Primary and Nonprimary Fatigue in Multiple Sclerosis

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Using the fatigue algorithm described in the Clinical Practice Guidelines for Fatigue and Multiple Sclerosis (MS), this study aimed to determine the frequency of fatigue related directly to the MS disease process (primary fatigue) versus that related to disease symptoms such as depression (nonprimary fatigue), differentiate primary from nonprimary MS fatigue, and identify any characteristics unique to primary MS fatigue. Consecutive clinically definite MS patients from the University of British Columbia MS clinic were invited to participate. The screening assessment included standardized scales and questionnaires. In total, 50 patients completed the study. Nonprimary fatigue was present in 36 individuals (72%), of whom all but 2 had multiple factors contributing to fatigue. The most common factors contributing to nonprimary fatigue were sleep problems (58%), mobility limitations (52%), and depression (40%). Compared with patients with nonprimary fatigue, those with isolated primary fatigue had lower fatigue scores and reported fatigue onset at midday (P < .05). Any attempt to study or manage MS fatigue should be preceded by identification and amelioration of treatable nonprimary fatigue factors before focusing on primary fatigue in MS. ***Int J MS Care*****. 2008;10:14–20.**

Fatigue is reported by 75–90% of people with multiple sclerosis (MS), and up to 50% of patients indicate fatigue as one of their worst problems.[1,2] Fatigue can negatively affect a range of issues, including quality of life and employment.[3-5] Despite its frequency, fatigue in MS remains elusive, partly because of the complexity of factors contributing to it and the lack of defined biological markers.[2]

Although identifying the presence of fatigue in individuals with MS is not a problem, methods of measurement are highly subjective, so determining the underlying cause is challenging.[4,6] Possible contributory factors to fatigue in MS include lesion site, nerve fiber conduction loss, sleep disturbances, physical disability, comorbidity, and iatrogenic causes.[7-11] Some of these factors, such as sleep disturbances, may be secondary to MS-related problems, including bladder dysfunction and leg spasms, that confound the assessment.[10,12,13] Some studies show fatigue to be present in patients with early disease and mild disability,[14] but others suggest that fatigue is worse with advanced disease or has no relationship with disability.[2,15-17] Fatigue correlates with depression in some studies and is independent in others.[14,16,18,19] This conflicting evidence highlights the need for a systematic and thorough evaluation and treatment for fatigue.[4] The Clinical Practice Guidelines for Fatigue and Multiple Sclerosis addresses this issue by using a sequential approach, described in a fatigue algorithm (Figure 1).[20]

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Definitions

Fatigue in MS can be described in two categories: primary fatigue (PF) and nonprimary fatigue (NPF). NPF results from other symptoms of MS such as depression, mobility inefficiency, or respiratory problems. NPF may be caused by acute situations such as flu, cold, or stress or chronic conditions such as chronic pain or cardiac problems. NPF may be of short duration or last several months to years.

PF is related directly to the MS disease process, when no NPF factors can be recognized. Because no laboratory, scanning, or other procedures that would isolate or identify PF are currently available, the diagnosis is one of exclusion. PF persists in MS even when NPF factors are eliminated or managed and lasts >6 months.[20] Although no characteristics specific to PF have been systematically identified, scholars have

observed that heat sensitivity,[1,22] time of fatigue onset,[3] and severity of fatigue[6] warrant further investigation.

Purpose

The primary objective of this study was to use the Clinical Practice Guidelines to systematically screen a consecutive cohort of patients with MS to evaluate the incidence of NPF and PF and the frequency of factors that contribute to NPF. The secondary objective was to determine whether the fatigue experienced was greater in PF. The final objective was to determine whether PF had any unique characteristics or descriptors such as heat sensitivity, time of fatigue onset, or relativity to the level of fatigue.

Fatigue Algorithm for MS

The fatigue algorithm is a flow chart that represents a process of identification, assessment, and intervention for the multiple variables associated with fatigue in MS.[20] An assumption embedded in the algorithm is that fatigue as experienced in MS may be associated with several factors. The cause-and-effect relationship between these factors and MS fatigue is tenuous at best because of the subjective outcome measures used and the inability to rigorously isolate each factor. The approach of the fatigue algorithm is to identify the presence of these factors and account for their possible contribution to and relationship with fatigue in MS patients.

The fatigue algorithm is organized into seven columns (Figure 1). Columns 1 and 2 identify fatigue as a problem and consider any relevant history. Column 3 confirms and treats or alternatively discounts potential acute onset of fatigue that is not related to MS. Column 4 considers any chronic fatigue factors that may or may not be related to MS (eg, sleep problems, depression, medications, deconditioning), concomitant medical problems (eg, anemia or thyroid disease), and significant chronic stressors. Column 5 identifies any factors that are secondary to MS symptoms that may result in excessive energy expenditure to compensate for reduced mobility or respiratory function. Collectively, columns 3–5 deal with NPF as defined in this study. In columns 6 and 7, PF of MS is addressed, focusing on pharmacological and rehabilitation interventions.

PF has been anecdotally observed to be at its worst in early and midafternoon, follow the body's diurnal temperature changes, and appear in the absence of other factors.[21] Environmental heat has been suggested to worsen fatigue in MS.[1,15,22] The experience and perception of fatigue in MS is unique to each individual and is optimally evaluated in the context of daily life.[6]

Based on the fatigue algorithm, evaluation and treatment for fatigue in MS initially targets the NPF factors (columns 3–5); when ameliorated, the algorithm addresses PF. Unfortunately, the frequency of the various NPF factors is unknown. As new pharmacological treatments are developed for MS fatigue,[23-26] differentiation and quantification of these types of fatigue is crucial before beginning clinical trials. Because this preliminary work has not yet been done, therapeutic trials, to date, have included heterogeneous groups of MS patients (with regard to fatigue), suggesting that caution is needed when generalizing the results of these studies.[27] Thus, understanding the frequency of NPF factors is imperative.

Methods

Patients were recruited through a posting in the University of British Columbia (UBC) MS clinic, by invitation from their neurologist, and through MS Society newsletters. Inclusion criteria for the study were age ≥19 years; a clinically or laboratory definite diagnosis of MS[27]; clinically stable MS, defined as no relapse within 30 days; an Extended Disability Status Scale (EDSS) score of <7.5; willingness to provide informed consent; and identification of fatigue as a problem (by answering the question: Is fatigue a problem for you?). Patients were excluded from the study if they had initiated disease-modifying therapy within the past 6 months, used oral or systemic steroids within the past 4 weeks, or been diagnosed with a serious psychiatric or medical condition that, in the opinion of their clinic neurologist, would preclude reliable participation in the study. This study was approved by the UBC Behavioural Review Ethics Board.

For this cross-sectional study, the coordinator screened each potential participant. Eligible patients were booked for a 1-hour assessment visit. Six self-report questionnaires—demographic form, two fatigue scales, sleep scale, fatigue questionnaire, and sleep questionnaire—were provided to participants and completed in advance of the assessment. The visit included a structured interview, review of completed questionnaires, evaluation of mobility, and a screen for depres-

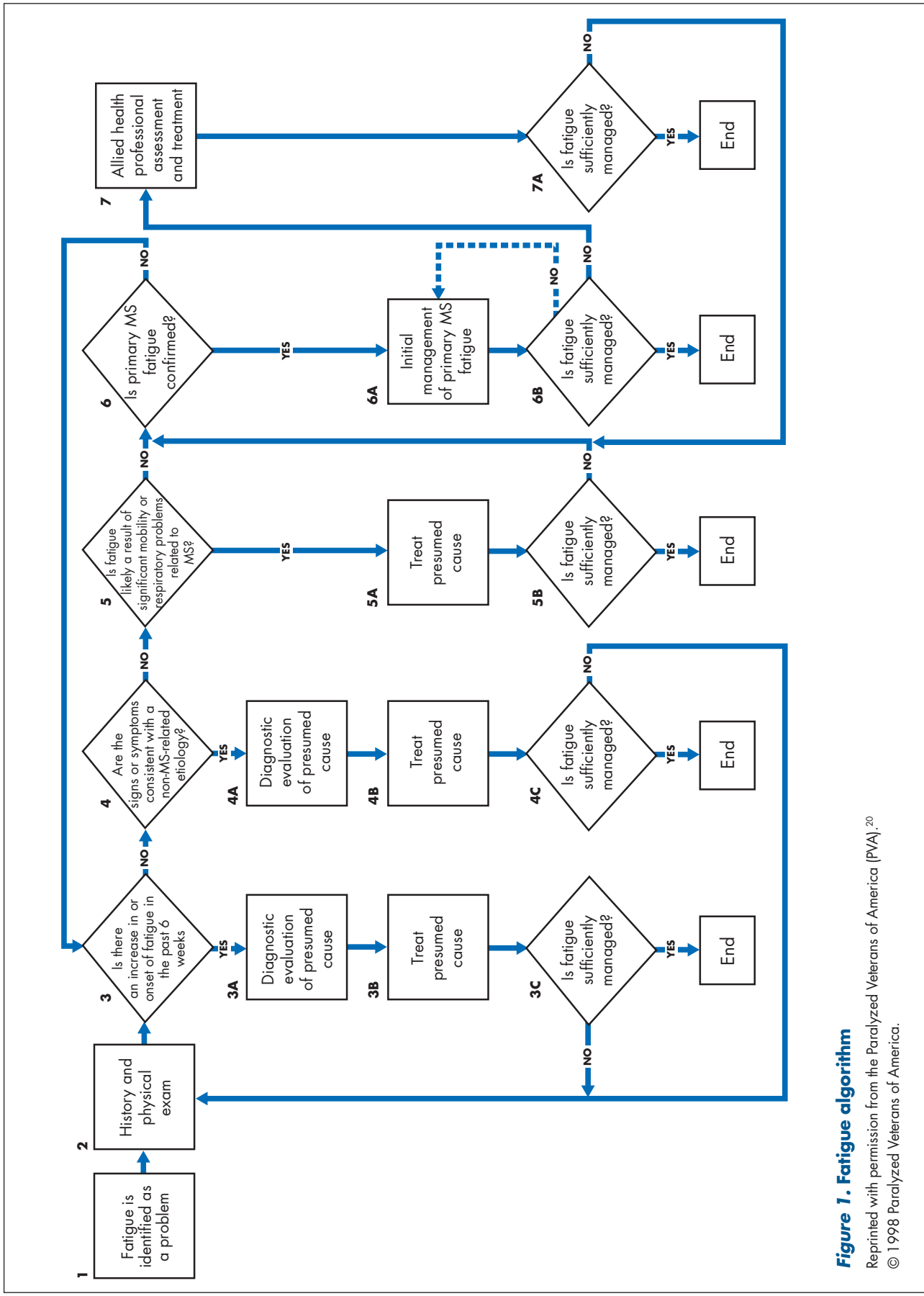

***Figure 1.* Fatigue algorithm**

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sion, respiratory function, and pharmaceutical and nonpharmaceutical medications.

The fatigue algorithm was used to guide the screening for PF and NPF.[20] The screening tools and questionnaires recommended in the Clinical Practice Guidelines were used.[20] Where no measure was recommended, a standardized scale or method was sought or developed. The measures used in this study were the Fatigue Severity Scale (FSS),[18] the Modified Fatigue Impact Scale (MFIS),[2,20] a fatigue questionnaire,[20] the Beck Depression Inventory 18 (BDI-18),[28,29] the Epworth Sleepiness Scale (ESS),[30] a sleep questionnaire,[20] the ambulation section of the Functional Independence Measure,[31] the dyspnea section of the Chronic Respiratory Diseases Questionnaire,[32] and EDSS.[33]

All prescription and nonprescription medications were systematically recorded, including careful screening of alcohol and caffeine intake, as well as alternative medications or therapies such as marijuana and herbal remedies. Each person's medications were reviewed for their possible contribution to fatigue. Medications that were known to cause drowsiness but were taken at appropriate times (ie, at night), were not deemed to affect fatigue adversely. Where the medication type, dosage, frequency, timing of dose, or potential interaction with other medications was suspected to affect fatigue, the case was reviewed by the study pharmacist or neurologist. The clinical opinion was used to code the medications as being contributory or noncontributory to fatigue. Note that the fatigue algorithm suggests a longitudinal process of data collection, which was not clinically feasible when pilot tested. To address this issue for the study, the self-report measures (first five listed above) were completed in advance of the study visit. The remaining measures were completed during the visit.

The two principal assessors reviewed all questionnaires and scales. Consistent with the Clinical Practice Guidelines algorithm,[20] PF was identified and coded in the absence of other factors or when factors were not considered significant for fatigue.

Statistical analyses were carried out with the Statistical Package for the Social Sciences (version10). Statistical significance was established at $P < .05$. Pearson χ^2 or Mann-Whitney test was used to analyze the differences between groups. Correlation between nominal ordered and interval nonnormal or ordinal variables was analyzed using Kendall's τb correlation.[34,35]

Results

Fifty-nine individuals with MS initially volunteered to participate in this study. Nine were excluded because of recent relapses (n = 2), presence of a psychiatric condition (n = 1), recent initiation of an immunemodulating therapy (n = 1), and lack of clinically definite MS (n = 1). Three individuals declined involvement in the study after initial contact, and one person's study visit could not be scheduled. Therefore, 50 participants completed the study and formed the cohort. Twenty-four patients (48%) were on disease-modifying therapies. Fatigue was ranked as the number one problem for 35 participants (70%) and had been present for at least 6 months in 49 individuals (98%). Demographic characteristics are shown in Table 1. A retrospective database search of all patient visits during the period of the study (n = 1865) was completed to determine how representative the study cohort was of the MS clinic population (Table 1). Statistical testing showed no significant difference in age, sex, or disease course between the study participants and patients seen in the MS clinic. The cohort, however, had a lower mean EDSS score (suggesting less disability) than the clinic population ($P < .05$).

The scores from the four standardized questionnaires (FSS, MFIS, ESS, BDI-18) and the sleep questionnaire are summarized in Table 2. Fatigue, as scored on the FSS and MFIS, ranged from mild to severe in impact and intensity for study participants. EDSS

***Table 1.* Demographic characteristics of study cohort (n = 50)**

Characteristic	Cohort	MS clinic*
Age, y, mean ± SD	47.4 ± 8.9	47.0 ± 10.9
Sex, *n* (%)		
Women	39 (78)	1393 (75)
Men	11 (22)	472 (25)
Disease duration, y, mean ± SD	7.2 ± 6.4	
Course, *n* (%)		
Relapsing remitting	35 (70)	1146 (61)
Secondary progressive	13 (26)	411 (26)
Primary progressive	2 (4)	144 (8)
Benign	0	13 (0.7)
Unknown	0	151 (8)
EDSS score, mean ± SD	3.2 ± 1.8	3.6 ± 2.3†
Groupings, *n* (%)		
0.0–3.5	34 (68)	
4.0–5.5	7 (14)	
6.0–7.0	9 (18)	

SD, standard deviation; EDSS, Expanded Disability Status Scale
*Patient visits during study.
†Significantly different at $P < .05$.

Table 2. Cohort scores on questionnaires

Questionnaire	*n* (%)	Mean (SD)	Range
FSS (9 items, 0–7 very severe)	50 (100)	6.0 (0.9)	3–7
MFIS (21 items, 0–84 severe impact)	50 (100)	54 (12)	31–79
ESS (7 items, max = 24)	50 (100)	8.4 (4.4)	0–18
Character of sleep			
Restorative	21 (42)		
Interrupted, poor quality	29 (58)		
BDI-18 (18 items, 0–54)	50 (100)	9.2 (6.5)	0–24
Groupings			
0–9 (none)	30 (60)		
10–14 (mild)	3 (6)		
15–20 (moderate)	13 (26)		
21+ (severe)	4 (8)		

SD, standard deviation; FSS, Fatigue Severity Scale; MFIS, Modified Fatigue Impact Scale; ESS, Epworth Sleepiness Scale; BDI-18, Beck Depression Inventory–18

scores showed no correlation with fatigue scores on either the FSS or MFIS (P = .30 and .24, respectively) or with sleep problems or depression as measured on the ESS and BDI-18 (P = .90 and .25, respectively.)

Objective 1: Frequency of PF and NPF

Of the 50 participants in the study, 36 (72%) were identified as having fatigue factors that may be related to NPF, including acute issues, chronic conditions, and problems secondary to MS symptoms. In the absence of other factors, the remaining 14 patients (28%) were deemed to have PF.

Of those with NPF, 34 experienced more than one factor possibly contributing to their fatigue. The most frequent NPF factors reported were sleep problems (58% of patients experienced more than two interruptions per night), unmanaged mobility impairments (52%), and depression (40%). Table 3 shows the frequency of each factor that may contribute to NPF, and Table 4 gives details of medications deemed to contribute to NPF. Note that PF may have been present in these subjects but could not be identified in the absence of known specific markers for PF.

Table 3. Frequency of factors contributing to fatigue in multiple sclerosis (MS) study subjects

Contributing factors	*n*
Nonprimary MS fatigue	36
Acute factors (eg, heat, infection, temporary routine disruption, recent stressors)	4
Chronic factors	36
Sleep problems	29
Depression	20
Medications	10
Deconditioning	10
Significant chronic stressors	3
Concomitant medical problems	2
Factors secondary to MS	26
Unmanaged mobility impairment	26
Respiratory problems	2
Primary MS fatigue	14

Objective 2: Unique Characteristics of PF

Three characteristics were investigated as possible discriminators of PF, as suggested in previous literature about fatigue and MS[1,15,20-22]: heat sensitivity, time of day of fatigue onset, and impact of fatigue. Forty subjects (80%) reported fatigue to be exacerbated by heat. However, no difference in fatigue scores was found between those reporting that fatigue worsened with heat and those indicating that heat was not a factor (P = .52 and .11, MFIS and FSS, respectively, Mann-Whitney test). In addition, no difference was found in reported heat sensitivity between the PF (11 of 14 [80%]) and NPF (29 of 36 [80%]; $P < .05$) groups. These results suggest that heat sensitivity is not a unique characteristic of PF or NPF.

Statistical analysis revealed that time of fatigue onset was significantly different between the PF and NPF groups. Individuals with PF were significantly more likely to report onset of fatigue at midday, ie, beginning in late morning and early afternoon (Pearson $\chi^2 = 4.77$; P = .03).

MFIS fatigue scores were significantly lower in the PF group than in the NPF group (P = .03, Mann-

Table 4. Medications deemed to contribute to fatigue taken by MS study subjects

Medication class	Medication (*n*)
Antidepressants	Amitriptyline (1), citalopram (2), fluvoxamine (1), trazodone (1), venlafaxine (3), St. John's wort (*Hypericum perforatum*) (1)
Analgesics	Butalbital-codeine compound (2), codeine (1)
Antimigraine (5-HT1 agonists)	Rizatriptan (1), sumatriptan (1)
Benzodiazepines and other hypnotics	Oxazepam (1), nitrazepam (1), triazolam (1), zopiclone (1)
Skeletal muscle relaxants	Baclofen (1), tizanidine (2)
Miscellaneous	Gabapentin (2), marijuana (2), oxybutynin (2)

Note: All subjects in group (n = 10) were taking multiple medications deemed to contribute to fatigue.

Whitney test), suggesting that the negative impact of fatigue is greater for those who experience fatigue from multiple concurrent NPF factors. No significant differences were found between groups for FSS scores ($P < .05$, Mann-Whitney test).

Discussion

By using the fatigue algorithm to identify the frequency of factors that may contribute to fatigue in a cohort of MS patients, contrary to what has often been reported, most of our patients were experiencing factors that fit the definition of NPF. This finding is seminal in addressing fatigue in MS for two reasons: many of the NPF factors can be treated, and, in the absence of correction of such factors, evaluation, treatment, or even study of PF will not be possible. Our study found that less than one third of the cohort had PF in isolation; however, PF may have been masked by the presence of NPF factors. The true proportion of patients experiencing PF remains elusive until factors defining NPF are treated. Another explanation for the low frequency of PF in this study group could be selection bias on the part of neurologists or patients. However, a comparison with the general UBC MS clinic population did not indicate any significant clinical or demographic differences.

With the definitions and criteria used in this study, a diagnosis for PF can only result once the NPF factors have been identified, treated, and resolved. Ideally, a positive, discerning definition for PF that includes its own set of characteristics and biological markers will evolve. The results from our study extend the possible list of discriminators for PF. We were able to show that time of fatigue onset and lower levels of fatigue were unique characteristics of isolated PF. Time of onset was consistent with Herndon's[21] observation that fatigue scores were significantly higher for those experiencing NPF, which was also supported by Bakshi.[6] Our findings suggest that as additional characteristics exclusive to PF emerge, more precise screening measures and targeted criteria for diagnosis can be developed. This will not occur, however, if the current confusion between PF and NPF is not eliminated.

Heat sensitivity was not found to be associated preferentially with the PF versus the NPF group, nor did it relate to increased levels of fatigue. Early research showed conflicting results or that heat worsened fatigue in MS compared with a healthy control group.[1,22] More recently, heat was shown to magnify fatigue, with the effect more pronounced among those who experienced severe fatigue and a higher EDSS score.[15] This variability across studies may be related to the subjective measures used to assess the relationship between heat and fatigue. Alternatively, results may be confounded by the inconsistent identification of other NPF factors, shown in our study to be highly prevalent.

More than 90% of individuals in the NPF group experienced multiple factors that could be identified as a possible cause for their fatigue. Although these factors are not considered part of PF, many are associated with MS. Patients with MS have a 50% lifetime risk of experiencing depression,[36] with point prevalence estimates ranging from 14% to 57%.[29] This was similar in our group, where 40% of the cohort experienced depression. Sleep problems have been reported to be three times higher in people with MS than in healthy control subjects, which is consistent with our findings.[11-13] Mobility problems are common in MS.[20] More than half of the patients in our study experienced mobility problems that, when associated with spasticity, may have accompanied increased fatigue.[37] In contrast to this, others have found no relationship between gait and perceived fatigue.[38] The tension in the literature suggests that, when various factors contributing to MS fatigue are isolated systematically, their contribution may be identified and targeted for treatment.

The fact that many of the causes of NPF are treatable may be the most compelling argument for a thorough systematic screening of these potential contributory factors. Such an approach would reduce their effect on the increased fatigue levels experienced by patients with NPF.[16] Indeed, when depression was managed effectively, fatigue was reduced.[39] This is an important and urgent issue for clinical practitioners. The therapeutic team must identify and treat factors that magnify the disabling fatigue experience in MS.

Finally, to study fatigue in MS, particularly in intervention research and therapeutic trials, the type of fatigue and factors being studied must be explicitly defined. Although many MS fatigue studies include a screening and control for depression, our study showed that sleep problems and mobility impairment had a higher frequency than depression, necessitating their inclusion for screening as confounding variables.[15,23] Overlooking this step would weaken the interpretation and generalization of fatigue intervention studies.

The modest sample size used in this study warrants cautious generalization of the findings. In addition, recruitment to the study was consecutive and based on participant response to posters and/or referral by a clinical neurologist. This recruitment method may have biased the study sample. However, the study cohort was demographically and clinically representative of the MS population from which it was drawn. □

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