The Correlation Between Whole-Brain N-acetylaspartate Quantification and Multiple Sclerosis Severity Score

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Introduction:

Relapsing-remitting multiple sclerosis (RR MS) is the most common subtype, representing 85% of all patients. Due to the cost and side effects of treatment, the ability to determine, early and accurately, the proper course of treatment on an individual basis is crucial. Yet, because of the inherent heterogeneity, there remains no reliable method of disease assessment. The Expanded Disability Status Scale (EDSS) is the most widely used system used to track clinical progression, but it is not without its limitations (*e.g.* subjectivity, weight towards locomotion, insensitivity to cognitive problems, etc.). In addition, many multivariate composite scores (*e.g.* BREMS), have proven too complicated, insensitive and of little use to the primary neurologist. We propose combining data from the Multiple Sclerosis Severity Scale (MSSS), an EDSS-based marker sensitive to small lesions in eloquent areas, with the global concentration *N*-acetylaspartate (WBNAA), a marker specific for diffuse neurodegeneration. We hypothesize that the two methods will have a high (~100%) concurrence. We test this hypothesis by comparing MSSS and WBNAA annual loss rate in a large cohort of RR MS patients.

Methods:

WBNAA amounts, collected as previously described [1], were analyzed retrospectively from 184 patients (95F, 89M) with RR MS. The annual loss rate is the difference between a patient's WBNAA and the average of healthy contemporaries (12.2 mM [2]) divided by disease duration from first symptom Their average age was 37.8±8.9 years (range: 20 - 71), average disease duration from first symptom of 8.8±8.2 years (range: 1 - 32), an average EDSS of 1.6±1.1 (range 0-6). All of the patients signed an IRB approved informed consent.

	BOTH	MSSS only	WBNAA only	NONE
TOTAL (n=184)	69 (37.50%)	22 (11.96%)	40 (21.84%)	49 (26.63%)
Benign Only (n=47)	43 (91.49%)	3 (6.38%)	1 (2.13%)	0 (0%)
Non-Benign (n=137)	26 (18.98%)	22 (16.06%)	40 (29.20%)	49 (35.77%)

Table 1: Cohort sub-populations partitioned according to MSSS and WBNAA annual loss rate.

Results:

The average MSSS for the entire cohort was 2.5±2.0. The average WBNAA loss rate for the entire cohort was 0.52±1.0 mM/year. Among the 184 subjects were 47 clinically confirmed benign MS patients, (defined as "full functionality", *i.e.,* EDSS ≤3.0, at disease duration ≥15 [3]). Their average MSSS was 0.98±0.6 and the average WBNAA loss rate for the benign patients was 0.19±0.1mM/year. Using this value (plus two standard deviations) as a standard for WBNAA loss rate and 2.0 for MSSS as the definition of benign MS based on accepted prevalence percentage, we then partitioned the patients as benign and not benign according to one, both or neither definition. The results are summarized in Table 1. There is a 64.13% (118/184) concordance of the two metrics within the entire cohort. Note that within the group of non-benign patients, 26/137 or 18.98% meet the benign definition of both metrics. This percentage is consistent with the accepted prevalence of benign MS (20%).

Discussion:

The inter-metric concurrence was not as high as hypothesized. However, among the non-benign MS patients, the concurrence (19%) was nearly identical to the generally accepted prevalence of benign MS. A disagreement between the methods can be explained by the following: An individual who has had substantial neuronal loss in non-eloquent areas at an early disease duration would likely be considered benign by MSSS but not by WBNAA. Detectable diffuse neurodegeneration, regardless of a measurable clinical deficit, may translate to a poor prognosis. Conversely, an individual who has suffered a small lesion to a particularly eloquent region, *i.e.* the optic nerve, but little overall neuronal loss, would be considered benign by WBNAA, but not by MSSS. Though the specific deficit(s) are likely irreversible, a high degree of neural integrity suggests temporal stability.

References:

(1) Rigotti, *et.al.AJNR* 2007;28:1843-1849.
(2) Benedetti, *et.al. AJNR* 2007;28:72-75.
(3) Lublin *et.al Neurolgy* 1996;46:907-911.