

Cognitive Dysfunction in Early-Onset Multiple Sclerosis

A Reappraisal After 10 Years

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Objective: To reassess, in a cohort of patients with early-onset multiple sclerosis, the long-term evolution of cognitive deficits, their relationship to the disease's clinical progression, and their effects on daily life.

Design: Ten years after our baseline assessment, we again compared the cognitive performance of patients and control subjects on a neuropsychological test battery. Clinical and demographic correlates of cognitive impairment and their effects on everyday functioning were determined by multiple linear regression analysis.

Setting: The research clinic of a university department of neurology.

Participants: Forty-five inpatients and outpatients with multiple sclerosis and 65 demographically matched healthy controls from the original sample.

Main Outcome Measures: Mean scores of both groups on the neuropsychological test battery in initial and 2 follow-up evaluations (about 4 and 10 years, respectively); number of cognitively impaired subjects, defined by the number of subtests failed; regression coefficients measuring the relationship between clinical variables and cognitive outcome and between mental decline and every-

day functioning assessed by the Environmental and the Incapacity Status Scales.

Results: Previously detected cognitive defects in verbal memory, abstract reasoning, and linguistic processes were confirmed on the third testing, at which time deficits in attention/short-term spatial memory also emerged. Only 20 of 37 patients who were cognitively unimpaired on initial testing remained so by the end of the follow-up, when the proportion of subjects who were cognitively impaired reached 56%. Degree of physical disability, progressive disease course, and increasing age predicted the extent of cognitive decline. Disability level and degree of cognitive impairment were independent predictors of a patient's handicap in the workplace and in social settings.

Conclusions: In the course of a sufficiently long follow-up, cognitive dysfunction is likely to emerge and progress in a sizable proportion of patients. As multiple sclerosis advances, neurological and cognitive involvement tend to converge. Limitations in a patient's work and social activities are correlated with the extent of cognitive decline, independent of degree of physical disability.

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IT IS NOW recognized that cognitive impairment in multiple sclerosis (MS), occurs in an estimated 30% to 70% of cases.¹ Studies of correlations between cognitive deficits and clinical variables have provided conflicting evidence.²⁻¹² It is probable that cognitive function is more vulnerable in chronic progressive disease than in the relapsing-remitting form,^{5,8-10} although this has not been a constant finding.⁷ In most surveys, the degree of neurological disability has been found either not to correlate with mental changes⁶ or to have only a minor influence.⁷ With few exceptions,^{11,12} the duration of disease has not emerged as a contributory factor.^{2,7} However, most studies on cognitive impairment in MS are cross-sectional in nature. So far, only a few

authors have undertaken longitudinal investigations of the evolution of these disturbances and their relation to the clinical course of the illness. Moreover, the follow-up intervals in these studies have tended to be relatively short, not exceeding 3 to 4 years.^{10,13-18} Furthermore, the effect of cognitive dysfunction on the social and working life of patients is still underestimated since MS is widely viewed as producing neurological defects primarily in the motor sphere.

In an earlier prospective study with a mean follow-up of about 4 years,¹³ we analyzed the development of cognitive deficits in a homogeneous cohort of patients in the initial stages of their disorder. Compared with healthy controls, even subjects whose illnesses were of recent onset and whose levels of neurological dis-

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PATIENTS AND METHODS

Our initial sample consisted of 50 subjects with early-onset MS and 70 healthy controls: we selected controls from the patients' relatives and friends who agreed to participate in the study and used group matching to obtain comparable distributions of sex, age, and educational level.¹³ At the time of the current follow-up, 2 of the patients and 5 of the controls had dropped out of the study and 3 patients had died. **Table 1** presents the main characteristics of the case and control groups during the entire course of our study.

Subjects were excluded if they were receiving psychoactive or steroid treatments or were in an acute relapsing phase. Subjects in the study were assumed not to be receiving any treatment or substance (licit and illicit) that would be expected to interfere with performance on cognitive tests. During the follow-up period, 5 relapsing-remitting patients were treated with a daily dose of 2 mg of azathioprine sodium per kilogram of body weight (mean \pm SD duration, 2.61 \pm 1.98 years) and 7 with interferon β -1a or interferon β -1b (mean \pm SD duration, 2.62 \pm 1.89 years).

We used an extensive neuropsychological battery composed of the following subtests: the Blessed Information-Memory-Concentration Test,²⁰ Digit Forward,²¹ Five Items and Paired Words from Randt's Memory Battery (acquisition and recall after 10 minutes and 24 hours),²² Corsi Block Tapping,²³ Set Test,²⁴ Token Test,²⁵ and Raven's Progressive Matrices.²⁶ Mood disturbances were assessed by the Hamilton Rating Scale for Depression.²⁷ Raw scores were corrected for age and education on the basis of a previous validation study of the test battery.²⁸ In that study, analysis of variance was used to examine statistical differences between various age and education subgroups, and analysis of covariance was used to derive the regression coefficient for correcting scores.²⁸ Interrater and test-retest reliability on the neuropsychological battery were substantial (weighted $\kappa > 0.80$), as were content and concurrent validity.²⁸ Alternative versions of the verbal memory tasks were used in each follow-up session to minimize possible learning effects owing to repeated exposure.

Mean scores of the MS and control groups were compared by the 2-tailed *t* test for independent samples. The

fifth percentile of the control performance on each evaluation was taken as the cutoff point for calculating the number of failed tests; in other words, we considered patients with MS whose scores fell below the fifth percentile of the control group during the same testing period to have cognitive impairment.

We used multiple linear regression analysis²⁹ to test whether different demographic and clinical characteristics can predict a patient's cognitive outcome. Since scores on individual neuropsychological battery subtests were significantly correlated with one another as well as with the total number of subtests failed by the subject ($r > .50$; $P < .001$), we selected the number of failed subtests as the variable representing the extent of cognitive decline. Likely predictors identified on the basis of the literature were age, sex, educational level, disease course (relapsing-remitting vs primary or secondary progressive), disease duration, and level of neurological impairment measured on the Expanded Disability Status Scale (EDSS).³⁰ To reduce these potential variables to a more manageable number for the multiple linear regression, we carried out a preliminary univariate linear regression analysis. The resulting predictors included in the model were age ($\beta = .50$; $P < .001$); disease duration ($\beta = .30$; $P = .04$); disease course ($\beta = .50$; $P < .001$); and EDSS score ($\beta = .60$; $P < .001$), all significantly correlated with the number of failed subtests while sex ($\beta = .14$, $P = .38$) and educational level ($\beta = -.16$; $P = .28$) did not. We again used multiple linear regression analysis to see whether cognitive impairment—expressed in terms of the total number of subtests failed—and other characteristics can predict the extent of a patient's handicap and disability in everyday life. Handicap was assessed by the Environmental Status Scale (ESS), a 7-item scale focusing on, among other factors, work, social life, and need for personal assistance.³¹ Disability was assessed by the Incapacity Status Scale (ISS), a 16-item scale measuring a subject's capacities in self-care and other daily living activities.³² In this phase of the study, the variables entered into the model were the number of subtests failed, age, disease duration, disease course, and EDSS score, which the preliminary univariate analysis had shown to be significantly correlated with ESS and ISS scores ($P \leq .006$).

ability were still low showed significant losses in verbal memory and abstract reasoning on initial testing; these deficits remained substantially unchanged 4 years later, by which time the pattern of cognitive disturbances had expanded to include linguistic functions as well. In this very early stage of MS, the main clinical variables, such as duration, course, and impairment level were poorly correlated with cognitive outcome. On the other hand, the extent of cognitive decline, over and above the degree of physical impairment, proved to be a significant and independent predictor of handicap in a patient's work and social activity.

In this study, we retested the same sample of subjects after another 5 years had elapsed, for a longer-term assessment of the pattern and evolution of cognitive deficits, their relationship to the clinical progression of MS, and their effect on a patient's everyday life.

RESULTS

Mean scores of patients and controls on the subtests of the neuropsychological battery on this third testing are presented in **Table 2**. The patients' deficits on the Blessed Information-Memory-Concentration test, Paired Word Acquisition, Five Items and Paired Words recall tests (both after 10 minutes and 24 hours), Set and Token tests, and on the Raven's Progressive Matrices followed the same pattern as those reported in our previous study.¹³ In addition, disturbances in short-term verbal memory assessed by the Digit Forward test, and in attention/short-term spatial memory as measured by the Corsi Block Tapping test, also emerged. Moreover, subjects with MS failed a significantly greater number of subtests. Finally, the MS group's mean score on the Hamilton Rating Scale for Depression was significantly higher. When a score of 16 on this scale

Table 1. Characteristics of the Study Sample*

	Initial Testing		Second Testing		Third Testing	
	Cases (n = 50)	Controls (n = 70)	Cases (n = 49)	Controls (n = 70)	Cases (n = 45)	Controls (n = 65)
Male:female ratio	18:32	26:44	17:32	26:44	14:31	26:39
Mean SD ± age, y	29.90 ± 8.48	29.30 ± 5.17	34.42 ± 8.32	33.82 ± 5.17	39.13 ± 8.30	39.35 ± 5.20
Mean SD ± educational level, y	11.44 ± 3.61	11.06 ± 3.48	11.41 ± 3.61	11.11 ± 3.45	11.38 ± 3.55	11.34 ± 3.44
Diagnostic level, No. (%) of cases ¹⁹						
Clinically definite	21 (42)	...	30 (61)	...	35 (78)	...
Laboratory-supported definite	24 (48)	...	18 (37)	...	10 (22)	...
Clinically probable	5 (10)	...	1 (2)
Disease course, No. (%) of cases						
Relapsing-remitting	44 (88)	...	38 (77)	...	26 (58)	...
Primary progressive	6 (12)	...	5 (10)	...	5 (11)	...
Secondary progressive	6 (13)	...	14 (31)	...
Mean ± SD disease duration, y	1.58 ± 1.62	...	6.11 ± 2.24	...	11.34 ± 2.31	...
Mean EDSS score ± SD	1.98 ± 1.48	...	2.89 ± 2.39	...	3.48 ± 2.55	...

*EDSS indicates Expanded Disability Status Scale; ellipses, not applicable.

Table 2. Scores of MS and Control Groups on Final Testing*

Neuropsychological Battery Subtests	Mean ± SD		P Value
	Patients With MS	Controls	
Information-Memory- Concentration Test	31.53 ± 3.1	33.74 ± 0.5	<.001
Digit Forward	5.04 ± 1.5	5.54 ± 0.8	.04
Five Items Acquisition	10.27 ± 2.8	10.69 ± 1.4	.35
Paired Words Acquisition	12.04 ± 3.5	14.86 ± 1.3	<.001
Five Items 10-minute Recall	15.38 ± 4.0	17.34 ± 1.6	.003
Paired Words 10-minute Recall	18.67 ± 5.3	21.88 ± 0.7	<.001
Five Items 24-hour Recall	11.40 ± 2.9	16.48 ± 2.4	<.001
Paired Words 24-hour Recall	14.78 ± 4.5	20.74 ± 1.1	<.001
Corsi Block Tapping Test	4.36 ± 1.7	4.95 ± 0.7	.03
Set Test	35.42 ± 3.8	38.85 ± 1.3	<.001
Token Test	33.13 ± 2.4	34.67 ± 0.6	<.001
Raven's Progressive Matrices	36.93 ± 10.4	48.02 ± 4.7	<.001
Hamilton Rating Scale for Depression	14.22 ± 6.25	10.91 ± 3.27	.001
No. of failed subtests	3.87 ± 3.55	1.52 ± 1.5	<.001

*MS indicates multiple sclerosis.

was taken as a cutoff,³³ 22 patients and 12 control subjects were classified as depressed.

To better trace the evolution of cognitive dysfunction, we divided the patients into 3 subgroups based on the number of tests failed: unimpaired (0-2 failed tests), mildly impaired (3-5 failed tests), and moderately impaired (>5 failed tests). The percentage of patients who were cognitively unimpaired decreased in the course of the follow-up, from 74% during the initial evaluation to 51% in the 4-year follow-up to 44% on this most recent retest. Correspondingly, the percentage with mild or moderate impairment tended to increase, reaching 34% and 22%, respectively, by the end of the study (**Table 3**). We also analyzed the cognitive outcome of every patient within each of the subgroups. On the whole, the likelihood that patients would display cognitive deficits tended to increase during the course of our observations. For instance, of the 37 patients classified as cognitively unimpaired on initial testing, 25 remained so on the second test while 12 had

Table 3. Evolution of Cognitive Dysfunction in Patients With MS*

No. of Failed Subtests	No. (%) of Patients		
	First Testing	Second Testing	Third Testing
0-2, no impairment	37/50 (74)	25/49 (51)	20/45 (44)
3-5, mild impairment	4/50 (8)	16/49 (33)	15/45 (34)
>5, moderate impairment	9/50 (18)	8/49 (16)	10/45 (22)

*MS indicates multiple sclerosis.

become mildly impaired (2 of these were reclassified as unimpaired on the final assessment). By the final testing, 18 of the 25 were still unimpaired, 3 had become mildly impaired, and 3 were moderately impaired (1 patient was lost to follow-up). Similarly, of the 4 patients classified as mildly impaired on initial testing, only 1 remained so and 3 had become moderately impaired by the end of the follow-up. Patients initially classified as moderately impaired were still in this subgroup on the final testing (1 subject was reclassified as mildly impaired).

The results of the multiple linear regression analysis are presented in **Table 4**. A higher EDSS score and a progressive disease course (primary or secondary), followed by increasing age, proved to be positively correlated with the severity of cognitive deterioration, defined as the number of tests failed.

The best predictor of the extent of a patient's handicap in social and workplace activities as measured by the EDSS score at the end of the follow-up period was the EDSS score followed by the number of tests failed (Table 4). When we focused on specific ESS items, we found that of the 25 patients with mild or moderate cognitive impairment, 17 had to modify or stop their work activity by the last examination. Moreover, 18 of these patients required substantial help in their personal lives (≥3 hours daily) and the social contacts of 18 were severely limited. Only 2 patients in the unimpaired group showed these limitations. Finally, the only predictor of disability in everyday functioning to emerge from the ISS was the degree of neuro-

logical impairment on the EDSS (Table 4). In this analysis the R^2 values expressed a high accuracy of prediction.

COMMENT

There is a marked lack of information on the natural history of cognitive dysfunction in MS, starting with the earliest phases of the illness. Results obtained from the few studies that have examined the evolution of cognitive functioning in MS have been controversial. Both cognitive preservation¹⁵⁻¹⁸ and progressive deterioration^{10,14} have been reported, and remarkable fluctuations have been noted during very brief follow-up periods.¹¹ Yet while the duration of follow-up has been short, the length of the observation period has been crucial for understanding whether these deficits are likely to progress or to remain stable.

Our findings are based on a relatively small sample of selected patients reporting to a specialized center, which may have led us to overestimate the occurrence of cognitive dysfunction in the MS population as a whole. Nevertheless, by extending the observations of our original cohort to about 10 years, this study has enabled us to expand our knowledge of the natural history of cognitive impairment in this disorder.

As already described,³⁴⁻³⁶ we confirmed that cognitive dysfunction can be detected in some patients even in the incipient phase of MS.¹³ As the disease progresses, the number of patients with cognitive defects tends to increase. The proportion of patients who were cognitively impaired at the end of our study was 56%, a finding consistent with results of previous cross-sectional surveys.¹ With time, the likelihood increases that subjects who do not have cognitive impairment may deteriorate; only 20 of the 37 patients in our sample who did not have cognitive impairment on initial testing remained unchanged by the end of this follow-up. Kujala et al¹⁴ reported that patients who initially did not have cognitive impairment were still unaffected 3 years later, whereas incipient cognitive decline seemed to be widespread and progressive in nature. The difference may be owing to the shorter follow-up in that study, since the appearance and progression of symptoms may require relatively long periods to manifest themselves. In any event, it seems reasonable to assume that, with the progressive buildup of pathological changes within the cerebral white matter, both neurological and cognitive deficits are bound to increase. Magnetic resonance studies, both cross-sectional and longitudinal,^{17,37-39} show a correlation between increased cerebral lesion load and the extent of cognitive deterioration; this relationship is generally stronger than that between cerebral lesion load and degree of physical incapacity. Cognitive defects may thus arise from apparently silent cerebral lesions not detectable by the standard neurological examination or by measurement of disability on the EDSS, a scale heavily weighted for ambulation and motor abilities. Further research carried out with magnetization transfer imaging^{40,41} reveals that in addition to cerebral alterations observable with conventional magnetic resonance methods, it is possible to identify changes in the normal-appearing cerebral white matter that are correlated with cognitive dysfunction.

As the disease progresses, the profile of cognitive deficits tends to expand as processes that initially appear in-

Table 4. Multiple Linear Regression Analysis: Predictors of Cognitive Dysfunction and Handicap in Social Life and Daily Living Activities in the Group With MS

Outcome	Significant Predictors	Coefficient (P Value)	R ²
Cognitive Dysfunction			
No. of failed subtests	EDSS	1.36 (.001)	...
	Progressive course	0.96 (.01)	0.51
	Age	0.33 (.01)	...
Handicap in Social Life and Daily Living Activities			
Total score			
ESS	EDSS	0.62 (.005)	...
	No. of failed subtests	0.24 (.004)	0.88
ISS	EDSS	0.58 (.003)	0.91

*EDSS indicates Expanded Disability Status Scale; ellipses, not applicable; ESS, Environmental Status Scale; and ISS, Incapacity Status Scale.

tact become involved. Among our patients' memory functions, learning (and in particular, recall) and abstract reasoning were the first to be compromised; impairment in linguistic abilities (on the Set and Token tests) and attention/short-term spatial memory disturbances (Corsi Block Tapping) set in later. Language functions have received less attention than other aspects of cognitive decline in MS and have been considered to remain relatively intact. However, carefully conducted studies focusing on linguistic functions of patients with MS^{42,43} have shown their difficulties with tests of naming, reading, verbal fluency, and verbal comprehension. It is hypothesized that such problems are not tied primarily to a breakdown of linguistic processes but rather derive from damage to other cognitive faculties. In general, it is highly debatable whether the heterogeneity of cognitive performance of subjects with MS can be adequately described by a single pattern. Beatty⁴⁴ found that only 12% of patients with MS in his study exhibited the pattern of impairment expected in subcortical dementia. Most of the neuropsychological investigations of patients with MS, including our own, are based on group studies, the conclusions from which may mask individual differences.¹

Analyses of correlations between clinical variables and cognitive deficits have up to now yielded conflicting findings.²⁻¹² When such an association has been found, its most frequent correlates are progressive disease course and degree of neurological disability.^{5,8-10} Among our patients, in contrast to our first study, after a mean disease duration of about 10 years, higher EDSS scores and progressive course of the disorder were correlated with the total number of tests failed. This suggests that, as the illness advances, neurological and cognitive deficits tend to converge. Similarly, in the article by Comi et al,⁴⁵ the onset of secondary progression after a relapsing-remitting phase is identified as a crucial event in the appearance and development of cognitive dysfunction. Age-related memory decline is well documented in the literature as a demographic predictor.⁴⁶

Finally, few authors have specifically assessed the effect of cognitive impairment on everyday life of patients with MS.^{7,13,47} In our study, while neurological impairment on the EDSS proved to be the only significant predictor of disability on the ISS, which mainly reflects motor abilities

in daily living activities, the extent of cognitive decline, independently of the degree of physical disability, again turned out to play a critical role in limiting a patient's social and workplace activities as measured by the ESS.

In conclusion, these results point to cognitive impairment as a common element in the natural history of MS that cannot be ignored. While present at times from the disease's earliest phases, only in the course of a sufficiently long follow-up is such dysfunction likely to emerge and progress in a sizable proportion of patients, although at different rates and with varying degrees of severity. Moreover, cognitive problems, together with neurological disability, constitute the principal determinants of a patient's handicap.

In the past few years, new therapies have been approved for patients with the relapsing-remitting form of MS. These therapies have proven to be effective in reducing the frequency of relapses and in limiting activity parameters as well as the cerebral lesion load on magnetic resonance scans.⁴⁸ On the assumption that the treatment might also positively influence cognitive outcome by containing lesions within the central nervous system, psychological assessment should accompany the neurological examination and become a factor in therapeutic decision-making.

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