Cognition, mood and fatigue in patients in the early stage of multiple sclerosis

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Summary

Question under study: Cognitive impairment occurs during multiple sclerosis (MS) and contributes to the burden of the disease, but its effect in the initial phase of MS still needs to be better understood.

Methods: We prospectively studied 127 early MS patients presenting with a clinically isolated syndrome (CIS) or definite MS, a mean disease duration of 2.6 years, and with minor disability (mean Expanded Disability Status Scale score 1.8). Patients were tested for long-term memory, executive functions, attention, fatigue, mood disorders, functional handicap and quality of life (QoL). Twenty-one CIS patients were excluded from study as the diagnosis of MS could not be confirmed.

Results: Over the 106 MS patients analysed, 31 (29.3%) were cognitively impaired (23.6% for memory, 10.4% for attention and 5.7% for executive functions). Cognitive deficits were already present in CIS patients in whom the diagnosis was not yet confirmed (20%). Impaired cognition was associated with anxiety (p = 0.05), depression (p = 0.004), fatigue (p = 0.03), handicap (p <0.001) and a lower QoL (p <0.001). After adjustment for QoL, handicap, depression, anxiety and fatigue were no longer associated with the presence of cognitive deficits.

Conclusions: In this well-defined early MS group one third of the patients already exhibited cognitive deficits, which were usually apparent in an effortful learning situation and were generally mild. Mood disorders, fatigue, handicap and decreased QoL were all associated with the occurrence of cognitive deficits. QoL itself appeared to take all the other factors into account. Our results confirm the existence of an interplay between cognitive, affective and functional changes and fatigue in early MS.

Key words: multiple sclerosis; cognition; mood; fatigue; functional handicap; quality of life

Introduction

Cognitive deficits have been estimated to occur in up to 70% of patients during the course of multiple sclerosis (MS) [1]. The impairment can affect a variety of cognitive functions, including long-term and working memory [2, 3], interhemispheric transfer, problem solving, executive functions, speed of information processing and attention [4, 5]. Such deficits have previously been evidenced in early MS but the prevalences reported were variable, ranging from 26% to more than 53% depending on the study [6–8]. Incipient cognitive deficits have also been assessed longitudinally, suggesting that such deficits could be used as predictive parameters of MS evolution and severity [9–11]. Most of the MS patients' samples studied were, however, heterogeneous with respect to MS duration and neurological disability, and included either long-lasting or moderate to severe MS subjects. Moreover, the sources of transient symptoms, such as the interval before or after relapses and the use of corticosteroids, as well as the other pharmacological treatments allowed at the time of testing, were not always reported [6, 7].

Fatigue [12, 13] and mood disorders [14–16] have also been suspected of contributing to a decline in cognitive performance, but the relationships between these factors and cognitive efficiency are still poorly understood, especially in early MS. The purpose of the present study was to assess the prevalence of cognitive deficits and to investigate the links between cognitive deficits and MS patients' functional handicap, fatigue, mood disorders and quality of life (QoL) using a well-defined sample of patients in the early phase of MS.

Patients and methods

The study population consisted of 127 patients with a diagnosis of possible MS (i.e. clinically isolated syndrome [CIS]) or definite MS based on the revised McDonald criteria [17, 18]. Of these 127, 72 had relapsing remitting (RR) MS, another 19 had experienced a single relapse and showed dissemination in time and space proven by magnetic resonance imaging (MRI; MRI proven MS), while 36 had CIS with positive oligoclonal bands in the cerebrospinal fluid and a positive MRI. Fifteen of these 36 CIS patients suffered a second relapse during follow-up, thus confirming the diagnosis of MS (mean interval to MS diagnosis confirmation 5.3 months, SD 4.4), and were thus retained for analysis.

To obtain a homogeneous population of early MS patients, only patients with both a minor neurological disability (Expanded Disability Status Scale [EDSS] 0–2.5) [19], and a short MS duration (3 months–5 years) were included. A minimum disease duration of 3 months was stipulated on the basis of the revised McDonald criteria [17, 18], which propose this time lapse following a first neurological episode suggestive of MS before repeating a new brain MRI to prove subclinical dissemination of the inflammatory lesions over time. This allowed us both to increase the proportion of patients with confirmed MS and to reduce as far as possible any influence on cognitive functioning of transient mood dysregulations related to the period close to the announcement of MS diagnosis. A maximum MS duration of 5 completed years was based on current knowledge of MS natural history. Patients receiving interferon-β1a and 1b, antidepressive drugs or amantadine as a symptomatic treatment for fatigue were accepted. Inclusions were performed at distance from exacerbations or corticosteroid treatment (≥6 weeks). All MS patients included had previously signed an informed consent form for participation in this study, which had been approved by the local Ethics Committee.

Cognition

Neuropsychological testing focused on 3 cognitive domains (long-term memory, executive functions and attention) which are commonly impaired in MS. Normative data were available for all the tests used. The presence of a cognitive impairment was defined by a performance 2 standard deviations (SD) below the given mean for a test. Long-term memory was assessed using *Rey's Auditory Verbal Learning Test* (RAVLT) [20], in which patients are asked to learn a list of 15 words presented orally over 5 trials; delayed recall was then tested 40 minutes later.

Executive functioning was evaluated using the *Behavioural Assessment of the Dysexecutive Syndrome* (BADS) [21], which consists of 6 different tasks (Rule shift cards, Action program, Key search, Temporal judgment, Zoo map and the Six elements) and provides an ecological evaluation of several of the executive functions' components, including planning, evaluative judgment and goal-oriented behaviour. Although first developed for the assessment of brain-damaged patients, the BADS has been validated in a large group of patients with various neurological disorders including MS [22]. Finally, the *Trail Making Test* (TMT) [23] was chosen to assess selective attention and processing speed. Impaired patients were those who failed in at least one neuropsychological measure.

Behaviour and functional abilities

A psychiatric interview using a French questionnaire (Questionnaire de Santé du Patient; QSP) was conducted to search for the presence of mood disorders according to the DSM-IV diagnostic criteria [24]. Mood modifications were also quantified by means of the Hospital Anxiety and Depression scale (HAD) [25]. Fatigue was assessed using the Fatigue Assessment Instrument (FAI) [26], a 29-item auto-evaluation scale validated in several pathological conditions including MS. A score for the severity of fatigue was calculated from the 11 FAI items dealing with severity of symptoms. Handicap was evaluated using the London Handicap Scale (LHS) [27], which assesses the 6 items of handicap: mobility, orientation, occupation, physical independence, social integration and economic self-sufficiency; each area was rated on a 6-point scale to provide a global score. Finally, QoL was assessed using the SEP-59 [28], a validated French version of the MSQOL-54 [29] which contains 15 dimensions of daily living validated by factor analysis [28].

Statistical analysis

We used the chi2 test to compare the distributions of categorical variables between two groups, e.g. with and without cognitive deficits. Means of continuous variables were compared using the *t* test, and the Wilcoxon rank test served to compare the mean number of relapses. A logistic regression, including QoL, depression, anxiety, fatigue and handicap scores, was used to determine the factors linked to impaired cognition. The significance of these factors was assessed using the Wald test and the likelihood ratio test. The goodness of the model was assessed by the Lemeshow test.

Results

Demographic and clinical data

Of 127 patients tested, 106 MS patients were finally retained for analysis. Twenty-one CIS patients were excluded as the diagnosis of MS was not confirmed during the follow-up period determined by the time necessary to complete this transectional study. The demographic and clinical data of the 106 MS patients are summarised in table 1. The group included a high proportion of women (70%), reflecting the sex ratio conventionally observed in the general MS population.

Concerning mood variables, 43 patients (47.3%) had a significant score for anxiety and 17 (18.7%) for depression on the HAD, although only 9 of them had a diagnosis of mood disorder according to the DSM-IV criteria. All these 9 patients were treated with antidepressive drugs. Forty-nine patients (53.3%) reported a high fatigue score on the FAI severity subscale. Of these, 6 were treated with selective serotonin reuptake inhibitors and 4 with amantadine. The prevalence of fatigue was 63% among patients receiving interferon-β1a or 1b vs 43% in those untreated (p = 0.06). Moreover, fatigue was significantly associ-

Table 1

Demographic and clinical data at inclusion for the 106 early MS patients retained for analysis.

Gender (women/men)		74 / 32
Mean age (years ± SD)		34.1±9.3
Schooling	≤12 years (minimum compulsory school; %)	13.2
	≥12 years (secondary school; %)	62.3
	Academic background (university; %)	24.5
MS phenotype	RRMS (n)	72
	MS confirmed by MRI (n)	19
	Possible MS[1] (n)	15
MS mean duration [years (SD)]		2.6 (1.8)
Number of relapses since MS onset [mean (SD)]		2.2 (1.4)
EDSS score [mean (SD)]		1.8 (0.4)
Immunomodulatory therapy	Interferon-β 1a or 1b	52
	No treatment	54

[1] MS was confirmed by a second relapse after inclusion in the study

Table 2

MS patients' performance in behavioural assessment.

	Scales		Mean score ± SD	Range (median)	% of patients with abnormal scores	Normative cut-off values
BEHAVIOUR	Mood	HAD-A	7.5±3.7	0–16 (7)	47.3	≥8
		HAD-D	4.2±3.4	0–15 (3)	16.7	≥8
	Fatigue	FAI severity	4.2±1.6	1.1–6.7 (4.5)	53.3	>4.26
	QoL	SEP-59 total score	46.3±11.1	25–73 (46.5)	-	NA (maximum possible score: 100)
	Handicap	LHS total score	8.6±3.3	0–18 (7)	-	NA (maximum possible score: 36)

HAD, Hospital Anxiety and Depression scale; FAI, Fatigue Assessment Instrument; LHS, London Handicap Scale; NA, not available. Remark: Statistics were computed on the available cases for the specific variables (n = 91 for HAD-A and HAD-D, n = 92 for FAI, LHS and SEP-59).

ated with anxiety (HAD-A; p = 0.01) and with depression (HAD-D; p = 0.02). Regarding functional abilities, the mean handicap score was 8.6±3.3 (the maximum score corresponding to the severest handicap = 36) and the mean SEP-59 total score was 46.3±11.1 (the maximum score corresponding to the lowest QoL = 100) (table 2).

Prevalence and nature of cognitive deficits

Thirty-one MS patients (29.3%) presented cognitive deficits (table 3). Memory impairment was the most frequent (23.6% of patients, n = 25), followed by attentional (10.4%, n = 11) and executive deficits (5.7%, n = 6). For 23 patients, cognitive impairment was mild, with only one cognitive domain being 2 SD below the appropriate mean for the test. Eight patients were more severely impaired, having deficits for two cognitive domains (e.g. both memory and attention).

The prevalence of cognitive deficits predominated in RRMS (32%), as compared with MRI-proven MS (26.3%) and with CIS patients who confirmed diagnosis after inclusion (20%). However, this trend was not statistically significant, a fact consistent with our requirement of a homogeneous early MS patients sample.

Comparison of MS patients with and without cognitive deficits

Demographic and clinical variables

MS patients with and without cognitive deficits were comparable in terms of age (36 vs 33 years; p = 0.1), gender (64% vs 72% females; p = 0.4) and education (16% vs 28% highly educated; p = 0.3). They were also similar for disease duration (2.5 vs 2.6 years; p = 0.6), mean number of relapses since MS onset (2.5 vs 2.1; p = 0.1) and EDSS score (1.8 vs 1.7; p = 0.7). The proportion of patients receiving interferon-β1a and 1b was comparable in the two groups (50% vs 49%; p = 0.9).

Mood disorders, fatigue, handicap and QoL

The prevalence of mood disorders and fatigue was significantly higher in patients with cognitive deficits than in those without (anxiety 63% vs 41%, p = 0.05; depression 37% vs 11%, p = 0.004; fatigue 70% vs 46%, p = 0.03). The LHS (10.4 [SD 4.1] vs 7.8 [SD 2.6]) and QoL scores (52.0 [SD 9.8] vs 43.8 [SD 10.7]) also differed significantly between patients with cognitive disorders and those without (p <0.001 for both scales). More specifically, memory deficits were associated with a lower QoL (51.9 [SD 10.7] in patients

Table 3

MS patients' performance in cognitive assessment.

	Scales	Mean score ± SD	Range (median)	% of patients with abnormal scores	Normative cut-off values
	Memory (RAVLT)				
	Learning condition	57.0±8.1	39–72 (58)	12.3	<44
	Delayed recall	12.6±2.1	6–15 (13)	16.0	<10
	Overall deficits			**23.6**	
	Executive functions (BADS)				
	Rule shift cards test	3.3±0.8	0–4	4.0	<2
	Action programme test	3.9±0.3	3–4	0	<2.73
	Key search test	3.2±1.0	1–4	0	<–0.04
	Temporal judgment	2.8±0.8	0–4	2.0	<0.33
	Zoo map test	3.2±0.9	0–4	1.0	<0.18
	Six elements test	3.7±0.6	1–4	1.0	<1.92
	BADS profile score	20.1±2.5	10–24 (21)	2.8	<11
	Overall deficits			**5.7**	
	Attention				
	TMT-A (time)	32.4±12.0 sec	16–83 (30)	1.9	>74 sec
	TMT-A (errors)	0.07±0.35	0–3 (0)	4.7	>1
	TMT-B (time)	72.2±28.0 sec	32–180 (66)	6.6	>131 sec
	TMT-B (errors)	0.24±0.7	0–4 (0)	3.8	>2
	Overall deficits			**10.4**	

(COGNITION)

RAVLT, Rey's Auditory Verbal Learning Test; BADS, Behavioural Assessment of the Dysexecutive Syndrome; TMT, Trail Making Test.

Table 4

Predictive prevalence of cognitive deficits according to each of the 4 factors (mood disorders, fatigue, degree of handicap and QoL) using univariate and multivariate regression. In univariate analysis, cognitive impairment showed the strongest link with low QoL (OR = 6.3, 95%CI [2.1; 18.7]).

	Cognitive deficits		Univariate OR (95%CI)	Adjusted OR Model 1	Adjusted OR Model 2
	Presence (%)	Absence (%)			
Mood disorders	40	20	2.7 (1.1;7.0)	1.9 (0.7;5.2)	1.0 (0.3;3.4)
Fatigue	39	19	2.8 (1.1;7.2)	1.4 (0.5;4.2)	1.1 (0.3;3.5)
Handicap (LHS >10)	60	21	5.7 (2.0;16.5)	3.8 (1.1;12.8)	2.5 (0.7;8.8)
Low QoL (MSEP >45)	46	12	6.3 (2.1;18.7)	–	4.2 (1.0;17.2)

with memory deficits vs 44.5 [SD 10.6] in those without; p = 0.006). In the memory task, delayed recall was associated with a lower QoL (52.1 [SD 8.4] in patients with impaired delayed recall vs 45.1 [SD 11.2] in those with normal delayed recall; p = 0.02), whereas learning capacities were not (51.1 [SD 13.6] in patients with impaired learning vs 45.6 [SD 10.6] in those with normal learning; p = 0.1). Since the prevalence of deficits in attention or executive tasks was low, a specific association between these cognitive domains and QoL was not further investigated.

Mood disorders, fatigue, handicap and QoL were associated with the presence of cognitive deficits. Furthermore, the complete matrix of odds ratio showed that each factor was associated with any of the other individual factors (data not shown).

Logistic model to predict the prevalence of cognitive deficits according to MS patients' characteristics

Table 4 shows the prevalence of cognitive deficits according to the presence or the absence of mood disorders, fatigue, significant handicap or low QoL. The univariate odds ratio (OR) was significantly >1 for each factor (table 4). For mood disorders, OR = 2.7 (95%CI = 1.1; 7.0), for fatigue OR = 2.8, (95%CI = 1.1; 7.2) and for handicap OR = 5.7 (95%CI = 2.0; 16.5). Cognitive impairment had a strong link with low QoL (OR = 6.3, 95%CI [2.1; 18.7]). A first multivariable logistic regression with cognitive deficits as a dependent variable, and handicap, mood disorders and fatigue as independent variables, showed that, after adjustment for handicap, mood disorders and fatigue were no longer linked to cognitive deficits (table 4, model 1). When QoL was added to handicap in the analysis, OR for mood disorders and fatigue became non-significant, indicating that QoL alone contained the entire information – including those of the other factors – for predicting the presence of cognitive deficits (table 4, model 2).

The sample size was rather small to accommodate 4 factors. However, OR were fairly similar when models including fewer variables were tested. Goodness of fit of both models has been successfully checked.

Discussion

Although the cognitive profile of MS patients has been widely documented in more advanced phases of the disease, studies focused on the initial phase of MS have often included populations that were heterogeneous in terms of phenotype, disease duration and disability [9–11]. Using the revised McDonald criteria [17, 18], we tested a large homogeneous group of MS patients with both a short disease duration and a minor neurological disability. The inclusion of CIS patients, who were then excluded from the analysis if MS diagnosis was not confirmed by the end of the study, allowed evaluation of MS patients at the earliest clinically detectable stage of MS.

Twenty-nine percent of our cohort presented cognitive deficits, but the impairment was mild, with generally only one single domain involved. The prevalence of cognitive deficits was comparable in RRMS, MRI-confirmed MS, and CIS patients confirmed as MS after inclusion. Most interestingly, a significant frequency of cognitive deficits was already present in the latter group (20%), suggesting that cognitive deficits may appear even before MS could be confirmed. In this homogeneous early MS group, the frequency of cognitive deficits was not influenced by disease duration, neurological disability or interferon-β treatment. We presented evidence that impaired cognition may be an initial symptom in MS patients without neurological disability, but we also found that it was associated with the presence of mood disorders, handicap and fatigue. This suggests that, at least at the early stage of MS, cognitive efficiency is closely linked to affective factors, and it confirms a complex interplay between fatigue, mood disorders, functional abilities and cognition in MS. More specific social-behavioural changes linked to cognitive deficits were not measured.

Compared with other studies [14–16], we detected a low prevalence of depressive symptoms whereas anxiety was frequent. The fact that we included only MS patients with a short disease duration and minor neurological disability may explain this discrepancy, as well as the fact that the scales we used were different from previous studies. We also confirmed a high prevalence of fatigue, commonly quoted as one of the most disabling symptoms of MS [12, 13] even at an early stage. Mood disorders and fatigue were closely associated, showing that these symptoms may overlap in MS. Given that the depression and anxiety scale we used (HAD) did not include items regarding neurovegetative complaints (possibly overlapping with MS symptoms and fatigue) and included only a single item evaluating mental efficiency, the overlap between mood disorders and fatigue was probably only marginally influenced by the questionnaires we used to measure these symptoms.

In accordance with previous reports, the most frequent cognitive impairment concerned effortful learning capacities, whereas processing speed/attention and executive functions were better preserved. Specific attentional impairment was only rarely found in our group, though we did not specifically focus on sustained attention, which is known to be frequently impaired in the MS process. The high prevalence of learning difficulties in our population is probably due in part to the fact that the RAVLT is a demanding task also sensitive to "effortful" attentional capacities not assessed here. Our results showed a link between cognitive impairment, particularly memory deficits, and the functional handicap and QoL reported by MS patients in daily living. Using a multivariate model including handicap, mood disorders and fatigue, we found that low QoL was an associated factor of cognitive deficits that summarized all the information contained in the other factors.

In conclusion, cognitive impairment is an early MS-related deficit but it remained relatively mild and still with a low prevalence (29.3%) in our cohort. Despite the fact that the topic has already been tackled by other groups in the literature, the clinical interest of our paper is double. On the one hand, it provides arguments for specific difficulties in the early phase of MS in dealing with "effortful" cognitive tasks rather than with individual functions (such as attention, planning or learning). On the other hand, it points to the importance for at least some MS patients of adapting their mental activity from the early symptoms of the disease onwards. Moreover, the results of this study highlight the importance of cognitive tests among patients in the early phase of MS when disability scores are still low, and point to the importance for clinicians of looking for cognitive difficulties, given the impact a cognitive impairment may have on MS patients' social and professional abilities. Cognitive efficiency was also associated in a complex interplay with non-neurological factors such as mood disorders, fatigue and handicap, whereas its association with QoL was major. This low prevalence of cognitive deficits may have been partly influenced by methodological factors, since we performed a neuropsychological assessement aimed at evaluating the 3 cognitive domains classically impaired in MS, in contrast to other studies using full-length neuropsychological batteries [6, 10]. Moreover, our study did not include a control group of healthy subjects and the use of standardised normative data may have contributed to lowering the sensitivity of the assessement. However, we were still able to evidence cognitive impairment at the earliest stage of the disease, that is, in CIS patients whose diagnosis was confirmed only after inclusion in the study (20%). To investigate the ques-

tion whether such early cognitive impairment could be predictive of MS evolution, we plan to assess our cohort longitudinally.

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