

Received: 2016.07.01
Accepted: 2016.07.20
Published: 2016.08.05

Effect of Chronic Medical Conditions in Veterans with Multiple Sclerosis on Long-Term Disability

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Source of support: Dr. Christopher Aston was funded by NIH 1 U54GM104938

Background: The goal of this observational study was to examine the effect of common chronic medical conditions (CMCs) on long-term disability (activity limitation) in veterans already diagnosed with multiple sclerosis (MS).

Material/Methods: We retrospectively reviewed the electronic charts of 124 veterans with MS who have been regularly followed in our MS clinic for 10 or more years. General linear model analysis examined whether MS-related severity as measured by the Expanded Disability Status Scale (EDSS) and the presence of CMCs affected long-term disability as measured by the total score on the Functional Independence Measure (TFIM).

Results: Commonly encountered CMCs were increased BMI (61%), hyperlipidemia (78%), hypertension (65%), current smokers (47%), and arthritis/arthralgia (24%). Results suggest that the number of CMCs was not predictive of final TFIM scores; of the variables examined, only initial EDSS score was predictive of final TFIM scores.

Conclusions: The presence of CMCs did not affect the long-term disability in veterans diagnosed with MS, this was due mainly to CMCs being closely monitored and co-treated with other medical specialties.

MeSH Keywords: **Comorbidity • Disabled Persons • Multiple Sclerosis**

Abbreviations: **BMI** – Body Mass Index; **CIS** – Clinical Isolated syndrome; **CMCs** – Chronic Medical Conditions; **EDSS** – Expanded Disability Status Scale; **MS** – Multiple Sclerosis; **NARCOMS** – North American Research Committee on Multiple Sclerosis; **PPMS** – primary-progressive MS; **RRMS** – relapsing-remitting MS; **SPMS** – secondary-progressive MS; **TFIM** – Total Functional Independence Measure

Full-text PDF: <http://www.medscimonit.com/abstract/index/idArt/900367>

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Background

Multiple sclerosis (MS) is a chronic progressive disease and a leading cause of disability (defined by the WHO as activity limitation) especially in young adults [1]. More and more patients with MS are living longer as treatments are being instituted at an early stage with the aim to reduce relapses, slow disease progression, and minimize MS-related complications.

Chronic medical conditions (CMCs) such as obesity, hypertension, and arthritis are common in the general population [2] and are responsible for functional limitations [3], increased hospitalization, and increased mortality [4]. Presence of 1 or more CMCs in people with an index disease is referred to as co-morbidity [5]. The number of CMCs afflicting an individual increases with age [6]. In the Framingham Heart Study, presence of vascular risk factors, a common CMC, caused systemic inflammation as evidenced by an increase in blood cytokine levels resulting in greater brain atrophy than expected for age; therefore, CMCs are likely to further worsen disability in MS patients with increase brain plaque load [7]. Finlayson et al. showed that MS-related fatigue was affected by the presence of diabetes mellitus and arthritis [8]. Presence of CMCs has been found to delay MS diagnosis and increase MS-related disability at diagnosis, negating efforts to initialize treatment at earlier stages [9]. Both of these studies [8,9] were based on data from the North American Research Committee on Multiple Sclerosis (NARCOMS) registry. Although this is a large data base comprising 18 000 patients with MS, the cohort is primarily white and based on self-reporting. This limits generalizability of its conclusions to other patient groups and presents a potential bias. The presence of CMCs complicates the treatment of MS. Franklin et al. [10], in their study of 136 542 discharges with a diagnosis of MS, found that 9.2% (n=12 504) had a comorbid cardiac condition that contraindicated the prescription of fingolimod. Subsequently, these patients had a significantly higher hospitalization cost compared to those patients with no cardiac condition (\$17 623 vs. \$11 663). Finally, just as the presence of CMCs affects immuno-modulatory treatment choices [11], the response, compliance, and administration of MS treatments can worsen the CMCs.

A veteran is a person who served in active military service and is now discharged or released from service. As long as the conditions of discharge or release were other than dishonorable, they qualify for Veterans Affairs (VA) health care benefits. VA operates the nation's largest integrated health care system providing basic to advanced and specialized medical care to 9 million veterans at 1400 sites, including university-affiliated teaching hospitals, community clinics, veteran's centers (nursing homes), and counseling centers.

Given that the risk of MS and the presence of CMCs increases with age, we wanted to study the impact of the presence of commonly encountered CMCs on long-term disability (activity limitation) in veterans already diagnosed with multiple sclerosis (MS). Compared to NARCOMS, the veteran population differs in being mainly white men, older, and with confirmed MS diagnosis. The CMCs selected for study was based on those chronic conditions that cause the most disability and death in the veteran population and account for a disproportionate health care utilization and rising health care cost [12]. These CMCs also are the most common cause of disability and death in the United States [13]. A rising prevalence of similar vascular risk factors have been found in MS patients in a recent Canadian study [14], and was associated with a more rapid progression of gait dysfunction than in MS patients without these co-morbidities [15]. The findings of the present study may help institute changes in the VA MS program to decrease the additive effect of CMCs-related disability on the overall MS-related disability.

Material and Methods

Participants and procedures

This retrospective study included eligible veterans already diagnosed with MS (using the McDonald criteria) [16] and followed every 4 months for 10 or more years (from 2000 to 2012). A minimum of 10 years of follow-up was selected to ensure a sufficient period for the presence of these commonly encountered CMCs to have an effect upon disability. There were no exclusion criteria. Data were obtained via chart review (Veterans Administration [VA] electronic record or paper chart from non-VA facilities of veterans who transferred their care to our facility). This study was approved by the Institutional Review Board for Human Subjects Research and the local VA Research and Development Committee.

Data recorded were basic demographics (age, sex, and ethnicity), and relevant clinical variables such as age at onset of MS, duration of the disease, clinical MS subtype: relapsing-remitting MS (RRMS), secondary-progressive MS (SPMS), primary-progressive MS (PPMS), and clinical isolated syndrome (CIS) [17]. Patients, who on direct questioning complained of depression and fatigue on their initial or follow-up evaluations, completed the Beck depression inventory, fatigue severity scale, and modified fatigue impact scale to confirm and quantify their depression or fatigue. Preexisting and new-onset commonly encountered CMCs selected for documentation were hypertension, diabetes mellitus, hyperlipidemia, elevated body mass index (BMI) (overweight: BMI ≥ 25 and < 30 ; obese: BMI ≥ 30), migraine headaches, seizure disorders, strokes; arthritis, benign prostatic hypertrophy, gastro-esophageal reflux disease,

chronic obstructive airway disease, coronary artery disease, and congestive cardiac failure. These CMCs were documented at initial evaluation and during the 10 years of follow-up. These CMCs are usually co-managed with other medical specialties in our VA facility as a team approach, since management of each of these diseases alone or in combination can be challenging and increasingly complex. Our aim in the clinic for good control of CMCs is to maintain: i) blood pressure at less than 140/90, ii) hemoglobin A1c around 6.0, and iii) cholesterol and triglycerides levels less than 200 mg/dl. This was achieved with dietary and life-style modifications in addition to medications use. Where indicated, patients were enrolled in the smoking cessation and weight management clinics. These CMCs are routinely monitored in the VA electronic medical record system for quality of care assessment and improvement.

The Expanded Disability Status Scale (EDSS) measuring MS-related severity (EDSS score: ≤ 3 -mild, 4–6.5-moderate, and ≥ 7 -severe) was used to assess disease progression and to monitor response to treatment [18]. It is considered the criterion standard in MS clinical trials [19]. The Total Functional Independence Measure (TFIM) was used to measure MS-related disability. The TFIM is a reliable [20] and valid [21] functional assessment instrument widely used in many rehabilitation settings [22] to measure the degree of disability based on the level of assistance required (dependency) [23]. The TFIM score ranges from 18 (totally dependent) to 126 (independent), with disability classifications of mild (≥ 91), moderate (55–90), and severe (18–54). The TFIM scale has been found to be a more sensitive measure of MS-related disability than the EDSS [24,25]. The EDSS and TFIM scores were documented on the initial clinic visit and annual follow-up evaluations by a board-certified neurologist who is also FIM-certified. For this study, the last annual TFIM was used to measure the final burden of disability. The EDSS scores were not measured during or after their relapses and all of the patients were on disease-modifying therapies.

Statistical analysis

Group statistics are expressed as mean \pm standard deviation and frequencies. Descriptive statistics were computed for the sample. Generalized linear model analysis assessed whether age at MS onset, age at entry into the study, duration of MS, length of follow-up, MS subtype (progressive or not), sex, frequency of chronic medical conditions, and initial MS-related disability scores (TFIM, EDSS) were predictive of final total disability (TFIM) in MS patients regularly followed for 10 or more years and of the change in TFIM over the study period. Logistic regression was conducted to test whether these same variables affected the probability of worsening disability, defined as a decline in TFIM of 7 or more points from intake to last annual follow-up [26]. A full model with all variables forced in,

and a minimal model through stepwise regression, were determined. Data were analyzed using SPSS (IBM SPSS Statistics for Windows, Version 20.0. Released 2011. Armonk, NY: IBM Corp). Significance was set at $p \leq 0.05$ for all analyses.

Results

Table 1 presents the demographics and clinical measures of the 124 patients with MS followed for 10 or more years (average follow-up 14 ± 1 years). The average age of this population was 49 ± 11 years, being predominantly white (85%) men (84%), which is similar to other MS populations. The age of MS symptom onset was 35 ± 11 years, with a disease duration of 24 ± 11 years. RRMS was the most common type (49%). Of the common CMCs followed in our clinic, those associated with vascular risk factors were most frequent: hyperlipidemia (74%), hypertension (65%), increased BMI (overweight or obese, 61%), and current smokers (47%). The average number of CMCs was 3.7 ± 1.9 (range 0–8), with 96% having at least 1 CMC; 59% had 3 to 5 CMCs.

Of the 15 (12%) patients who died, 7 had 4 or more CMCs; the average number of CMCs was 3.9. No association was found between number of CMCs and mortality ($p=0.55$). Recorded frequency of CMCs for these patients who died were hypertension (11), DM (7), hyperlipidemia (9), increased BMI (5), arthralgia (4), asthma (3), GERD (3), BPH (3), and seizure (1); 10 were current smokers. Known causes of death (excluding MS) in these 15 patients were: cardiovascular (1), pneumonia/respiratory failure (4), cancer (2), sepsis/infection (3), and other (1), and 4 had unknown cause. The disease duration in those who died was 23 ± 10 years. The EDSS and TFIM scores at initial clinic evaluation were 6.3 ± 2.8 and 76 ± 32 , respectively, and at last follow-up visit were 7.6 ± 1.4 and 64 ± 36 , respectively. These were significantly ($p < 0.05$) worse than the corresponding averages for those that were still living. However, the decline in the EDSS and TFIM scores was not significantly different between those that were dead and those still living ($p > 0.05$). A decline of less than 7 tended to be in relapsing-remitting MS, while those with a decline greater than 7 tended to be in primary/secondary-progressive MS ($p=0.0042$).

Comparison of those with a decline in TFIM of less than 7 and those with a decline of 7 or more (Table 1) showed that those with a TFIM decline of 7 or more were older at entry into the study ($p=0.018$) and had been diagnosed with MS for longer (0.049). The mortality rate for those with a decline of 7 or more was over twice that for those with a decline less than 7 ($p=0.042$). The TFIM and EDSS scores at initial clinic evaluation and at last follow-up visit for those with a decline of 7 or more were significantly ($p < 0.05$) worse than the corresponding averages for those with a decline less than 7. However,

Table 1. Demographics and clinical measures of MS patients followed for 10+ years [mean ±SD or n (%) where applicable].

	All subjects	TFIM decline <7	TFIM decline ≥7	p-value
N	124	86	38	
Age at entry (years)	49±11	48±11	53±11	0.018
Follow-up (years)	14.3±1.4	14.4±1.2	13.9±1.8	0.053
Sex (male)	104 (84%)	73 (85%)	31 (82%)	0.65
Ethnicity (White)	105 (85%)	73 (85%)	32 (84%)	0.92
Age of MS onset (years)	35±11	34±11	37±12	0.42
Duration of MS (years)	24±11	23±11	27±12	0.049
MS type				0.0042
Relapsing remitting	61 (49%)	51 (59%)	10 (26%)	
Secondary progressive	37 (30%)	19 (22%)	18 (47%)	
Primary progressive	21 (17%)	12 (14%)	9 (24%)	
Fatigue (yes)	81 (71%)	55 (70%)	26 (74%)	0.61
Depression (yes)	83 (67%)	55 (64%)	28 (74%)	0.29
BDI score	4.7±4.7	4.5±4.7	5.2±4.7	0.52
Chronic Medical conditions				
Hypertension	74 (65%)	50 (64%)	24 (67%)	0.79
Diabetes Mellitus	26 (23%)	16 (20%)	10 (29%)	0.26
Hyperlipidemia	78 (74%)	56 (74%)	22 (76%)	0.82
Body Mass Index				
Overweight	37 (31%)	30 (37%)	7 (19%)	0.13
Obese	36 (30%)	24 (29%)	12 (32%)	0.73
Current Smoker	53 (47%)	39 (51%)	14 (39%)	0.24
Arthritis/arthralgia	30 (24%)	22 (26%)	8 (21%)	0.59
Chronic Obstructive Airway Disease	14 (11%)	10 (11%)	4 (11%)	0.86
Gastroesophageal reflux disease	27 (22%)	16 (19%)	11 (29%)	0.20
Cancer	5 (4%)	2 (2%)	3 (8%)	0.15
Benign prostate hypertrophy	18 (15%)	11 (13%)	7 (18%)	0.41
Headaches	9 (7%)	8 (9%)	1 (3%)	0.19
Seizure disorder	6 (5%)	6 (7%)	0	0.11
Stroke	5 (4%)	3 (4%)	2 (5%)	0.64
Mortality	15 (12%)	7 (8%)	8 (21%)	0.042
Chronic medical conditions (categorized)				0.87
0	5 (4%)	4 (5%)	1 (3%)	
1–3	48 (40%)	32 (39%)	16 (43%)	
4–6	57 (48%)	39 (48%)	18 (49%)	
7–9	9 (8%)	7 (9%)	2 (5%)	

Table 1 continued. Demographics and clinical measures of MS patients followed for 10+ years [mean \pm SD or n (%) where applicable].

	All subjects	TFIM decline <7	TFIM decline \geq 7	p-value
Number of chronic medical conditions	3.7 \pm 1.9	3.8 \pm 1.8	3.6 \pm 1.9	0.77
Initial EDSS score	4.6 \pm 2.9	4.0 \pm 2.0	6.0 \pm 2.4	0.00033
Final EDSS score	5.5 \pm 2.8	4.7 \pm 2.7	7.3 \pm 2.0	0.000001
EDSS change	0.9 \pm 1.8	0.7 \pm 1.8	1.3 \pm 1.5	0.087
Initial TFIM score	103 \pm 25	106 \pm 25	96 \pm 25	0.047
Final TFIM score	98 \pm 31	110 \pm 24	72 \pm 31	0.000000
TFIM change	-5 \pm 18	4 \pm 10	-24 \pm 19	—*

EDSS – Expanded Disability Status Scale; TFIM – Total Functional Independence Measure; BDI – Beck Depression Inventory. * Testing TFIM change is not valid since this was used to construct the groups.

the change in EDSS score was not significantly different between these groups ($p=0.087$).

Both MS-related severity (EDSS) and level of disability (TFIM) increased from initial clinic evaluation to last follow-up visit ($p<0.0001$ and $p=0.0042$, respectively). Both initial and final EDSS and TFIM scores showed significant correlation (Spearman's r) with age at entry to the study and with duration of MS ($p<0.05$) but not frequency of CMCs. Neither change in EDSS nor change in TFIM scores showed significant correlation with age at entry to the study, duration of MS ($p<0.05$), or frequency of CMCs.

A generalized linear model analysis was used to predict the TFIM score at final follow-up and for change in TFIM score (Table 2). While initial TFIM, initial EDSS, MS type, and length of follow-up were significant ($p<0.05$) predictors of both the TFIM score at final follow-up and for change in TFIM score, the number of CMCs was not significantly associated with either.

Among 124 patients with follow-up TFIM scores, 38 (31%) demonstrated clinically significant increases in the level of disability at final follow-up, as defined by decline in TFIM score of 7 or more points. Logistic regression analysis showed again that number of CMCs was not associated with the probability of clinically significant TFIM decline (Table 2).

Discussion

Results of this study suggest that in patients with MS, disability is primarily influenced by the disease itself (MS-related severity) and not by the presence of commonly encountered CMCs, especially vascular risk factors. This finding was not surprising given that our VA MS clinic program has been proactive in preventing MS-related complications and aggressively treating

preexisting common CMCs, especially vascular risk factors, and when they arise during patient follow-up. Recently, VA Medical Centers have been shown to be providing quality care to veterans with commonly encountered CMCs, especially cardiovascular risk factors, by incorporating an electronic medical record system and focusing on quality assessment and improvement [27–29]. Prevention and treatment of commonly encountered CMCs, specifically vascular risk factors, helps to prevent synergistically increasing disability and death in MS patients, especially as they are now living longer. It serves to prevent deterioration in their quality of life and helps lower health care costs through efficient use of scarce health care resources [10,30]. Evidence that the presence of CMCs causes increased disability has been conflicting. In a study of 279 cancer patients, presence of CMCs was modestly correlated with increased disability for the total sample; however, it was highly correlated with increased disability for patients younger than 60 years of age [31]. No such correlation between the presence of CMCs and increased disability was found in 536 patients with acute stroke admitted to a rehabilitation setting [32].

Confavreux et al. [33], in a study of 1844 patients with multiple sclerosis who were followed an average of 11 \pm 10 years, found that length of time living with MS, MS type (progressive or not), and length of follow-up significantly influence progression of MS-related disability. In our study, MS type (progressive or not), initial EDSS, and initial TFIM scores were the only consistent factors affecting both absolute final TFIM and change in TFIM. Age, duration of MS, and duration of follow-up predicted final TFIM score.

Our other study findings worth noting are: (a) the frequency of common CMCs present in this sample of veterans with MS mirrored the general (Oklahoma state) population from which the veteran population is derived for some of the CMCs (e.g., diabetes, obesity, cancer, and stroke) but was higher for others

Table 2. Generalized linear model analysis for TFIM scores at final annual follow-up and change in TFIM score; logistic regression for decline in TFIM more or less than 7.

Source	TFIM final Wald p	TFIM change Wald p	TFIM decline logistic regression Wald p
Full model			
Chronic medical conditions	0.92	0.92	0.35
Age at entry	0.011	0.011	0.16
Age at onset	0.020	0.020	0.061
Gender	0.30	0.30	0.083
MS subtype	0.076	0.076	0.13
Duration of MS	0.010	0.010	0.027
length of follow-up	0.0064	0.0064	0.13
Initial TFIM	<0.00001	<0.00001	0.00047
Initial EDSS	0.00024	0.00024	0.22
Minimal model			
MS subtype	0.030	0.0022	0.012
length of follow-up	0.037		
Initial TFIM	<0.00001		0.00050
Initial EDSS	0.0010		

(hypertension [MS patients 65% vs. general population 56%], hyperlipidemia [74% vs. 39%], and current smoker [47% vs. 26%]); (b) there was no association between risk of dying and the number of CMCs; and c) there was no association between the initial level of dependence (TFIM) and the number of CMCs.

Our study has several limitations. First, this study is limited to primarily male veterans who have ready access to quality healthcare; thus, it is difficult to generalize to the general population of MS patients. Second, this study is limited to just 1 institution. Third, the sample size is small and may preclude detecting all effects determining MS-related disability. Despite these limitations, these longitudinal data inform the clinician about the effect of controlled common CMCs on the long-term disability for a given MS-related severity. A strength of this study lies in the CMCs being documented and actively

managed rather than being self-reported as in the NARCOMS study [8,9] or as administrative data relying on diagnostic codes [16].

Conclusions

The presence of controlled commonly encountered CMCs in veterans already diagnosed with MS does not significantly affect long-term disability. However, this is a VA population in which the CMCs were closely monitored to achieve a high level of care.

Disclosure statement

Authors have no conflict of interest to disclose and have not received any funding for this study.

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