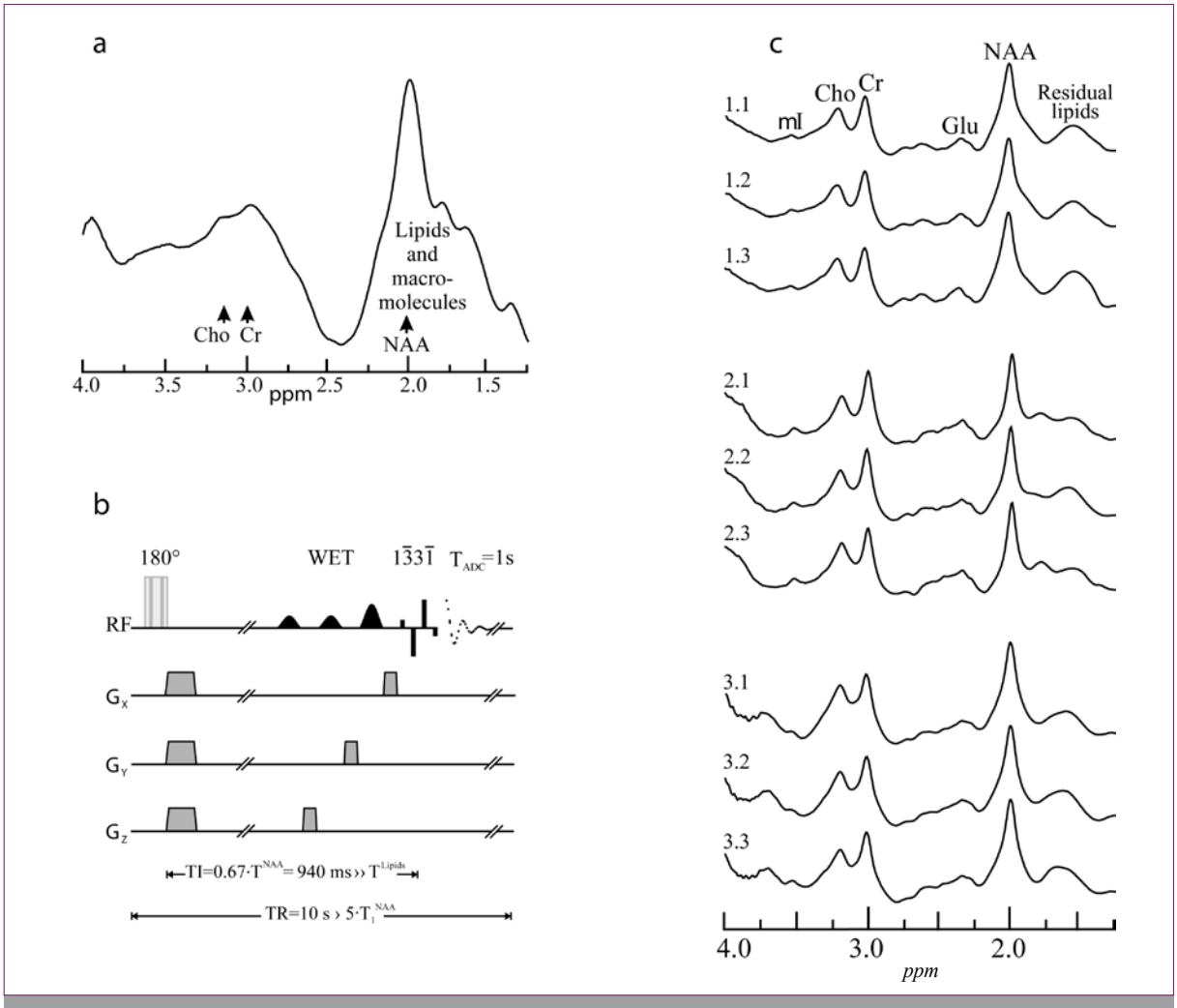

Figure 1 *Top left, a: Whole-head water-suppressed [WET followed by a 1$\bar{3}3\bar{1}$ (100 μs rectangular pulses, 2 ms delays at 3 T) for a 90° readout] single-acquisition ^{1}H proton spectrum. Note the extreme lipids contamination from the bone marrow and subcutaneous adipose tissue distorting and obscuring the NAA signal and confounding its quantification. Bottom left, b: The WBNAA sequence comprising a BIR4 adiabatic 180° (every second acquisition) followed by a TI=940 ms to null the NAA signal. WET and a 1$\bar{3}3\bar{1}$ (100 μs rectangular pulses, 2 ms delays at 3 T) for a 90° readout with acquisition commencing immediately. Each even transient is subtracted from every odd. Since the TR is long, 10 s, and TE=0, minimal T_1 or T_2 weighting are incurred by the NAA. Right, c: Real part of the whole head ^{1}H spectra from a male volunteer labeled i.j, where "i" (=1..3) is the number of the session in the magnet and "j" (=1..3) is the number of the back-to-back acquisition (subject at least 10 minutes outside the magnet) in that session. Note the excellent (CV=5.8) intra-session and CV=10.6 inter session reproducibility.*

erence and subject, reflecting by reciprocity the relative coil sensitivity.

To normalize for brain size, Q_{NAA} is divided by the brain parenchyma volume, V_B, obtained, for example, using the Structural Image Evaluation of Normalized Atrophy (SIENAx) package[52], Firevoxel[53], or an SPM variant[54, 55], to yield the whole-brain NAA concentration:

$$WBNAA = Q_{NAA}/V_B \text{ mM.} \quad [2]$$

Both the back-to-back and serial reproducibility of whole-head ^{1}H spectra of one individual, are shown in Figure 1c. The method's back-to-back coefficient of variation (CV) was shown to be 5.8% and the serial CV, 10.6%[48], precision suggest a reproducibility suitable for both cross-sectional and serial clinical studies[56].

Since MS pathology is diffuse throughout the CNS[57], it is not surprising that WBNAA has also shown substantial deficits in RR MS patients relative to matched controls[44, 58, 59], that correlate with disease duration[60, 61]. To that end, this paper will describe recent work that has been done using WBNAA to

study benign MS, specifically the recent studies using WBNAA as a marker for diffuse neurodegeneration and how the subtype is likely nothing more than the confluence of fortuitous sparing of eloquent brain regions and effective brain plasticity.

❑ WBNAA in benign MS

The contradictory results from small voxel ^{1}H-MRS studies of lesion and regional brain matter in benign MS patients led to the assumption that their mild clinical course was the result of minimal global neuronal loss. This assumption, along with the need for reliable criteria to identify patients who will remain mildly disabled over the long term[24, 62] and link between disability and neuronal damage[27, 63], prompt two hypotheses: (i) that benign patients suffer (characteristic) low global neuronal injury, reflected by WBNAA similar to controls' and (ii) that their WBNAA is significantly higher than in more disabled patients of similar disease duration.

❑ Benign MS *versus* age-matched controls

To test the first hypothesis (that the global NAA concentration of benign patients will be similar to healthy contemporaries, reflecting minimal neuronal damage) WBNAA was measured in 43 (30F, 13M) benign MS patients (EDSS score ≤3.0 after 15+ years of disease), with 21.0±4.4 years of disease duration and average EDSS score of 1.9 (range: 0-3). Eleven were on disease-modifying medication (6 on β-interferon and 5 on glatiramer acetate). All had been relapse- and steroid-free for at least three months prior to their clinical exam, which included EDSS rating by the same neurologist. Twenty-four (13 F, 11 M) age-matched healthy controls with no history of neurological disease, underwent the same MR procedure as the patients. The resulting average WBNAA in benign MS patients (8.3±1.8 mM) was ~35% less than controls (12.8±1.2 mM), as shown in Figure 2a. This finding refutes the hypothesis that the mild disability these patients exhibit also reflects in minimal neuronal damage.

It is noteworthy that although the study was cross-sectional (only one WBNAA point acquired per patient), the average annual projected rate of change in the i-th patient can be estimated assuming that: (a) at first symptom, their $WBNAA_i$ was similar to the $\overline{WBNAA}$=12.8 mM average of healthy contemporaries; (b) WBNAA change(s) are monotonic throughout the subsequent years and (c) that the time elapsed from first symptom, ΔT_i, years is a good (although admittedly under) estimate of disease duration. The projected rate of decline is then[44]:

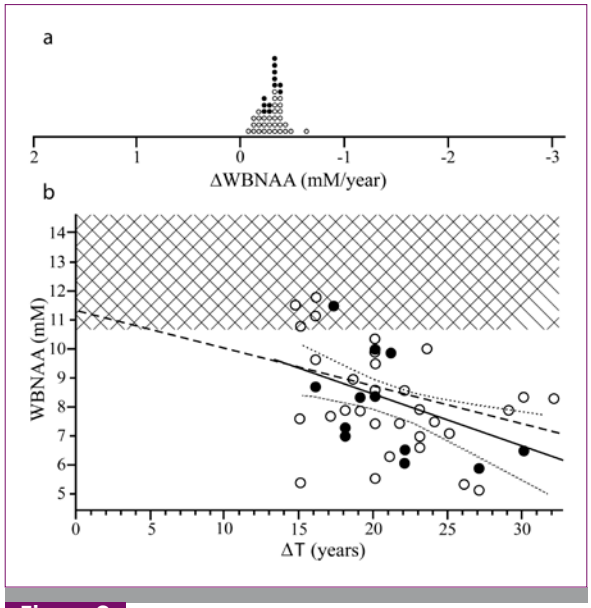

Figure 2 *Top, a: Dot plot of the 43 individual benign patients' average rate of WBNAA decline per year of disease duration. Closed circles (•) are patients on disease-modifying treatment at the time of the scan. Note the narrow distribution (0.16 mM/year full-width-at-half-height) and slow decline (ΔWBNAA≈0.22 mM/year) of these benign compared to the +1...-3 mM/year range exhibited by general RR MS patients[60]. Bottom, b: The 43 benign patients $WBNAA_i$ concentration as a function of their disease duration from first symptom -ΔT_i (filled circles (•) represent patients on treatment at the time of the study). Also shown are linear prediction previously reported for RR MS patients of shorter (3 - 12 years) disease durations (dashed line), the regression for the benign cohort with its 95% confidence intervals (solid and dotted lines) and the ±95% confidence interval for the WBNAA of the 24 healthy controls (cross hatch). Note that the regression line for the short duration RR patients falls within the 95% confidence range of the benign MS patients and their significant decline from healthy controls.*

$$\Delta WBNAA_i = \frac{WBNAA_i - \overline{WBNAA}}{\Delta T_i} \text{ mM/year.} \qquad [3]$$

The average $\Delta WBNAA_i$ from Eq. [3], was -0.22 ±0.09 mM/year (~1.7%), as shown in Figure 2a. Each patient's WBNAA value was also plotted as a function of his or her disease duration in Figure 2b, together with the linear regression and its 95% confidence intervals. Since the WBNAA of non-benign patients of similar disease duration was not available for this study, use of the rate, $\Delta WBNAA_i$ instead of the WBNAA itself normalizes for different disease duration to allow comparison to MS patients scanned earlier in their disease course. Indeed, the dependence reported before for RR MS patients of shorter disease durations[60], and controls are shown for comparison in

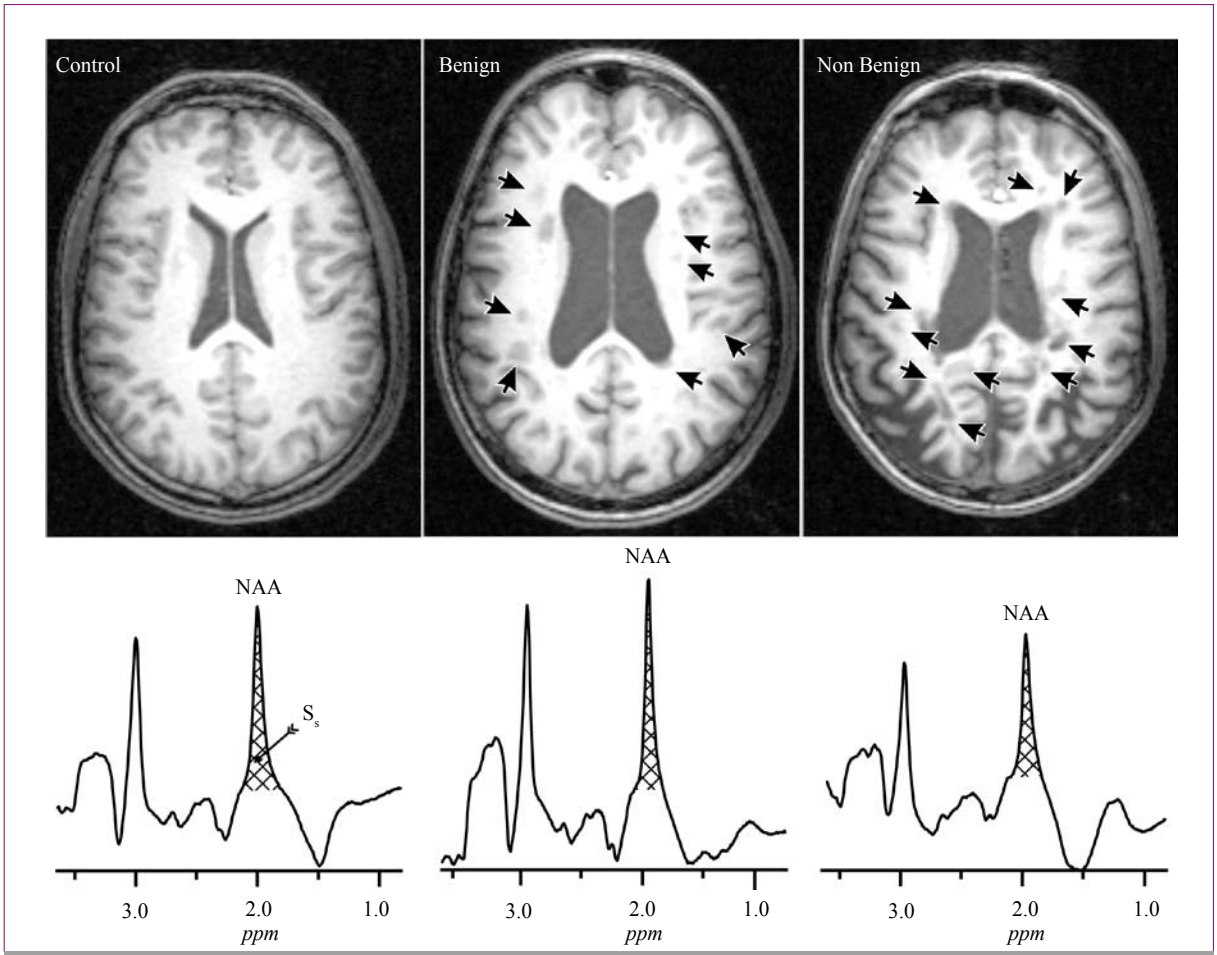

Figure 3 *Top: Representative axial T1-weighted MP-RAGE brain slices of a healthy 47 year old control; a 45 year old benign and a 48 year old non-benign MS patient, all male. Note the relatively similar atrophy of both patients compared with the control and the higher T_1-hypointense lesions load of the non-benign patient (marked by arrows). Bottom: These subjects' corresponding whole-head ^{1}H-MRS (not normalized for V_B) on common intensity and chemical shift scales. Note the NAA peak at 2 ppm, lipids suppression performance and that of all the other metabolite peaks seen in the head spectrum only the NAA is implicitly localized by its biochemistry to just the brain. Subject NAA peak area, S_S, was obtained by integration for use in Eq. [1].*

Figure 2b. The data demonstrates that the benign cohort is similar in terms of projected rate of WBNAA decline to "moderate" RR MS patients since the 95% confidence interval for the difference between these rates extends from -0.01 to 0.3 mM/year.

❑ Benign MS *versus* Age-matched MS patients

To test the second hypothesis (that benign MS patients would have healthier global neural structure than non benign patients of similar disease duration) WBNAA was obtained in another cohort of 24 (20F, 4M) benign MS patients with 23.1±7.2 years of disease duration and average EDSS score of 2.1 (range: 0-3). They were compared with an additional 30 (19F, 11M) non-benign MS patients of similar (22.9±5.8 years) disease duration and EDSS score of 4.7 (range: 3.5-7). Of these patients, 16 exhibited a relapsing-remitting course, 10 were secondary-progressive, 2 progressive-relapsing and 2 were primary-progressive. At the time of MRI all patients underwent a comprehensive clinical assessment including standardized neurological examination by trained and certified physicians (http://www.neurostatus.net) and a comprehensive disease history[4]. All patients were clinically stable. Finally, 17 healthy contemporaries (9F, 8M) also underwent the same MR protocol. Informed consent was obtained in writing from all participants, in accordance with the local ethics committee approval.

Representative axial MP-RAGE images from age- and gender-matched control, benign and non-benign MS patients, shown in Figure 3 illustrate the

relative atrophy of the MS patients' brains as well as the relative similarity between the two phenotypes, in extent of tissue loss and T_1-hypointense lesion loads. Indeed, the fBPV, an index of brain atrophy (see methods below), was highly significantly higher in controls, 86.2±3.3%, than in the benign, 76.4±6.7% (11%, $p<0.0001$), and non-benign: 76.2±8.4% patients (12%, $p<0.0001$), with no difference between the patient groups ($p>0.6$).

Overall, the controls' WBNAA concentration, 12.2±2.3 mM, was significantly higher than either the 10.5±2.4 mM of benign (14%, $p=0.031$) or the 9.7±2.2 mM of non-benign MS patients (20%, $p=0.002$), as shown in Figure 4a. There was, however, no statistical difference between the two patient groups ($p>0.2$), reflecting similar degree of neural damage in both phenotypes, thereby rejecting the second hypothesis.

Additionally, although there was a significant difference between the groups in their T_1-hypointense lesion loads, there was none in T_2-hyperintense lesion load or whole head NAA (WHNAA) concentration, defined as,

$$\text{WHNAA} = Q_{NAA}/V_{IC} \text{ mM}, \qquad [4]$$

which accounts for both atrophy and decline in the quality of the remaining brain tissue, as shown in Figure 4b. Here V_{IC} is the intracranial volume, which does not change throughout the adult life. V_{IC} were obtained from the MP-RAGE images using MRIcro, a free downloadable software package: http://www.mricro.com[64] that employs a brain extraction tool to skull-strip the intracranial surface using a deformable model[65]. 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 VOI masking the extracted brain was then used to calculate the intracranial volume, V_{IC}. The fractional brain parenchyma volume, fBPV was expressed in % as $V_B/V_{IC}\times 100$.

The benign and non-benign patients WBNAA concentrations are plotted against their brain atrophy (fBPV) in Figure 5. Two observations are apparent from that plot: First, there appears to be no predictive relationship between the WBNAA level and fBPV (R^2 values less than 0.1 for either phenotype). Second, the benign and non-benign patients' distributions are similar. These again combine to reject all MR metrics employed (T_2 lesion load, atrophy, WBNAA and WHNAA) as reliable metrics to differentiate benign from non benign patients of otherwise similar disease duration.

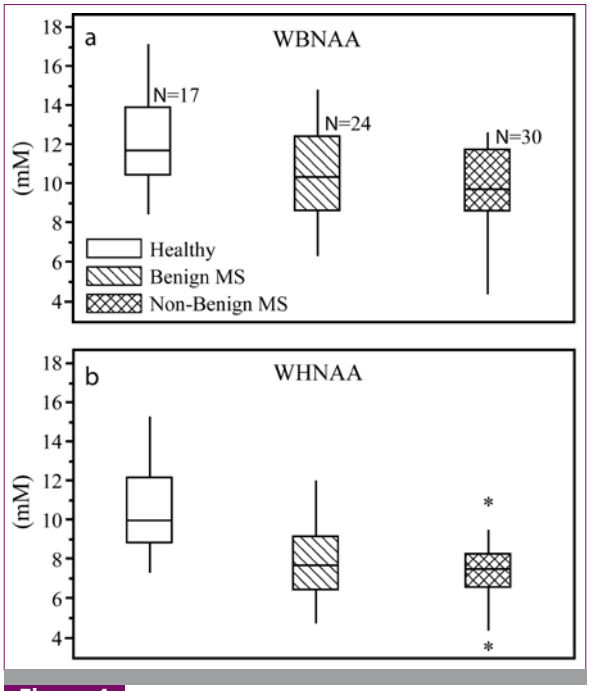

Figure 4 *Box plots showing the first, second (median) and third quartiles (box), ±95% (whiskers) and outliers (*) of the WBNAA (a); and WHNAA (b) distributions of the 17 controls (solid), 24 benign (hatched) and 30 non-benign MS patients (cross-hatched) groups. Note that both patients groups are significantly lower in WBNAA and WHNAA than the controls but not statistically different from each other.*

❑ Discussion

Despite the need for reliable prognostic measure(s) of a benign MS course, there remains no consensus. Although other conventional and quantitative MR techniques have not delivered an accurate assessment of disease progression, it seemed possible that a marker for global neuronal loss may be uniquely suited. Therefore, it was hypothesized that benign patients would enjoy neural sparing reflected by a WBNAA concentration similar to healthy matched controls and that their WBNAA would also be higher than their more clinically disabled contemporaries. Unfortunately, the significant average WBNAA loss in benign patients compared with controls, their similar disease course extrapolated from RR MS patients of shorter disease duration and their indistinguisability from non-benign patients of similar disease duration leads us to reject both hypotheses.

Taken together, these findings may have several implications: First, patients labeled as "benign" are likely RR MS patients who have inherently more effective compensatory mechanisms, such as increased brain plasticity, when dealing with the same amount

of tissue damage. Second, the comparable lesion load that develops in benign MS does so fortuitously in (so far) non-eloquent brain regions. Certainly their spinal cords have been spared, an insult to which would produce a clinically noticeable clinical (EDSS) change without a big lesion load increase. Third, the criterion used to differentiate "benign" from "non-benign" long disease duration patients has a sharp cutoff contingent solely on an EDSS≤3. Thus, for example, of two patients with the same 20 year disease duration, the one with an EDSS score of 3.0 is "benign," while another with 3.5 is not despite a small 0.5 EDSS unit difference that distinguishes only between "mild disability in three or four functional system" *versus* "mild disability in five functional systems"[4].

Unfortunately, these explanations combine to form an unfavorable prediction: that once the compensatory mechanisms are exhausted, or eloquent brain regions begin to be impacted, these patients may experience a precipitous and irreversible clinical decline. Indeed, although serial studies following benign MS patients are very difficult due to the great length of time involved and, consequently, rare, the longest, a 21-year follow-up of 47 such patients, substantiates this prediction[16]. They report that based on EDSS alone only seven (15%) were still considered 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. This suggests that benign may be an overly optimistic misnomer as only a small fraction of these patients (who initially comprise approximately 20% of the RR MS population) persist in qualifying under the strict criteria and how the rest experienced swift clinical decline.

These results also suggest that since there is effectively no neuropathological difference in benign MS patients from other phenotypes, a mild clinical course should probably not a be a determination factor for withholding or deferring treatment. Specifically, although these patients exhibit a stable clinical course they seem to experience typical neural degeneration rates that characterize more active forms of the disease. It is therefore, possible that early intervention may avert or delay the ultimate rapid decline.

Though the previous results were suggestive of WBNAA's temporal sensitivity to an ongoing pathogenesis, they were nevertheless derived from cross-sectional data. This made it impossible to determine when in the disease course the NAA loss actually occurred. As indicated in Figure 2, however, the distribution of WBNAA decline rates of benign patients is both (i) uniformly narrow, 0.16 mM/year full-width-at-half-height; and (ii) slow, 0.22 mM/year. In other words, the rate histogram is only the width of one year's decline; a finding distinct from previous reports in the general RR MS patient populations[44, 60]. This refutes reports that most neuro-axonal damage (NAA loss) accrues early in the disease course[59, 66, 67], for if it were true, longer disease duration (ΔT_i in Eq. [3]) would lead to lower WBNAA loss rates. Furthermore, the fact that the regression line extrapolated from shorter disease duration patients also describes the WBNAA benign MS subjects (Figure 2b), indicates a decline that continues even beyond the earlier years. Given the range of disease durations, the narrow distribution of decline rates suggests that the notion that the bulk of the decline is encountered early on in the disease course is probably not the case.

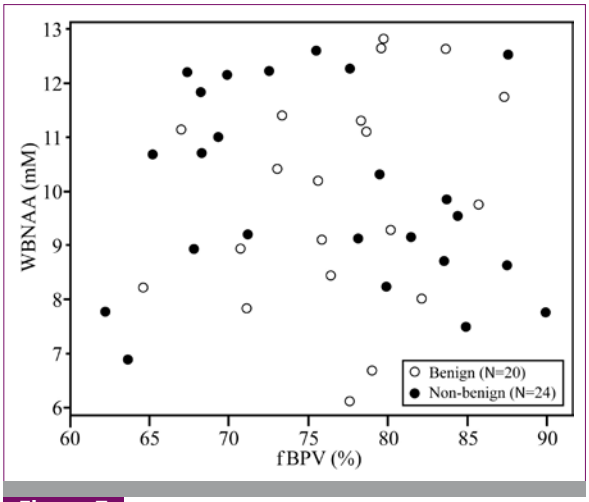

Figure 5 *Plot of the benign (○) and non-benign (●) MS patients WBNAA versus their fBPV. Note that there is no predictive relationship (R^2 <0.1 for either phenotype) between the WBNAA level and the fBPV; and that the two patients groups' distributions overlap.*

Even though it is cross sectional, there is an estimable WBNAA decline rate of 1.7%/year (see Figure 2a) assuming average normal concentration at first symptom with monotonic decline. Based on the 6-8% intrinsic precision of each WBNAA measurement, a longitudinal study would require patients to be scanned at least twenty times, each separated by at least six months, in order to establish statistical significance for such a slow rate. The ten to twenty years that would be required for such a serial study would render it susceptible to research team turnover, patient cohort attrition and several (possibly confounding) MR equipment upgrades, making it prohibitively difficult, and therefore, unlikely.

The WBNAA approach admittedly trades localization for sensitivity and acquisition speed, incurring two main limitations[58]: First, global changes

smaller than the 6-8% sensitivity threshold remain undetected. Second, potentially severe regional NAA variations, e.g., in T_1-hypointense lesions, get "averaged out" and are subject to the first limitation. Additionally, the rate decline estimates reported are based on several assumptions about the mechanisms decline, specifically, that it is monotonic and does not only occur at the preclinical stages or later in the disease where inflammation gives way to neuronal loss. In addition, as this is not a longitudinal study, it is impossible to ascertain exactly when in the disease course has the NAA loss occurred. Given the 15+ year disease duration of these patients and uncertainty early on of who will become "benign" 15 years later, however, would make such a serial study extremely difficult and costly. Finally, there was no account for possible effects of medication, the variable duration or the changes in type and dose that the patients may have experienced in their long disease courses.

❑ Conclusions

Retaining neural function, reflected by a WBNAA similar to healthy contemporaries, does not appear to be a characteristic of benign MS. Since overall neuronal integrity does not correlate with a mild clinical course, benign MS is the likely the result of a combination of fortuitous sparing of clinically eloquent brain regions that influence the EDSS score and adept compensatory mechanisms. The extent of NAA decline in benign MS suggests that clinical presentation is a false indicator for the extent of overall damage and that even these patients should be considered for the same treatment options as their more malignant counterparts.

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