MSJ Experimental Translational Clinical

Original Article

Detection of cortical lesions in multiple sclerosis: A new imaging approach

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Multiple Sclerosis Journal – Experimental, Translational and Clinical

1: 1–4

DOI: 10.1177/2055217315606465

Abstract

Cortical lesions occur early in multiple sclerosis (MS) and are thought to have clinical implications. Conventional MRI is insensitive to cortical pathology. Investigational imaging modalities show improved but incomplete cortical lesion detection and are time and resource intensive. Gradient echo plural contrast imaging (GEPCI) is sensitive to MS white matter pathology and can be performed on standard MRI scanners. Here we used GEPCI to examine autopsied MS frontal brain tissues. Two cortical MS lesions were visually distinguished from surrounding tissue by GEPCI and immunohistochemical staining. Furthermore, these lesions were quantitatively differentiated from healthy tissue using GEPCI-derived metrics.

***Keywords*:** Multiple sclerosis, imaging, diagnostic, magnetic resonance imaging, brain imaging, gray matter, cerebral cortex

Date received: 29 May 2015; accepted: 19 August 2015

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Introduction

Focal inflammatory lesions of the gray matter have been observed on histopathological studies in multiple sclerosis (MS). More recently cortical abnormalities have been detected on investigational imaging and such findings have been associated with clinical measures. Cortical lesions can arise early in the disease course and are present in all MS clinical phenotypes.[1,2] The presence of cortical imaging abnormalities is associated with increasing disability.[2] The rate of accumulation of such findings is associated with clinical deterioration. Further, the volume of cortical pathology may have prognostic significance predicting disability progression.[3]

Unfortunately, detection of cortical lesions in vivo has proven to be challenging. Conventional magnetic resonance imaging (MRI) has limited ability to identify cortical pathology. Herein we use gradient echo plural contrast imaging (GEPCI), an MRI technique providing quantitative information on T2* relaxation, which reflects the severity of tissue destruction in lesions.[4–6] GEPCI-derived metrics of white matter lesions have shown strong associations with clinical markers.[5,6] The potential to detect cortical pathology using GEPCI has not been explored. Here we describe a preliminary analysis demonstrating the quantitative detection of two cortical lesions using this technique in autopsied brain tissues from a patient with secondary progressive MS (SPMS).

Methods

Case report

A 95-year-old Caucasian woman with an extended history of SPMS died and underwent rapid autopsy. At the age of 36 she developed numbness of the right hand. Over ensuing years, her numbness became bilateral and she began dragging her right foot. The diagnosis of MS was made five years after initial symptoms. She was treated with adrenocorticotropic hormone, which was followed by clinical improvement. She presented again after 30 years with gait instability. A neurologic examination showed intention tremor in the right upper extremity, an ataxic gait, and bilateral upgoing toes to plantar stimulation. Conventional MRI demonstrated numerous periventricular lesions, a high cervical lesion at the level of the foramen magnum, and another focal cervical lesion at C5. She improved partially

following a three-day course of intravenous methylprednisolone. Over the subsequent decade her symptoms progressively worsened without relapses. She developed difficulties with ambulation, fatigue, vertigo, incontinence, and impairment of fine motor tasks such as writing. She died at the age of 95 from respiratory failure related to a comorbid congestive heart failure. She never received immunomodulatory therapies other than corticosteroids.

Tissue examination

Within seven hours of her death, her brain was fixed in formalin. Seven days afterwards a grossly unremarkable $4.25 \times 2.5 \times 2.5$ cm section of frontal brain tissue was evaluated without replacement of formalin on a Varian DirectDrive^{TM} 4.7T MR scanner using a 3 cm diameter birdcage transmit/receive radio frequency (RF) coil. Data were collected using three-dimensional (3D) multi-gradient echo sequence with four echoes, matrix $256 \times 192 \times 32$; in-plane resolution 0.207 mm by 0.208 mm; repetition time (TR) = 260 ms, first echo time (TE) = 4.6 ms, echo spacing = 12.8 ms, flip angle (FA) = 60 degrees, susceptibility weighted (SW) = 40.3 kHz, acquisition time = 26.6 minutes. T2* maps were calculated as previously described.[4] T2* maps were calculated and lesions were identified by visual inspection. Tissue was then embedded in paraffin, sectioned with guidance from imaging, and stained for myelin proteolipid protein (PLP). Regions of interest (ROIs) were defined on the basis of corresponding features of pathology and imaging. Formal coregistration was deferred to avoid the introduction of bias from directed alignment of imaging abnormalities to lesioned tissue. T2* values were sampled from ROIs and compared.

Results

Two cortical lesions, one leukocortical and one intracortical, were detected on T2* images (Figure 1 (b) and (d)) and were confirmed by immunohistochemical staining for PLP (Figure 1 (a) and (c)). T2* values within the lesioned cortical areas were compared to normal-appearing white matter (NAWM) and normal-appearing gray matter (NAGM). Both cortical lesion types displayed significantly greater T2* than nearby NAWM and NAGM (Table 1). No subpial lesions were detected in the regions examined by GEPCI or by immunohistochemistry.

Discussion

Herein, we demonstrate the ability of GEPCI to distinguish cortical MS lesions from normal-appearing tissues qualitatively and quantitatively. In brain tissue scanned post-mortem, GEPCI allowed visual detection of the cortical lesions. T2* values sampled from cortical MS lesions were significantly higher than those of nearby normal-appearing cortical tissue. Both NAGM and the cortical lesions displayed higher T2* values than NAWM.

The GEPCI technique generates high-resolution and quantitative T2* maps, fluid-attenuated inversion recovery (FLAIR)-like images, T1-weighted images

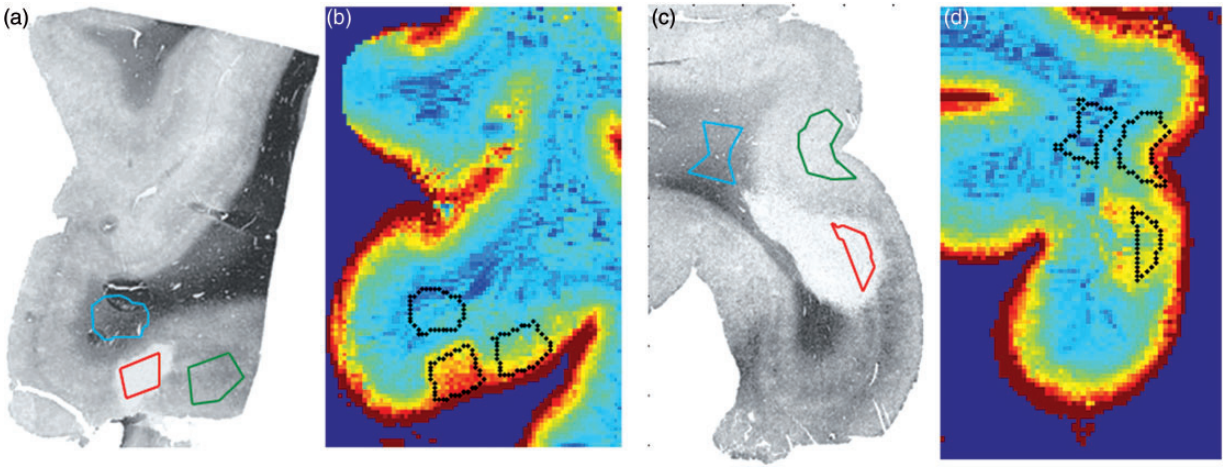

Figure 1. Histopathological specimens of tissue with intracortical (a) and leukocortical (c) lesions are demonstrated along with corresponding T2* images ((b) and (d)) calculated using the GEPCI technique. The histological specimens were immunolabeled for PLP. ROIs of similar size were drawn in lesioned cortical tissue (red border) and nearby NAWM (blue border) and NAGM (green border). GEPCI: gradient echo plural contrast imaging; PLP: proteolipid protein; ROIs: regions of interest; NAWM: normal-appearing white matter; NAGM: normal-appearing gray matter.

Table 1. T2* values from ROIs from lesions, NAGM and NAWM.

	INTRACORTICAL		LEUKOCORTICAL	
ROI	*n*	$\bar{x} \pm \sigma$	*n*	$x \pm \sigma$
NAGM	135	55.39 ± 11.82	133	50.77 ± 12.62
NAWM	133	32.37 ± 5.43	108	32.78 ± 6.10
Lesion	131	74.00 ± 10.77	74	58.91 ± 6.20

The number of sampled voxels is displayed along with mean T2* values and standard deviations. Bonferroni-corrected *t*-tests comparing each lesion to nearby similarly sized areas of NAGM and NAWM were determined for each specimen. Intracortical: Lesion vs NAGM: $t = -13.41$, $p < 0.0001$; Lesion vs NAWM: $t = -39.73$, $p < 0.0001$. Leukocortical: Lesion vs NAGM: $t = -5.21$, $p < 0.0001$; Lesion vs NAWM: $t = -28.20$, $p < 0.0001$. ROIs: regions of interest; NAGM: normal-appearing gray matter; NAWM: normal-appearing white matter.

and phase (frequency) maps from a single scan.[4,7] Compared with existing methods, GEPCI may have advantages for detecting cortical pathology. Two techniques, double inversion recovery (DIR), and phase-sensitive inversion recovery (PSIR), have been developed to improve sensitivity for cortical lesions over standard MRI, but these methods fail to detect most cortical pathology (~37% of pathologically identified lesions are identified using DIR). Both DIR and PSIR also suffer from low signal-to-noise ratio, have low inter-observer agreement, and require extended scanning times.[8] Ultra-high-field (>3T) techniques are more sensitive to cortical pathology than lower magnet strength techniques[9] but cannot be implemented on a wide scale because of the scarcity and costs of ultra-high-field scanners. Although magnetic transfer ratio imaging (MTR) can be performed in clinically feasible times, reported sensitivities for cortical pathology vary significantly among studies, with reports at field strengths used in clinical settings (1.5T) showing poor sensitivity.[10] Previous studies have demonstrated that GEPCI sequences collected at 1.5T or 3.0T in clinically feasible time frames (<15 minutes) have been sensitive to white matter lesions.[5,6] The present result suggests that the technique may also be sensitive to cortical pathology, but further investigation in living patients using a protocol appropriate for clinical use is needed.

This preliminary study was limited to examination of single leukocortical and intracortical lesions in an ex vivo section from a single patient. Forthcoming studies will investigate the technique's sensitivity for cortical pathology in vivo and its clinical feasibility. Its sensitivity for all cortical lesion types including subpial lesions, and its sensitivity relative to other advanced imaging methods including DIR, PSIR, and MTR, will be characterized.

Funding

This work was supported by the Washington University Institute of Clinical and Translational Sciences from the National Center for Advancing Translational Sciences (NCATS), a component of the National Institutes of Health (NIH) (grant number UL1 TR000448, CO6 RR020092, and K23NS052430-01A1), the National MS Society USA (RG4463A18), and the Barnes-Jewish Hospital Foundation. Its contents are solely the work of the authors and do not necessarily represent the official view of NCATS, NIH, NMSS or the Barnes-Jewish Hospital Foundation.

Conflicts of interest

Dr Alvarez has received consulting honoraria from Biogen Idec, Genzyme, and Teva Neurosciences. He was supported by a Sylvia Lawry Physician Clinical Fellowship from the National MS Society and Gateway NMSS chapter (FP 1772-A-1) and the Predoctoral Training Program at Washington University (TR000448). Dr Piccio was supported by the Harry Weaver Neuroscience Award from the National MS Society (JF 2144A2/1) and the Fondazione Italiana Sclerosi Multipla (FISM) (2009/R/33).

Dr Cross has received consulting honoraria from Biogen, Genzyme, Mallinckrodt, Novartis, Roche, and Teva Neurosciences. She serves on advisory boards for the National MS Society and Roche. She was supported in part by the Manny and Rosalyn Rosenthal-Dr. John L. Trotter Chair in Neuroimmunology.

Drs Patel, Luo, Schmidt, and Yablonskiy have nothing to declare.

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