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A medical definition of fatigue in multiple sclerosis

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Summary

Background: The symptom of fatigue has been described in a variety of ways but absence of a single taxonomy may be hindering research into this prevalent symptom.
Objective: To define the symptom of fatigue, as experienced by patients with multiple sclerosis (MS), in terms of a common framework, typical of a medical history.
Design: Qualitative phase followed by cross-sectional questionnaire survey.
Method: Forty patients, with clinically definite MS, underwent semi-structured interviews which were analysed within a common framework of: experience (with derived themes of motor, cognitive, somatic/energy, sleep, other features) cadence (i.e. short-term variability), chronicity, precipitating and aggravating factors, relieving factors, severity and associated features. The prevalence of each feature of fatigue, emergent from the interviews, was subsequently determined by questionnaire survey of a further 635 MS patients.
Results: Despite variance across patients, fatigue could be described within the derived themes and framework. Nearly all themes were endorsed by the majority of questionnaire respondents. In summary, fatigue could be defined as reversible motor and cognitive impairment, with reduced motivation and desire to rest. It could appear spontaneously or may be brought on by mental or physical activity, humidity, acute infection and food ingestion. It was relieved by daytime sleep or rest without sleep. It could occur at any time but was usually worse in the afternoon.
Conclusion: A framework, not only derived from patient experience but also meaningful in a medical context, was shown to be capable of describing fatigue in a large cross-section of MS patients. The definition may facilitate inter-disease comparison of fatigue as well as physiological enquiry.

Background

The medical definition of many symptom-related medical terms is clear. Some of these terms can be defined by a simple description of the subjective experience of the symptom e.g. photopsia is the visual sensation of flashing lights. Other terms represent more complex symptoms and, as such, their definition requires more than a simple description of the subjective experience. For instance, medical students are taught that cardiac pain is a gripping pain in the centre of the chest (angina pectoris) that may radiate to the arm or jaw, is made worse by exertion and relieved by rest and may be associated with shortness of breath, sweating and nausea. Note that this form of clinical definition comprises a description of the subjective experience, aggravating and relieving factors and associated features. The clinical definition represents, or implies, the consequences of an underlying pathophysiology (in this case, myocardial ischaemia) and, in turn, each clinical feature is capable of physiological explanation. A medical symptom also has an 'impact' on the life of its sufferer, which is determined by a myriad of external circumstances; it is an entirely separate concept from the clinical definition.

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There are few symptom-related, medical terms in common use that remain to be clearly defined, one such term is fatigue. There is growing interest in the symptom of fatigue and, in the field of MS, there already exists a substantial body of work on the subject. However, barely without exception, each MS study begins with comment concerning the lack of a clear definition of fatigue, lack of understanding of the pathophysiological basis of the symptom and lack of effective treatment whilst acknowledging its complexity, importance as a cause of disability and social cost. Such a complex symptom is likely to require a definition extending beyond a simple description of the subjective experience in order to allow a better understanding of its underpinning mechanisms, as has been the case with cardiac pain.

Current definitions of fatigue, as a clinical symptom in MS, include: overwhelming sense of tiredness, lack of energy or feelings of exhaustion,[1] difficulty initiating or sustaining voluntary effort,[2] feelings of physical tiredness and lack of energy distinct from sadness or weakness,[3] a subjective lack of physical and/or mental energy that is perceived by the individual or the caregiver to interfere with usual or desired activity.[4] It can be seen that these definitions limit themselves to simplified descriptions of the subjective experience, which itself may contain unclear terms such as 'lack of energy', or even admix impact of the symptom.

Strict definition is crucial to scientific enquiry, without clear definition there can be no useful measurement. Krupp[5] herself, states that 'clinical trials are currently limited by the lack of a well validated definition of fatigue'. This study attempts to produce a definition for the symptom of fatigue, upon which further science may be based.

Method

The study was conducted in two parts. First, the features of the definition of fatigue were derived using qualitative methods. Secondly, the prevalence of those features, in a large cross-section of an MS population, was determined by questionnaire survey. The study had local ethics approval in each institution (Sefton EC.115.03 and Hammersmith 05/Q0401/7). All subjects gave written consent to take part in the study.

Qualitative phase

Forty unselected patients were recruited to undergo a semi-structured interview, as they attended the out patient clinic at The Walton Centre. The only entry criteria were a diagnosis of clinically definite MS,[6] the ability to converse intelligibly in English and consent to the study. Subjects were excluded if they had a second neurological disease; no exclusions were made on the basis of concomitant medication. The same interviewer (R.J.M.) was used throughout. Basic demographic and clinical information were obtained both directly from the subject and from their case notes.

All but two people, approached to be interviewed, consented; the two that declined cited other time commitments as a reason for not taking part. All interviewees were aware that the interviewer was a doctor (neurologist) who was not involved in their ongoing, clinical care. The subject's spouse or partner was free to attend and contribute if the subject wished. The conversation was tape recorded and later transcribed verbatim, interview length ranged between 30 and 50 min and transcript length between 2500 and 4500 words. All the final transcripts were verified against the tape recording by the investigator (R.J.M.). The transcripts and the transcribing process remained anonymised.

Structure of analysis and interview

The purpose of the interviews was to generate a detailed, medical description of the symptom of fatigue, explicitly excluding its impact. The opportunity was also taken to explore the lay definition (semantics) of the word fatigue. The medical description of any symptom has a framework of standard features. Thus a framework approach[7] to the analysis was adopted (see Appendix 3). This approach still generates theory 'grounded' in the data but starts deductively from *a priori* reasoning and requirements, which, in this study, were those of essential symptom description as per any standard medical history.[8,9]

The interviews were conducted in a semi-structured way. A schedule of topics (including, for example, headings such as: own words description, aggravating/relieving factors, sleep pattern, appetite, effects of medication, effects of relapse, jet lag, mood) was used, as an aid, by the interviewer. However, both the order and the way in which each topic was addressed were directed, as much as possible, by the interviewee; for instance, many topics were often spontaneously volunteered. New topics were added, as the study progressed, if induced in previous interviews (e.g. motivation, prophylaxis and loss of access to prelearned skills). The opening gambit, however, was standard: 'Can you tell me what *you* understand by the term fatigue?'.

Quantitative estimation

The themes, emergent from the qualitative phase, were used to create a symptom inventory, which

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could be completed by self-report. Additional subjects were selected from research databases, held at two UK institutions (Walton Centre, Liverpool and Charing Cross, London). An inventory pack was sent by mail to 1223 patients with clinically definite MS,[6] from these centres.

Besides the inventory, the packs contained questions regarding basic demographics, disease information, whether help was required to complete the pack and a modified visual analogue scale (VAS—see Appendix 1) for fatigue over the previous 2–4 weeks, in order to provide a simple indication of overall fatigue level. The inventory itself contained 46 questions each with a four point Likert response scale (strongly disagree/disagree/agree/strongly agree). Respondents were instructed to relate their responses to the previous 2–4-week period. The responses to each question were scored 0, 0, 1, 1 thereby dichotomising the data into disagree/agree.

The questions in the inventory were designed to capture the essence of each theme in a succinct manner and thus lengthy qualification was avoided for simplicity. Similarly questions which might not be universally applicable, such as explicitly identifying particular activities or enquiring after features only relevant to sub-populations e.g. MS relapse, were omitted. The individual themes used will not be listed here but will be apparent in the Results section.

Percentage prevalence was calculated for each theme. Some of the themes were grouped, by the operation of logical OR, in order to represent broader aspects of the symptom: the prevalence of these grouped themes therefore included any subject who had endorsed at least one of any of the constituent themes. Where appropriate, cross-comparison of the grouped themes was made by contingency table with associated chi-square probability.

Data were transcribed to a computer database; statistical analyses were performed using SPSS 11.0.4 for Mac.

Results

Subjects

Subject characteristics are given in Table 1. For the qualitative analysis, an inadequate recording meant that one interview could not be transcribed. The response rate from the questionnaires was 51.9% (635/1223). The VAS scores were normally

Table 1 Subject characteristics

		Qualitative interviews	Mailout respondents
	Total number of subjects	40	635
	Mean age (SD, min.-max.)(years)	49.0 (9.7, 34–78)	46.6 (10.9, 21–83)
	Number female (%)	32 (80)	451 (71.0)
	Mean disease duration (SD, min.-max.)(years)	16.3 (9.4, 1–41)	15.1 (9.5, 2–49)
	pp	5 (12.5)	54 (8.5)
Disease type, *n* (%)	rr	19 (47.5)	337 (53.1)
	sp	16 (40.0)	177 (27.9)
	Unknown	–	67 (10.6)
EDSS, *n* (%)	0–4.0	13 (32.5)	214 (33.7)
	4.5–6.5	18 (45.0)	196 (30.9)
	7.0–7.5	4 (10.0)	136 (21.4)
	8.0–9.5	5 (12.5)	80 (12.6)
	Unknown	–	9 (1.4)
Centre, *n* (%)	WCNN	40 (100)	430 (67.7)
	CX	–	205 (32.3)
Status, *n* (%)	Married/cohabiting		430 (67.7)
	Single		111 (17.5)
	Divorced/separated		69 (10.9)
	Widowed		14 (2.2)
	Working	–	215 (33.9)
	Had help completeing		94 (14.8)
	Mean 100 mm VAS fatigue score (SD, min.–max.)		53.92 (23.85, 0–100)

EDSS: expanded disability status scale;[10] rr: relapsing remitting; sp: secondary progressive; pp: primary progressive.

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distributed (see Appendix 1) with a median score of 60 mm and a modal score of 70 mm.

Semantics of fatigue

Nearly all patients used the word tiredness (or derivatives) to describe fatigue, if not initially then at least in other parts of the interview. However, there was a variety of other words and concepts used when describing fatigue which included: sleepiness and sleeping; a need to rest with or without sleep; weariness; pure muscle weakness and, specifically, use dependent weakness; having no motivation, 'can't be bothered'; being shattered or exhausted; having no energy or being drained of energy (one patient used the word 'enervated', others used the metaphor of recharging/discharging a battery); being 'zonked', 'wiped out' or like 'wilted lettuce'; cognitive problems of poor concentration, being 'drugged', and poor memory; ataxia or incoordination.

The word 'tiredness' had two meanings; that of physical tiredness, including muscle tiring leading to a need to rest without sleep and that of pressure to sleep. Many patients used the different meanings at various times during the interview, which would be clarified by the interviewer.

Symptom framework

The *a priori* part of the framework was based on the principles of clinical description: (1) subjective experience of being fatigued, (2) cadence i.e. variation in the short term, (3) chronicity, (4) precipitating and aggravating factors, (5) relieving factors, (6) severity, (7) associated features. Dictated by the data, the subjective experience was further divided into: (a) motor features, (b) cognitive features, (c) problems centred around motivation and energy expenditure, (d) sleep and behavioural responses and (e) other features. Combination of these topics produced a framework that allowed categorization of all the data.

Definition of the symptom

(1a) Subjective experience: motor features

Nearly all patients had motor features as part of fatigue and these were largely characterized by paresis. Paresis increased as a function of use of muscle more quickly than expected compared to past experience when healthy. Such a phenomenon could be experienced in areas of pre-existing motor deficit or in areas not usually subject to weakness, common examples being dragging of a foot after walking any distance or inability to maintain an erect posture after prolonged standing. In this context, 'heaviness' in limbs or body was a common descriptor. There could be associated sensation of aching in these muscle groups. Paresis affecting the bulbar muscles was also reported during speech with both dysarthria and hypophonia being possible. Concomitant with paresis could be incoordination and tremor. Patients also described difficulties with executing complex movements that were apparent only when feeling fatigued, this seemed to be a loss of access to prelearned skills and examples included problems walking, 'having to think of putting one foot in front of the other', and problems with fine motor tasks. Section 1a of Table 2 gives the prevalence of some of the salient motor features of fatigue, as determined by the questionnaire survey. All themes were endorsed by the majority of MS subjects.

(1b) Subjective experience: cognitive features

Cognitive dysfunction was clearly a feature of fatigue. Mostly, this was an inability to sustain mental functioning when doing mentally intensive tasks such as form filling or working at a computer or doing perhaps more mundane activities such as preparing a meal. There was a perception of increased mental effort, particularly when performing motor tasks and here there is overlap with some of the motor features (section 1a). Cognitive dysfunction was also manifest as poor attention, nominal dysphasia and other problems with memory and recall. Section 1b of Table 2, gives the prevalence of some of the salient cognitive features of fatigue, as determined by the questionnaire survey. All themes were endorsed by the majority of MS subjects.

(1c) Subjective experience: motivation, energy and need to rest

A core component to the conscious perception of fatigue was a sense of lack of motivation to either sustain or complete a task, whether it might be mental or physical, or to begin a new task. This demotivation either occurred because of the development of other features of fatigue e.g. weakness, or inappropriately excessive sense of effort, or was based on past experience when a task had caused fatigue and was expressed as a behavioural response of putting things off or of activity avoidance. The very thought of an action would prevent that action being carried out, there was a sense of 'can't be bothered'. Sometimes, lack of motivation to sustain a task was felt to be involuntary with patients being compelled to stop prematurely, by some unknown force. Striving to counter such feelings, patients often described pushing themselves or forcing

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Table 2 Prevalence of themes within the symptom framework

Section	Framework	Theme	Description	Prevalence % (n = 635)	
1a	SE: motor features	1	Can develop weakness	81.3	18.7
		2	Limbs heavy	83.9	16.1
		3	Use dependent weakness	86.8	13.2
		4	Speech problems	52	48
		5	Coordination worsens through day	65.2	34.8
1b	SE: cognitive features	6	Concentrate on simple tasks	75	25
		7	Mistakes when tired	82.4	17.6
		8	Concentration worsens through day	69.8	30.2
1c	SE: motivation, energy, need to rest	9	Lack energy	84	16
		10	Need day rest	74.2	25.8
		11	Need day sleep	49.2	50.8
		12	Forced to stop activity	77.9	22.1
		13	Put things off	73.9	26.1
		14	Cannot be bothered to do things	79.7	20.3
		15	Thought puts off doing	66.9	33.1
		16	Force self to do things	78.3	21.7
1d	SE: sleep and behavioural response	17	Sleeps in day	50.9	49.1
		18	Do everything in morning	52.7	47.3
1e	SE other1	19	Excessive yawning	47.8	52.2
2	Cadence	20	Occurs quickly	77.7	22.3
		21	Worse in afternoon	66.5	33.5
		22	Carry over	77.7	22.3
		23	Tired most days	76.5	23.5
		24	Weak at rest	60.4	39.6
3	Precipitating/ aggravating factors	25	Physical exertion induces weakness	79.6	20.4
		26	Mental effort worsens fatigue	54.7	45.3
		27	Mental exertion induces weakness	50.9	49.1
		28	Mental dysfunction in heat	62	38
		29	Heat and humidity induce weakness	77.5	22.5
		30	Heat and humidity induce sleepiness	66.1	33.9
		31	Heat and humidity induce general dysfunction	59.9	40.1
		32	Postprandial sleepiness	46.9	53.1
		33	Disrupted sleep worsens fatigue	84.9	15.1
		34	Stress/anxiety worsens fatigue	81.8	18.2
4	Relieving factors	35	Stimulus avoidance	87.4	12.6
		36	Day sleep restorative	64.1	35.9
		37	Day rest restorative	88	12
		38	Prophylactic sleep/rest	61.7	38.3
		39	Paces activities	76.7	23.3
5	Severity	40	Easily tired	86.6	13.4
		41	Exhausted after minimal activity	76.3	23.7
6	Associated features	42	Wake in night for no reason	52.7	47.3
		43	Unrefreshing nocturnal sleep	63.3	36.7
		44	Broken nocturnal sleep	63.7	36.3
		45	Feelings of defeat	67.9	32.1
		46	Important to remain active	96.5	3.5

Grey bars represent the percentage of subjects ($n = 635$) endorsing (ticked agree or strongly agree) each theme. Disagree/ strongly disagree is represented by the white bar. SE: subjective experience.

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themselves to do things; this, in many cases, was felt to be beneficial even though it did not always lead to task completion.

There was a notion that the body had an energy reserve that facilitated activity. Such energy was perceived to be in a fixed quota that could be expended and fatigue was felt when no energy was left. Patients recognized that tasks which seemed to consume an inappropriately large amount of energy were fatiguing. Conversely, fatigue was improved by anything that would raise energy levels. In addition to using the actual word 'energy', it is here that patients would use the metaphor of 'battery' and derivatives of 'draining'.

The conscious sensation of fatigue was not only couched in terms of lack of motivation but also as a positive desire to cease activity and, more specifically, beyond this a desire for a period of rest with or without sleep. Section 1c of Table 2, gives the prevalence of some of the salient motivation and rest features of fatigue, as determined by the questionnaire survey. All themes were endorsed by the majority of MS subjects, apart from needing day sleep that was endorsed by a half of subjects.

(1d) Subjective experience: behavioural response including sleep

A sensation of fatigue led to a marked change in behaviour namely, activity cessation and subsequent rest. Resting could involve either simply being inactive without sleep, often in an environment arranged to be devoid of extraneous stimuli, or could progress to sleep. Patients learned to avoid activity that was potentially fatiguing. Section 1d of Table 2, gives the prevalence of some of the salient behavioural features of fatigue, as determined by the questionnaire survey. Both themes were endorsed by approximately half of the MS subjects.

(1e) Subjective experience: other

Other features included excessive yawning not only when feeling fatigued but also at other times; sweating was also noted as a feature concomitant with feeling fatigued, especially during exercise. Section 1e of Table 2 gives the prevalence of excessive yawning that was endorsed by just under half of the MS subjects.

(2) Cadence

In the main, fatigue was a daily phenomenon. For a small number of patients, fatigue would occur at any time during the day and could even be present on waking, however, for most patients there was a clear circadian rhythm to the development of fatigue. In the morning, normal activity would be well tolerated but by the afternoon, usually 2–3 p.m., any activity would evoke fatigue much sooner i.e. the ease with which fatigue developed was greater, indeed in many cases this facility was so great that fatigue could be felt in the afternoon despite absence of activity. Variation was not only in the time of onset of the development of fatigue, but also in the speed of development: if activity levels were fairly uniform throughout the day then fatigue could be felt building up gradually towards a peak and then gradually subsiding; for some however, the development was quite rapid over minutes. It was when the ease with which fatigue developed was greatest (i.e. in the afternoon) that relieving strategies (section 5) were employed. Relief itself was often rapid with only ten to thirty minutes of rest or sleep required; sometimes less time was required, sometimes more (hours). The ease with which fatigue developed could be altered depending on the amount or type of previous activity, or disruption to the previous night's sleep. Interestingly, this effect of previous activity could be delayed by up to 48 h and so the *'payback'* time for some particularly strenuous event could be one or two days later. In some patients there was little day to day variation, none of the patients noticed overt month to month variation apart from that caused by temperature change (section 4). Section 2 of Table 2, gives the prevalence of some of the salient cadence features of fatigue, as determined by the questionnaire survey. All themes were endorsed by the majority of MS subjects.

(3) Chronicity

On the whole, fatigue had caused disability on a timescale measured in the order of years, in some it appeared as though fatigue had become worse as the duration of MS increased, in others fatigue was no longer a prominent symptom. Marked, long-term changes in fatigue were seen to accompany marked changes in either lifestyle, e.g. stopping work, or disease, e.g. confinement to wheelchair.

(4) Precipitating/aggravating factors

Fatigue could be induced directly by both physical and/or mental activity. Conversely, long periods of inactivity or immobility could lead to the development of fatigue. Fatigue could occur postprandially, many patients, however, felt this to be unrelated to MS. Fatigue was universally associated with relapse, often being viewed as a major feature of that event. Pain, usually neuropathic, was another factor that could possibly exacerbate fatigue, as was intercurrent infection. Disrupted or unrefreshing nocturnal sleep could worsen fatigue. Perhaps the most

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striking precipitating factor was heat. An increase in ambient temperature could incapacitate someone by florid fatigue even if, ordinarily, they had only minimal symptoms. Specifically, it was humidity rather than temperature *per se* that seemed to cause problems, indeed many patients made the distinction between the heat as experienced in Britain to the 'dry heat' experienced in other climates which actually could be beneficial. Other hot or humid environments could cause fatigue such as a warm room, hot shower or a car without air conditioning. Some patients, however, did not notice any changes in either hot or humid weather. Finally, psychological distress worsened fatigue, principally in the forms of anxiety, stress and depression. Section 3 of Table 2, gives the prevalence of some of the salient aggravating features of fatigue, as determined by the questionnaire survey. All themes were endorsed by the majority of MS subjects, apart from mental exertion inducing weakness and postprandial sleepiness that was endorsed by about a half of subjects.

(5) Relieving factors

Many relieving factors were simply the opposite of the precipitating factors, however, some were the same reflecting apparent contradiction in the data. Sleep, in the day, would universally abolish all the features of fatigue. The amount of sleep required varied between 5 min and 3 h. Nearly all patients felt refreshed or 'revitalized' after such sleep, by contrast nocturnal sleep was often unrefreshing. Some patients did not sleep and simply used rest or inactivity to recover from fatigue, again the amount of time required varied from a few minutes to a few hours. Many patients recognized that both physical *and* mental inactivity was required. A few patients found that being physically and mentally active, e.g. during work, actually prevented fatigue. This was distinct from formal, rhythmic aerobic exercise which seemed to have two benefits: in the short term (hours) it could provide a sense of well-being, in the long term it could improve exercise tolerance and thus reduce the ease of development of fatigue. An interesting relieving strategy was that of prophylactic rest or sleep, this occurred as preparation for an event that was anticipated to be fatiguing. Often this was for events in the evening but was also seen for events in the day. Rest would be taken, even if not feeling fatigued at the time, in an effort to 'store up energy' that would then extend subsequent activity duration or performance. This was seen on a larger scale in that patients would try to keep the days preceding an important event relatively quiet. Perhaps related to this was the practice of pacing, which was based on the notion of metered energy expenditure i.e. deliberately limiting the rate of activity in order to avoid developing fatigue. If heat was the precipitating factor then cooling manoeuvres were employed in addition to rest or sleep. It was not obvious that any patient employed active cooling (e.g. cold shower) as prophylaxis in the same way as sleep or rest, although high ambient temperature would be avoided. Finally, some relief was gained from pharmacotherapy, in this sample amantadine was the only agent. This did seem to reduce the tendency for developing fatigue, when effective, with patients finding less need to rest or sleep in the day. Section 4 of Table 2, gives the prevalence of some of the salient relieving factors of fatigue, as determined by the questionnaire survey. All themes were endorsed by the majority of MS subjects.

(6) Severity

There was a wide range of severity of fatigue, however, *all* the patients had at least some of the above features. Mild fatigue could simply be a slight reduction in dexterity in the afternoon. Severe fatigue was all consuming with even the slightest activity requiring great effort and limitation by repeated or prolonged periods of rest. Section 5 of Table 2, gives the prevalence of some of the severity features of fatigue, as determined by the questionnaire survey. Both themes were endorsed by the majority of MS subjects.

(7) Associated features

It was unusual for patients to have uninterrupted, nocturnal sleep. This was mostly due to nocturia or pain, but for some patients nocturnal waking occurred for no obvious reason. Patients commonly found nocturnal sleep unrefreshing. Most patients had a good appetite and in fact there were frequent references to being overweight and some thought this was possibly a contributory factor to fatigue. In some patients that had been on recent, long haul flights, jet-lag was not found to be a problem, particularly in contrast to their partners. Several patients intimated problems with disordered thermoregulation, this was noticed at night either being very cold and under two sets of bedclothes even in warm weather or very hot even in cool weather when a partner was under thick bedclothes. One (postmenopausal) patient regularly felt cold but hot to touch in the day, for which she took paracetamol. Cold weather was noted to worsen spasticity and this was recognized by most as something different to fatigue, although some thought it a possible contributory factor. There were some affective consequences to fatigue, mainly frustration and

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Table 3 Prevalence of grouped themes (constituent themes are given in brackets)

	Theme	Description	Prevalence % (n = 635)
Grouped themes	N1	Cognitive features (6|8|26|28)	87.8 / 12.2
	N2	Motor features (1|2|3|25|29)	96.8 / 3.2
	N3	Abnormal sleep (42|43|44)	86.5 / 13.5
	N4	Rester (17|36|37|38)	93.7 / 6.3
	N5	Heat sensitivity (28|29|30|31)	85 / 15

Grey bars represent the percentage of subjects ($n = 635$) endorsing (ticked agree or strongly agree) each theme. Disagree/strongly disagree is represented by the white bar.

irritation and sometimes embarrassment. Many felt, on occasion, defeated by their symptoms, this was recognized to be detrimental and produced notions of defiance and importance of remaining active. Section 6 of Table 2, gives the prevalence of some of the associated features of fatigue, as determined by the questionnaire survey. All themes were endorsed by the majority of MS subjects.

Homogeneity

There were no features of fatigue which appeared to be exclusively associated with particular time points in the disease or indeed which were specific to disease type, the age or the sex of the subject.

Grouped themes: motor and cognitive features

Table 3 shows the prevalence of the grouped themes. Theme N1 was formed by the operation of logical OR of themes 6, 8, 26 and 28 in order to be representative of cognitive dysfunction. The prevalence of this theme included any subject who had endorsed at least one of any of the constituent themes. N2 was similarly created from themes 1, 2, 3, 25 and 29 in order to represent motor features. Table 4 shows a contingency table for these two themes.

It was very uncommon (1.1% of total) for MS patients to have pure cognitive features of fatigue in isolation from motor features. Slightly more (10.2%) subjects had motor features of fatigue without concomitant cognitive features but the vast majority (86.8%) had both features simultaneously.

Grouped theme: abnormal sleep

Grouped theme N3 was derived from themes 42, 43 and 44 to represent abnormal sleep. Analysis of this grouped theme confirmed a high prevalence of abnormal sleep MS subjects (Table 3).

Grouped theme: rest/sleep as relieving factor

Grouped theme N4 was derived from themes 17, 36, 37 and 38 to represent those that used rest or sleep to gain relief from fatigue. The prevalence of this theme (Table 3) reveals that almost all (>90%) MS patients employed some form of rest as a relieving strategy.

Table 5 shows a contingency table of those who slept in the day and those who found day sleep

Table 4 Numbers of subjects having both cognitive and motor features of fatigue

			Motor features	
			n	*y*
Cognitive features	*n*	Count	12	64
		% of total	1.9	10.2
	y	Count	7	546
		% of total	1.1	86.8

Chi square $P < 0.001$
y-those that endorsed (ticked agree or strongly agree) any of the constituent themes, *n*-those that did not endorse (ticked disagree or strongly disagree) any of the constituent themes. Chi square P = chi-square probability for the 2×2 matrix.

Table 5 Numbers of subjects finding day sleep restorative

			Day sleep restorative	
			n	*y*
Sleeps in day	*n*	Count	179	123
		% of row	1.9	10.2
	y	Count	44	276
		% of row	1.1	86.8

Chi square $P < 0.001$
y-those that endorsed (ticked agree or strongly agree) any of the constituent themes, *n*-those that did not endorse (ticked disagree or strongly disagree) any of the constituent themes. Chi square P = chi-square probability for the 2×2 matrix.

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restorative. Of those that slept in the day, most (86.3%) found the sleep restorative.

Grouped theme: heat sensitivity

Grouped theme N5 was derived from themes 28, 29 30 and 31 and represented heat sensitivity. The prevalence of this theme (Table 3) revealed that 85% of patients admitted to be affected by heat and humidity.

Summary definition

In summary, fatigue is defined as reversible, motor and cognitive impairment with reduced motivation and desire to rest, either appearing spontaneously or brought on by mental or physical activity, humidity, acute infection and food ingestion. It is relieved by daytime sleep or rest without sleep. It can occur at any time but is usually worse in the afternoon. In MS, fatigue can be daily, has usually been present for years and has greater severity than any premorbid fatigue. Appendix 2 provides a reference summary of the features of fatigue.

Discussion

Features of definition

There have been other qualitative studies of fatigue in MS.[11,12] These were mainly concerned with the impact of fatigue, a more usual aim of qualitative research, none had a structured clinical description as presented here. Inevitably, some of the clinical features were elucidated and were similar to the present findings.

One of the first studies of fatigue in MS,[13] identified, by questionnaire survey, the major features of fatigue as motor dysfunction, sleepiness and the need to rest, which were worse in the afternoon and aggravated by heat; there was no mention of cognitive dysfunction. Krupp *et al*.[3] found similar features during an interview-based study of both MS patients and normal subjects. The differences between MS and 'normal' fatigue were the degree of severity, heat sensitivity and symptom impact; cognitive involvement was not commented upon. Both these studies provided a basic clinical description but omitted key features. An internet-based survey of factors affecting MS[14] demonstrated that stress, high temperature, insufficient sleep, hot baths, infection and high physical and mental work 'worsened' MS. Likewise aerobic exercise, cool weather and low humidity 'improved' MS. A diary study of the variability of fatigue, using visual analogue scales to record fatigue severity throughout the day, found that fatigue was worse in the afternoon.[15] Again, these studies support the present results.

All the themes, included in the present questionnaire survey, were endorsed by over 45% of MS patients, and many had much higher prevalence, approximately 80%. This lent validity to the qualitative analysis and suggested that the qualitative results were typical of a larger population.

Some notable features of fatigue in MS that have not been obvious in the literature were: bulbar dysfunction (i.e. dysarthria and hypophonia), loss of access to prelearned skills, onset of fatigue delayed from its precipitating factor with carry over of discrete episodes of fatigue across one or more periods of nocturnal sleep, the intimate relation between cognitive and motor features, the specificity of humidity (as distinct from heat *per se*) as a precipitating factor, stimulus avoidance and the use of rest/sleep/activity avoidance in a prophylactic manner.

The definition of fatigue, as outlined in this present work, was considered to augment the existing definitions, mentioned in the introduction, in that it encompassed not only the quality of the subjective experience of being fatigued but also the aggravating and relieving factors, time course and associated features necessary for making an unambiguous diagnosis without being confounded by the impact of the symptom. Clinical definitions ought to have a physiological basis: the features of the current definition appear to have the potential of physiological interpretation; they certainly pose physiological questions such as: why does high ambient humidity worsen fatigue, why is twenty minutes of daytime sleep restorative whereas many hours of nocturnal sleep may not be, why does cognitive work produce motor dysfunction, what underlies the circadian variation in fatigue, and what is the mechanism to explain prophylactic rest?

Methodology

For deriving the features of fatigue, the semi-structured was considered to be a convenient method with inherent flexibility, not only allowing expression ad libitum from the interviewee but also detailed probing by the interviewer, when necessary, to ensure the meaning of that expression was explicit. There was potential for bias: the interviewer may have let preconceptions regarding fatigue unduly influence not only the interviews themselves but also the data analysis. This was countered by having a second analyser and a large sample size. The interviewees were aware that the interviewer was a doctor and the interviews took place in a

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hospital setting; this may have improved data quality since the focus was on clinical features. Theoretical saturation was achieved after ten interviews; however, further interviews were conducted in order to ensure that the description of the symptom remained consistent across a wide range of disease phenotypes. The unselected method of recruitment also captured patients who may not have regarded their fatigue as being severe enough to take part in the study; it produced a sample with characteristics fairly typical of an MS population. A full range of disease type and a broad range of disability were represented in the sample, the lower age limit of 34 years was not unexpected for a study considering clinically definite MS (patients with clinically isolated syndromes were excluded); a recent population study of MS revealed mean age of onset for relapsing remitting or secondary progressive disease to be approximately 30 years and for primary progressive disease to be approximately 40 years.[16] There was a higher female to male ratio (4 : 1) than the expected ratio of 2 : 1.[16]

Whilst the first sample of forty patients was perhaps large for a qualitative study, it was too small to determine thematic prevalences, which could then be said to be reflective of a larger population. Determining the prevalence of each theme in a larger sample was important in order to discover if any theme was actually very uncommon, having arisen due to some unexpected sampling bias in the qualitative phase. Postal surveys can be efficient ways of collecting data and have the advantage of excluding observer bias but can be susceptible to non-response bias.[17] In the present study, response rates were both reasonable and comparable to others studies.[18] A degree of non-response was expected not only from patients with severe disability or cognitive impairment but also from patients with minimal symptoms, perhaps not regarding themselves as having fatigue. However, the samples were felt to be representative of (and therefore generalizable to) a wider population for three reasons. First, approximately 15% patients, admitted to having been helped to complete the pack. This was likely to be because they had a disability preventing them from completing the pack themselves and suggested that this group of patients, with higher disability, was not systematically excluded. Secondly, the demographic and disease characteristics of the samples were comparable to those of population-based studies[16] indicating no obvious exclusion of particular sub-groups. Finally, the fatigue VAS scores were normally distributed, as might be expected for any symptom in a cross-sectional survey, implying that subjects who did not feel themselves to have fatigue were adequately represented.

Conclusion

A comprehensive definition, in clinical terms, of the symptom of fatigue as experienced by those with multiple sclerosis was described in a medically relevant form. This, not only, may be used as a clinical reference, during assessment of the symptom, but also may facilitate both qualitative and quantitative comparison to the fatigue experienced in other neurological illnesses. By combining possible explanations of the individual features of fatigue, it may be feasible to begin to understand the physiology of the symptom as a whole. Much further work in this direction is required.

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Appendix 1

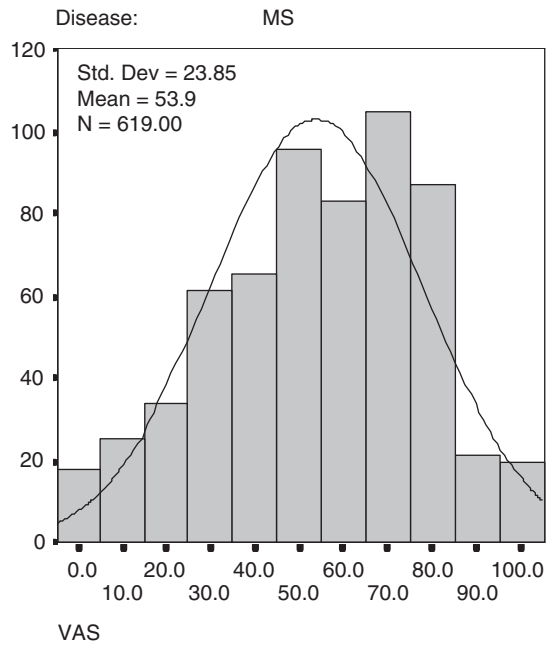


Figure A1. Histogram showing the distribution of fatigue VAS scores for the MS patients. The VAS had anchors of 'lively and alert' (0 mm) and 'absolutely no energy to do anything at all' (100 mm).

Appendix 2

Table A Summary of the features of the symptom of fatigue in MS

Subjective experience	
Motor (all reversible)	Use dependent weakness; bulbar dysfunction; incoordination; tremor; loss of access to prelearned skills
Cognitive (all reversible)	Work-dependent dysfunction; error making; poor attention; nominal dysphasia; other problems with memory and recall
Motivation and rest	Reduced motivation for task completion or initiation; positive desire to cease activity; desire for subsequent rest/sleep; activity avoidance
Behavioural response	Daytime resting/sleep with stimulus avoidance; learned response of activity avoidance
Other	Excessive yawning; sweating
Cadence	Generally circadian (peak in afternoon) with superimposed 'homeostatic' mode with variable onset, from acute to insidious; often rapid offset with rest; carry over possible across periods of nocturnal sleep; immediate or delayed response from precipitator
Chronicity	Generally on timescale of months or years
Precipitating/aggravating factors	Mental or physical activity; relapse; long inactivity; humidity (compounded by heat); food ingestion; intercurrent infection; neuropathic pain; broken/unrefreshing sleep; neurotic states
Relieving factors	Daytime rest/sleep with stimulus avoidance (5 min to hours); nocturnal sleep; prophylactic rest/sleep/activity avoidance; pacing; cooling manoeuvres/heat avoidance
Severity	Wide range from non-intrusive to all consuming
Associated features	Disordered nocturnal sleep; features of possible thermoregulatory dysfunction

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Appendix 3

There are five steps in the framework approach to data analysis:[7]

(1) *Familiarization*: immersion in the raw data.
(2) *Identifying a thematic framework*: identification of key issues, concepts and themes, drawing on *a priori* objectives as well as other themes raised by the respondents themselves. This produces an index of the data in shorter segments, easing subsequent retrieval and analysis.
(3) *Indexing* (*coding*): application of the thematic framework systematically to all data. Involves marking the data with codes from the index or themes, either manually or using dedicated computer software.
(4) *Charting*: rearrangement of the data back to the appropriate parts of the framework and forming a chart.
(5) *Mapping and interpretation*: use of the charts to define concepts, description of phenomena, association between themes and explanation of findings. This will be influenced by the original objectives as well as by themes that have emerged from the data themselves.

Steps 1, 2 and 5 were undertaken by both authors; differences were resolved by consensus. Steps 3 and 4 were performed by R.J.M.

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