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MRI T2 hypointensity of the dentate nucleus is related to ambulatory impairment in multiple sclerosis

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Abstract

Objectives: MRI T2 hypointensity in multiple sclerosis (MS) gray matter, suggesting iron deposition, is associated with physical disability, disease course, lesion load, and brain atrophy. Ambulatory dysfunction limits quality of life; however correlation with conventional MRI remains poor.
Methods: Normalized intensity on T2-weighted images was obtained in the basal ganglia, thalamus, red nucleus, and dentate nucleus in 47 MS patients and 15 healthy controls. Brain T1-hypointense and FLAIR-hyperintense lesion volume, third ventricle width, brain parenchymal fraction and timed 25 foot walk (T25FW) were measured in the MS group.
Results: T2 hypointensity was present throughout gray matter in MS vs. controls (all $p<0.01$). Dentate T2 hypointensity was the only MRI variable significantly correlated with T25FW (Pearson $r=-0.355$, $p=0.007$) and was also the best MRI correlate of physical disability (EDSS) score in regression modeling ($r=-0.463$, $R^2=0.223$, $p=0.004$).
Conclusions: T2 hypointensity is present in subcortical gray matter nuclei in patients with MS vs. normal controls. Dentate nucleus T2 hypointensity is independently related to ambulatory impairment and disability, accounting for more variance than conventional lesion and atrophy measures. This study adds more weight to the notion that T2 hypointensity is a clinically relevant marker of tissue damage in MS.

Keywords: MRI; Multiple sclerosis; Iron; Gray matter; T2 shortening; Ambulation

1. Introduction

While conventional MRI measures have demonstrated efficacy in the diagnosis and longitudinal monitoring of patients with multiple sclerosis (MS), these conventional measures, primarily white matter lesion assays, correlate poorly with clinical measures of physical disability, disease activity and disease progression [1,2]. As neuroimaging technology matures, improvements to both scanning and analysis platforms have produced advanced MRI-based measures with improved sensitivity and specificity relative to conventional measures [2–7]. These advanced measures, which include diffusion weighted imaging [2,4,5], magnetic resonance spectroscopy [2,6], and magnetization transfer imaging [2,7] have revealed a more widespread disease process extending beyond overt white matter lesions and, in turn, improved clinical-imaging correlation [2]. MRI measurement of CNS atrophy has also emerged as a particularly powerful tool to assess the continuously destructive disease process in MS, showing better clinical predictive value than conventional lesion assessments [2,8].

T2 hypointensity in the gray matter is another innovative MRI measure of disease that is related to physical disability, disease course, and brain atrophy in cross-sectional MS

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studies [9–13] and is predictive of atrophy that will occur subsequently [14]. Abnormal T2 hypointensity, thought to represent iron deposition [12], can be found in the cerebral cortex, basal ganglia, and thalamus of MS patients [9–13]. While abnormal in MS patients in comparison to age-matched controls [9–11], it is not as yet clear whether T2 hypointensity is a disease epiphenomenon, contributes to pathogenesis or whether it has a role as a surrogate marker of disease progression.

Advances in structural imaging have been paralleled by development of more sensitive clinical measures of disease progression. In addition to the standard ordinal rating system of Kurtzke—the Expanded Disability Status Scale (EDSS) [15], newer measures of neurologic disability, such as the MS Functional Composite (MSFC), have been proposed as advantageous due their continuous and quantitative nature [16,17]. Both of these measures incorporate assessment of ambulatory dysfunction, perhaps the most debilitating aspect of MS regarding quality of life [18]. The MSFC directly measures ambulatory function with the timed 25 foot walk (T25FW). The T25FW is an evolved version of the ambulatory index (AI) [19], using a continuous rather than ordinal scale. T25FW has efficacy in distinguishing treatment effects in MS [20], but correlates poorly with conventional MRI findings [21,22]. T25FW has been shown to correlate weakly with MRI calculated brain atrophy [23]. A stronger clinical-MRI correlation has been seen with the parent MSFC [22].

The purpose of this study was to: (1) determine if the dentate nucleus is a site of T2 hypointensity in patients with MS vs. age-matched normal controls. This seemed plausible due to the avidity of the dentate nucleus for iron in normal aging [24] and our suspicion that this process is accelerated in MS, (2) evaluate the relationship between T2 hypointensity in the dentate and clinical impairment—we focused on the dentate given its anatomic relationship with ambulation [25], (3) parcel out the independent contribution of T2 hypointensity towards explaining the variance in clinical impairment by adjusting for the effect of conventional MRI lesion and atrophy measurements.

2. Methods

2.1. Patients

Forty-seven patients with MS meeting McDonald criteria [26] were consecutively imaged on the same MRI scanner using the same pulse sequences. Patient characteristics are summarized in Table 1. Patients were clinically evaluated at a University-affiliated MS clinic for this cross-sectional study. The cohort was limited to patients with age between 20 and 60 years old (mean ± S.D. age 42.39 ± 8.49 years, 32 females or 68%). Patients were excluded if they had other major medical illnesses, corticosteroid use or acute relapse within 4 weeks prior to MRI. Of the 47 patients examined, 41 had a relapsing–remitting disease course, while 6 were classified as secondary progressive patients [27]. None had a primary progressive course in this consecutive patient sample. Disease duration ranged from 1 to 43 years (mean 11.19 ± 7.98 years). Neurologic disability was assessed by a single experienced neurologist blind to the MRI findings using EDSS [15] and T25FW (see below) within 1 week of MRI. EDSS ranged from 1.0 to 7.0 (mean 3.37 ± 1.69). Different aspects of these patients are being reported as part of separate publications [28–30]. This study was approved by our institutional review board.

2.2. Controls

Fifteen normal (healthy) controls (NL) underwent MRI using the same protocol as the patients. Mean age was 37.6 ± 17.89 years, range 25 to 53. The 47 patients were slightly older than NL, with the age difference approaching significance ($p = 0.061$), Thus, age adjustment was used in the between group statistical analyses (see below). Controls were sex-matched (10 females, 67%, $p = 0.735$) to the MS group.

2.3. Timed walk

Ambulatory dysfunction was measured based on published guidelines for the T25FW [31]. Briefly, a patient was asked to walk a clearly demarcated 25-foot course as quickly possible, safely. Patients were then asked to walk back the same distance. Assistive devices (cane or walker but not wheelchair) were permitted. The rater recorded the time in seconds with a maximum time set at 3 min. The results were from a single 25 foot walk. The patients did not undergo the complete MSFC, however.

2.4. MRI acquisition

MRI was performed on each subject using the same scanning protocol at a tertiary care university facility on a Philips Gyroscan ACS-NT 1.5-T scanner (Best, The Netherlands). Axial images were obtained through the brain including conventional spin-echo T1-weighted (TR/TE:

Table 1
MS patient characteristics

Disease status	Sex	EDSS score	Disease duration (years)	FLAIR lesion load (mm^3)	T1 lesion load (mm^3)	BPF	3VW (mm)
41 RR, 6 SP	15 M, 32 F	3.39 (1.0–7.0)	11.11 (1–43)	13372 ± 17561	3903 ± 4971	0.83 ± 0.05	4.5 ± 2.5

RR = relapsing–remitting, SP = secondary progressive, BPF = brain parenchymal fraction, 3VW = third ventricular width. Values are mean ± standard deviation.