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Preliminary investigation of cognitive function in aged multiple sclerosis patients: Challenges in detecting comorbid Alzheimer's disease

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ABSTRACT

Background: Cognitive impairment can be seen in patients of all ages with multiple sclerosis (MS). However, there is limited research on neurocognitive disorder in older adults with MS and how to detect Alzheimer's disease (AD) or its prodromal stage, amnestic mild cognitive impairment (aMCI). Thus, the MS clinician is challenged to discriminate between signs of MS-related cognitive decline versus a secondary neurodegenerative process.

Objective: Compare cognition in older MS patients to patients with AD and aMCI.

Methods: We evaluated cognitively impaired and unimpaired MS patients, AD patients, aMCI patients, and healthy controls (HCs), all elderly (n = 20 per group). AD and aMCI diagnoses were derived by consensus conference independent of the MS research project. Neuropsychological measures assessed domains commonly affected in AD, including verbal memory and expressive language.

Results: Cognitively impaired and unimpaired MS groups did not differ on any measures sensitive to AD. Unimpaired MS patients were comparable to HCs. Impaired MS patients showed decreased semantic fluency, similar to aMCI patients. Lastly, while both AD and aMCI groups had deficient memory retention, there was no evidence of a retention deficit in either MS group.

Conclusion: Our findings suggest that the cognitive profiles of MS and AD are distinct. In contrast to AD, MS is not associated with impairment of memory consolidation. However, there may be overlap between cognitive deficits related to MS and aMCI. Thus, evidence of poor memory retention, in an older MS patient may merit comprehensive dementia evaluation. The study is preliminary and includes no AD biomarkers (e.g., amyloid imaging) to confirm or rule out AD pathology.

1. Introduction

Multiple sclerosis (MS) is an autoimmune disease characterized by inflammation, demyelination, and in some cases neurodegeneration of the central nervous system. Life expectancy is reduced by an estimated seven years (Marrie et al., 2015a). However, with recent advancements in disease modifying therapies, prognosis is improving - the aged MS population is growing and with it, new challenges for the MS clinician. Among these is the management of comorbid conditions associated with aging. Mood disorder, hypertension, and hyperlipidemia are among the most common comorbidities (Marrie et al., 2015b), all related to disability progression, lower quality of life, and lower treatment adherence (Marrie and Hanwell, 2013).

Another comorbidity as yet unstudied in MS is Alzheimer's disease (AD), and its prodromal state amnestic mild cognitive impairment (aMCI) which is found in 10–20% of older adults above age 65 (Petersen, 2011). MS is also associated with cognitive dysfunction, although the presentation differs from aMCI and AD in that cognitive processing speed is more often affected than episodic memory and there is minimal involvement of expressive language (Benedict et al., 2002a). However, MS patient samples in the majority of existing studies on cognitive dysfunction are limited to younger or middle-aged adults (Amato et al., 2013; Jonsson et al., 2006). Also, with elucidation of the MS neurocognitive profile, neuropsychological studies typically limit

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Table 1
Participant characteristics (n = 20 per group).

	Healthy controls		MS unimpaired		MS impaired		Amnestic MCI		Alzheimer's disease	
	M	SD	M	SD	M	SD	M	SD	M	SD
Age	61.7	8.9	60.3	5.0	61.9	8.5	62.9	9.2	63.9	7.3
Sex (M/F)	4/16		3/17		5/15		4/16		4/16	
Education	16.2	2.4	14.9	1.9	15.7	2.4	14.5	2.2	14.6	2.4
Disease Course (RR/SP/RP/PP)			16/2/1/1		17/3/0/0					
Disease Duration			16.9	8.6	20.1	14.3				
EDSS (median, range)			3.0, 1.5–6.0[a]		4.0, 2.0–8.0					

EDSS: Expanded Disability Status Scale.
[a] EDSS score is missing for 1 MS Unimpaired patient.

the appraisal of cognition to a few consensus standard tests (Modica et al., 2015; Sandroff et al., 2014). Focusing on processing speed and learning/memory, higher cortical functions such as language and memory consolidation are often ignored, measures of which are more sensitive to cognitive dysfunction in AD (Clark et al., 2009; Hori et al., 2010). Thus, the cognitive profile of the aged MS patient is not well characterized, making it difficult to recognize the presence of comorbid early AD.

We recently investigated motor and cognitive deficits in MS and healthy controls from ages 18–72 (Roy et al., 2016). In line with other recent studies, cognitive assessment was limited to tests emphasizing processing speed and learning, in this case operationalized with the Brief International Cognitive Assessment in Multiple Sclerosis (BICAMS) (Benedict et al., 2012). Replicating an earlier report (Bodling et al., 2009), the degree of MS impairment was not magnified by age. These results suggest that aging does not differentially impact the rate of cognitive decline among MS patients without comorbidities. Therefore, we reason, if an MS patient were to exhibit marked cognitive impairment with increasing age, one might suspect a comorbid neurodegenerative process such as early AD. Unfortunately, there are little data on neuropsychological profiles of aged MS patients incorporating tests typically utilized in a dementia clinic setting.

Only a few cross-sectional studies have compared cognition in MS and aMCI or AD. The first was an early study comparing MS and AD patients (Filley et al., 1989). Findings demonstrated that cognitive impairment in MS is less severe than in AD. However, cognitive performance was based on a test battery lacking in specificity for either disease, and the groups were not matched on age (mean age MS = 41 years, AD = 65 years). More recently, Muller and colleagues compared 40 secondary progressive MS patients and 40 persons with aMCI (Muller et al., 2013). The Consortium to Establish a Registry for AD (CERAD) battery was administered (Polman et al., 2011) – it emphasizes domains related to AD pathology such as confrontation naming, constructional praxis, and verbal episodic memory. Measures of executive functioning were also added (CERAD-Plus). Results suggested that memory impairment in MS is related to executive dysfunction, rather than a consolidation deficit as in AD. Although this design represents an improvement in that tests sensitive and specific to AD were employed, the MS group was not evaluated with tests known to be sensitive to MS. In other words, there was no method for determining the degree of cognitive impairment in the MS sample. What is needed is a research design wherein MS patients are appropriately characterized as normal versus cognitively impaired, as defined by consensus standard testing, and to compare them with age and education matched aMCI and AD patients. Inclusion of both aMCI and AD samples would allow for comparison to the broader spectrum of AD pathology. It was our objective to carry out such a study and to possibly identify MS patients who may have comorbid AD, based on neuropsychological evaluation.

In summary, there is a clear need for research aimed at understanding how the cognitive profile of older MS patients differs from AD, and its prodromal state aMCI. There are clear treatment implications as the approved therapies for AD have minimal if sometimes equivocal benefit in MS but are nevertheless sometimes used off-label in MS care. In the current study, we examined how older MS patients perform in comparison to healthy older adults and patients with AD pathology on cognitive measures typically used to assess for AD.

2. Method

2.1. Participants

The total sample consisted of 100 participants including 20 healthy controls (HC), 20 AD patients, 20 aMCI patients, and 40 MS patients all from retrospective data. As data for 20 HCs was available at the time, it was determined that a sample size of 20 would allow for equal groups. The mean and standard deviation of the HC group was calculated for each BICAMS measure to determine which MS patients were impaired and unimpaired (< 1.5 SD on at least one BICAMS measure). Then, 20 patients were randomly selected from the impaired and unimpaired groups to be included in the study sample. These two groups were distinguished based on cognitive status in order to address possible issues related to sample bias (e.g., if only cognitively healthy MS patients enrolled in the research project). Similarly, 20 AD and MCI patients were selected at random to be included in the study sample, blind to results.

The five groups were statistically equivalent on age, sex, education, and score on the Geriatric Depression Scale. The MS impaired and unimpaired groups did not differ on disease duration, course, or EDSS score. Demographics are presented in Table 1.

HCs and MS patients were recruited through an ongoing study on aging and MS. These participants were recruited through flyers, word of mouth, and by approaching patients at the time of clinic visits at the MS Clinic at the Buffalo General Hospital. Patients with MS had an existing diagnosis by an MS clinician, based on the McDonald criteria (McKhann et al., 1984).

Patients with AD (MMSE M = 22.3, SD = 5.7) and aMCI (MMSE M = 26.2, SD = 3.0) underwent clinical evaluation in the University of Buffalo Alzheimer's and Memory Disorders Center (UBAMDC) and consented to have their data entered into an archival dementia research database. Diagnoses were based on widely accepted criteria for AD (Petersen, 2004) and aMCI (Morris et al., 1989). Consensus diagnoses were derived from a team of neurologists, neuropsychologists, and psychiatrists, utilizing manifold sources of information including neurological exam, brain MRI, psychiatric interview, informant reports of symptoms and history, serum chemistry tests, and in some cases positron emission tomography of cerebral blood flow.

This research was approved by the Institutional Review Board of the University at Buffalo, and informed consent was obtained from all participants.