Multiple Sclerosis and Related Disorders (2014) 3, 473–481

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/msard

Cognitive impairment in multiple sclerosis: An 18 year follow-up study

Lauren B. Strober[a,b,*], Stephen M. Rao[c], Jar-Chi Lee[c], Elizabeth Fischer[c], Richard Rudick[c]

[a]Kessler Foundation, 300 Executive Drive, Suite 70, West Orange, NJ 07052, USA
[b]Rutgers, the State University of New Jersey, New Jersey Medical School, Department of Physical Medicine and Rehabilitation, USA
[c]Cleveland Clinic Foundation, Cleveland, OH, USA

Received 29 August 2013; received in revised form 24 March 2014; accepted 27 March 2014

KEYWORDS
Multiple sclerosis;
Cognition;
Longitudinal investigation

Abstract
Background: Cognitive impairment occurs in 40–65% of patients with multiple sclerosis (MS). Less is known about the rate and pattern of cognitive decline over the course of the illness.
Objective: To examine long-term changes in cognition among patients enrolled in the phase III clinical trial of intramuscular interferon beta-1a (IM IFNβ-1a).
Methods: Twenty-two patients underwent a longitudinal investigation comparing neuropsychological test performance at study entry and 18-year follow-up.
Results: Over the 18 year interval, significant declines were observed on measures of information processing speed, simple and complex auditory attention, episodic learning and memory, and visual construction. Nine patients (41%) were found to be cognitively impaired at study entry. At follow-up 13 patients (59%) were cognitively impaired. While both the impaired and unimpaired patients at baseline experienced declines on these measures, only one measure, the Symbol Digit Modalities Test (SDMT), demonstrated a group (cognitively impaired versus intact at baseline) × time interaction. This interaction was characterized by a steeper decline in the unimpaired than the impaired group at baseline.
Conclusions: Over an 18 year period, our results suggest that cognitive impairment in MS progresses, with declines being most evident on measures known to be most sensitive to MS-related cognitive difficulties both cross-sectionally and longitudinally.

1. Introduction

Cognitive impairment is common in MS with prevalence estimates ranging from 40% to 65% (Bobholz and Rao, 2003).

*Corresponding author at: Kessler Foundation, 300 Executive Drive, Suite 70, West Orange, NJ 07052, USA. Tel.: +1 973 324 8459; fax: +1 973 324 8373.
E-mail address: lstrober@kesslerfoundation.org (L.B. Strober).

http://dx.doi.org/10.1016/j.msard.2014.03.004
2211-0348/

Cross-sectional studies comparing individuals with MS and healthy controls have identified impairments in speed of information processing, working memory/sustained attention, and visual and verbal memory. To a lesser extent, reduced performance on measures of attention and concentration, language, cognitive flexibility/abstraction, and visuoperceptual/spatial processing have also been reported (Amato et al., 2008; Chiaravalloti and Deluca, 2008; Rao, 1986; Rao et al., 1991a, Zakzanis, 2000). While there is an extensive cross-sectional literature pertaining to the prevalence and pattern of cognitive impairment in MS, much less is known about the rate and pattern of cognitive deterioration that occurs over the course of the illness.

To date, the majority of longitudinal investigations aimed at understanding the course of cognitive impairment have spanned a relatively short time interval (<5 years), potentially under-estimating the rate of cognitive decline in a disease that does not appreciably reduce the normal lifespan. These relatively short-term investigations of three to five years have suggested a slow and sometimes inconsistent deterioration of cognitive abilities (Amato et al., 2006), predominantly in information processing speed (Kujala et al., 1997; Denney et al., 2008; Amato et al., 2010), visual memory (Kujala et al., 1997; Amato et al., 2010; Feinstein et al., 1992), verbal learning and memory (Kujala et al., 1997; Patt et al., 1998), and attention/working memory (Kujala et al., 1997; Feinstein et al., 1992; Amato et al., 2010; Reuter et al., 2011), as well as reports of changes in verbal skills (Kujala et al., 1997; Amato et al., 2010; Reuter et al., 2011) and executive functions (Reuter et al., 2011). Several of these studies also note a greater level of deterioration among those with a progressive course (Patti et al., 1998; Feinstein et al., 1992) or among those who were determined to be cognitively impaired at baseline (Kujala et al., 1997)

Longitudinal investigations with a longer-term follow-up period (spanning approximately seven to 10 years) suggest notable declines in long-term verbal memory (Piras et al., 2003) information processing speed, motor speed, reaction time, visuospatial ability, and visual short-term memory (Haase et al., 2004; Bergendal et al., 2007). Bergendal et al. (2007) also demonstrated a greater deterioration among individuals with a secondary progressive course, compared to individuals with a primary progressive or relapsing remitting course. In a 10 year follow-up study, individuals with early onset MS demonstrated difficulties on measures of concentration, verbal memory, and abstract reasoning at study entry, but developed additional impairments in verbal fluency, verbal comprehension, and short-term verbal and spatial memory/attention (Amato et al., 2001). Over the 10 year period, the rate of cognitive impairment increased from 26% at entry to 56% at follow-up, a nearly twofold increase. This result contrasts with a 10 year follow-up of participants in a clinical trial with glatiramer acetate, in which the overall rate of cognitive impairment increased only from 50% at baseline to 55% at follow-up (Schwid et al., 2007) However, using an alternative criterion of examining individual measures, 27 ≃ 44% of participants demonstrated a .5 standard deviation decline on measures assessing verbal and visual learning and memory, information processing speed, and working memory.

The present investigation aimed to extend these findings by examining the longitudinal cognitive changes that occurred during an 18 year period in a sample of MS patients followed with an extensive neuropsychological battery. The primary aims were to (1) determine the change in the frequency of cognitive impairment in MS over an extended time period; (2) identify those neuropsychological measures that are most sensitive to change over time; and (3) examine whether cognitive impairment at entry is a predictor of long-term outcome.

2. Methods

2.1. Participants

Participants were recruited from the phase III clinical trial of intramuscular interferon beta-1a (IM IFNβ-1a) conducted in the early 1990s (Jacobs et al., 1995) At entry to the phase III study, participants were required to be between the ages of 18 and 55, diagnosed with definite relapsing-remitting MS for at least one year, and had an Expanded Disability Status Scale (EDSS) (Kurtzke, 1983) score between 1.0 and 3.5. At four sites, study subjects were administered a comprehensive neuropsychological battery at entry and at various time intervals over the course of the two year trial (results summarized by Fischer et al., 2000). In the current study, individuals originally enrolled at the Cleveland Clinic site were re-administered a neuropsychological examination 17.2–18.7 years (mean=17.9) after entry into the clinical trial. These individuals were selected for this study because they were participating in an ongoing longitudinal investigation of brain atrophy since 1999. Study visits for that study included yearly neuroimaging and neurological exams, including the Multiple Sclerosis Functional Composite (MSFC) (Fischer et al., 1999).

Table 1 Baseline demographic and disease characteristics comparing MS patients who underwent 18 year follow-up neuropsychological evaluation versus those patients lost to follow-up.

	Followed (*N*=22)		Lost to follow-up (*N*=53)	
Female (%)	63.6%		79.2%	
	Mean (SD)	Range	Mean (SD)	Range
Age (years)	36.1 (6.03)	24-44	37.1 (7.05)	25-52
Education (years)	14.9 (3.45)	10-26	14.2 (2.56)	11-25
Disease duration (years)	6.6 (5.87)	1-27	6.9 (6.68)	1-31
EDSS	2.1 (.85)	1.0-3.5	2.4 (.80)	1.0-3.5