Original Research Paper

Multiple Sclerosis

Multiple Sclerosis
0(00) 1–6

DOI: 10.1177/1352458509350311
msj.sagepub.com
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Cognitive impairment predicts conversion to multiple sclerosis in clinically isolated syndromes

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Abstract

Significant cognitive impairment has been found in 20–30% of patients with clinically isolated syndromes suggestive of multiple sclerosis. In this study we aimed to assess the prognostic value of the presence of cognitive impairment for the conversion to multiple sclerosis in patients with clinically isolated syndromes. All patients with clinically isolated syndromes consecutively referred to our centre since 2002 and who had been followed-up for at least one year underwent cognitive assessment through the Rao's Battery and the Stroop test. Possible predictors of conversion to clinically definite multiple sclerosis were evaluated through the Kaplan Meier curves and Cox regression analysis. A total of 56 patients (41 women; age 33.2 ± 8.5 years; expanded disability scale score 1.2 ± 0.7) were recruited. At baseline, 32 patients (57%) fulfilled McDonald's criteria for dissemination in space. During the follow-up (3.5 ± 2.3 years), 26 patients (46%) converted to a diagnosis of multiple sclerosis. In particular, 64% of patients failing ≥ 2 tests and 88% of patients failing ≥ 3 tests converted to multiple sclerosis. In the Cox regression model, the failure of at least three tests (HR 3.3; 95% CI 1.4–8.1; $p = 0.003$) and the presence of McDonald's dissemination in space at baseline (HR 3.8; 95% CI 1.5–9.7; $p = 0.005$), were found to be predictors for conversion to multiple sclerosis. We conclude that cognitive impairment is detectable in a sizable proportion of patients with clinically isolated syndromes. In these subjects cognitive impairment has a prognostic value in predicting conversion to multiple sclerosis and may therefore play a role in therapeutic decision making.

Keywords

multiple sclerosis, cognitive impairment, clinically isolated syndromes

Date received: 29th June 2009; accepted: 30th August 2009

Introduction

The McDonald diagnostic criteria have allowed formal diagnosis of multiple sclerosis (MS) in patients presenting with clinically isolated syndromes (CIS) through a magnetic resonance imaging (MRI) follow-up.[1,2] Given that MS involves ongoing accumulating damage, minimizing damage with an early diagnosis and potentially early treatment would seem important. Evidence from research suggests that many patients with CIS or early MS should be treated with disease-modifying drugs, since disease experience during the first few years is likely to have a significant impact on the long-term evolution of the disease.[3] Reliable prognostic factors, however, are not well established. Awareness of the prognostic features of the CIS can aid subsequent therapeutic decisions. The role of the baseline MRI in defining the risk of developing clinically definite multiple sclerosis (CDMS) is well recognized.[4] As for clinical predictors, the role of multisystem involvement or of an incomplete recovery has been pointed out, albeit less consistently.[4] However, the possible prognostic role of cognitive involvement for clinical conversion has never been investigated. Indeed, cognitive impairment is a core feature of MS and it has been documented in the earliest stages of the disease.[5–8] In particular, recent research has focused on patients with CIS, showing prevalence of cognitive impairment ranging from 27% to 57% according to different reference criteria.[5,6,9,10]

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In this study, we assessed the possible prognostic role of cognitive dysfunction on the development of CDMS in a clinical cohort of subjects presenting with a first episode suggestive of MS.

Methods

This observational study included all patients who, since 2002, were consecutively admitted to the Department of Neurology at the University of Florence for CIS suggesting a demyelinating event. Inclusion criteria were onset of symptoms within three months of clinical, brain MRI and neuropsychological (NPS) examinations and at least a one-year follow-up. The main demographic and clinical data of the patients were prospectively recorded in a computerized database.

We considered any first attack which included monofocal and multifocal symptoms as CIS. Brain MRI was obtained at 1.5 T, including T1-weighted, T1-weighted gadolinium (gd)-enhanced and T2-weighted images. Over the follow-up period a neurological examination was repeated every 3 months, and additionally in the case of relapse, and an MRI scan was performed at least every 12 months. In particular, a relapse was defined according to the McDonald criteria[1] and required confirmation by a neurological examination. In the baseline reference scan (performed within 3 months of the onset of symptoms), we applied the McDonald criteria for dissemination in space (DIS).[1] The MRI interpretation was provided by a well-trained radiologist with specific experience in the use of MRI criteria included in the MDC, blinded to the clinical follow-up.

Cognitive performance was assessed through the Brief Repeatable Neuropsychological Battery (BRB)[11] and the Stroop Test,[12] administered by the same neuropsychologist. The BRB assesses the cognitive domains most frequently impaired in patients with MS and incorporates tests of verbal memory acquisition and delayed recall (Selective Reminding Test), visual memory acquisition and delayed recall (10/36 Spatial Recall Test), attention, concentration and speed of information processing (Paced Auditory Serial Addition Test; Symbol Digit Modalities Test) and verbal fluency on semantic stimulus (Word List Generation).

Moreover, the Stroop word-colour task was administered to evaluate frontal lobe executive functions, which are not assessed by the BRB. A 100-item version of the Stroop Test was applied.[12,13] The procedure comprised three trials. In the first trial, the subject was instructed to read a list of words indicating colours printed in black ink as quickly as possible; in the second trial the subject was instructed to name the colour of strings of dots as quickly as possible; in the third trial (interference condition), the subject had to name the colour of the ink of words indicating conflicting colours as quickly as possible. Performance was assessed by calculating the time required to name 50 items in the third trial (higher scores indicate worse performance).[12,13]

We also assessed depression through the Montgomery and Asberg Depression Rating Scale (MADRS)[14] and fatigue through the Fatigue Severity Scale (FSS).[15]

Performance on each test of the BRB and on the Stroop Test was assessed by applying the available Italian normative values.[16] To assess the predictive value of cognitive impairment we analysed the failure of two or three tests using two standard deviations (SDs) below the mean normative values. In particular, the failure of two tests was observed in 5.5% and the failure of three tests in 2.5% of the subjects in the normative sample.

The study was approved by the Department's Medical Ethics Committee and written informed consent was obtained from all patients.

Statistical Analysis

Parametric and non-parametric statistics were performed according to the distribution of the variables. The χ^2 test was performed to compare categorical variables.

Kaplan–Meier curves and the Cox-regression model for multivariate analysis were used to identify possible predictors of conversion to CDMS. Variables included in the model as possible predictors were age, gender, educational level, age at disease onset, onset symptoms (type of symptoms and mono or multifocal onset), Expanded Disability Status Scale (EDSS) score at onset, McDonald's DIS, presence of cerebrospinal fluid (CSF) oligoclonal banding, presence of fatigue, depression and cognitive impairment. We conducted two separate analyses according to the failure of two or three tests to define cognitive impairment.

SPSS software version 12.1 running on Windows (SPSS, Chicago, IL, USA, 2002) was used.

Results

Among 61 patients with CIS admitted to our Department, five refused NPS examinations. The study sample included 56 patients whose main characteristics are detailed in Table 1.

At baseline, 36 patients (64.3%) fulfilled the DIS-MRI criteria; oligoclonal bands in CSF were present in 30 out 45 patients who performed lumbar puncture (67%). Significant fatigue (FSS score >4)[15] was found in 13 patients (23%), and 16 subjects (28%) were

classified as depressed using a cut-off score of 9 on the MADRS.[14] Fourteen (25%) patients failed at least two tests and eight (14.3%) at least three tests.

The mean follow-up was 3.5 ± 2.3 years (range 1.0–6.0). During this period, 26 patients (46%) presented a second clinical attack, achieving a diagnosis of CDMS. The mean EDSS score at follow-up was 1.2 ± 1.0.

Table 2 shows the proportion of subjects who converted to CDMS using as reference criterion the two different definitions of cognitive impairment. In particular, definition of cognitive impairment as failure of at least three tests ($\geq$2 SDs below the mean of normative values) identified evolution to CDMS in seven out of eight patients (88%). Patients who corresponded to this criterion were not different from the remaining subjects in terms of gender, education, age, symptoms and EDSS at onset, presence of depression and fatigue ($p < 0.1$). Moreover, the two groups did not differ in terms of MRI DIS (75% versus 62.5%, $p = 0.5$) and oligoclonal band presence in CSF (50% versus 46%, $p = 0.5$).

In the Cox regression analysis (Table 3), the failure of at least three tests (hazard ratio (HR) 4.0; 95% CI 1.5–11.1; $p = 0.007$) and the presence of McDonald's DIS at baseline (HR 4.8; 95% CI 1.4–16.4; $p = 0.013$) were the only predictors for conversion to CDMS. Using the other definition of cognitive impairment, only MR DIS predicted evolution to CDMS (HR 4.7; 95% CI 1.4–15.9, $p = 0.013$).

The results were also confirmed using only Barkhof criteria of MRI DIS, without including CSF results. In particular, conversion to CDMS was confirmed as being associated with the failure of at least three tests (HR 3.3; 95% CI 1.4–8.1; $p = 0.009$) and the presence of MRI DIS at baseline (HR 3.8; 95% CI 1.5–9.7; $p = 0.005$).

Finally, we analysed Kaplan–Meier curves for conversion to CDMS using the failure of two or three tests for identifying cognitive impairment (Figure 1). In particular, the differences were significant for patients failing at least three tests, who converted to CDMS six times more rapidly (0.50 versus 3.00 years; $p = 0.002$).

Conclusions

In patients presenting CIS, the crucial question is whether and when they will develop MS. Clinical trials on patients with CIS have pointed to the

Table 1. Clinical and demographic characteristics of the patients at disease onset

Number of patients	56
Gender (Men/Women)	15/41
Education, years (mean $\pm$ SD)	13.3 ± 3.5
Age, years (mean $\pm$ SD)	33.2 ± 8.5
Symptoms	
• Optic nerve	14 (25%)
• Brainstem/cerebellar	13 (23%)
• Spinal	12 (21%)
• Multifocal	17 (30%)
EDSS (mean $\pm$ SD)	1.2 ± 0.7
McDonald's DIS	36/56 (64.3%)
OB presence	30/45 (67%)

SD, standard deviation; EDSS, Expanded Disability Status Scale; DIS, dissemination in space; OB, oligoclonal bands.

Table 3. Predictors of conversion to clinically definite multiple sclerosis

Predictor	HR	95%CI	*p*-value
McDonald's DIS	4.8	1.4–16.4	0.013
Failure of $\geq$3 tests ($\geq$2 SDs below the mean of NV)	4.0	1.5–11.1	0.007
McDonald's DIS*	4.7	1.4–15.9	0.013

HR, hazard ratio; CI, confidence intervals; DIS, dissemination in space at baseline; NV, normative values. Variables included in the models: age, gender, age at disease onset, onset symptoms, expanded disability severity scale score at onset, McDonald's DIS, presence of fatigue, depression and six definitions of cognitive impairment.
*Definition of cognitive impairment based on the failure of two tests.

Table 2. Proportion of patients who converted to clinically definite multiple sclerosis according to the two definitions of cognitive impairment

Definition of CI	Number of patients with CI (%)	Patient with CI who converted to CDMS (%)	Patient without CI who converted to CDMS (%)	*p*-value
$\geq$2 test $\geq$2SDs below the mean of NV	14 (25)	9 (64)	17 (40)	0.10
$\geq$3 test $\geq$2SDs below the mean of NV	8 (14)	7 (88)	19 (40)	0.01

CI, cognitive impairment; CDMS, clinically definite multiple sclerosis, SD, standard deviation; NV, normative values.

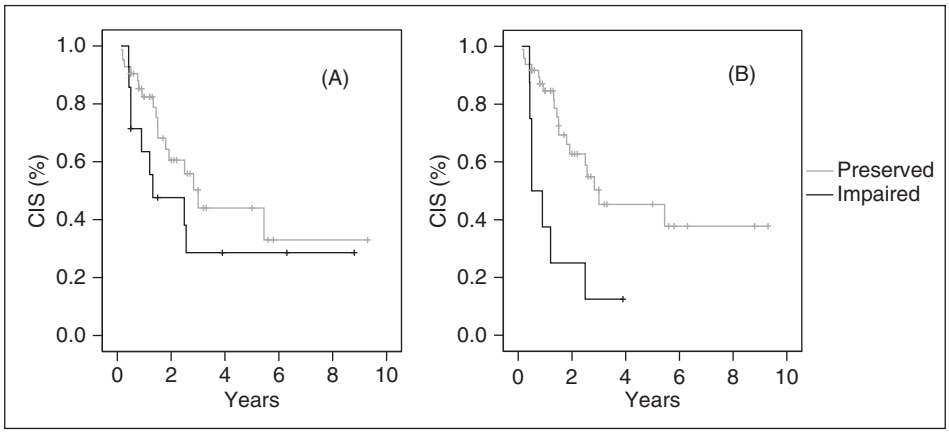

Figure 1. Kaplan–Meier curves of probability of conversion to clinically definite multiple sclerosis in patients during the follow-up according to the two definitions of cognitive impairment. A. Failure of ≥2 tests (≥2 SDs below the mean of NC); B. Failure of ≥3 tests (≥2 SDs below the mean of NC) CIS (%): Percentage of patients with clinically isolated syndromes. Time to conversion to clinically definite multiple sclerosis in patients failing at least three tests versus the remaining patients: 0.50 years (95% CI 0.2–1.06) versus 3.00 (95% CI 0.38–5.63), $p = 0.0018$.

prognostic importance of MRI features at baseline and, less consistently, of multisymptomatic onset.[17–19] However, large observational studies, while confirming the prognostic role of MRI,[20–23] have not identified differences in the clinical behaviour of different CIS topographies. Therefore, to date there is no valid clinical predictor of further evolution in patients with CIS which may assist clinicians in therapeutic decision making. No previous study, however, has taken into account the possible prognostic role of cognitive impairment.

Our results confirm the prognostic role of McDonald's MRI criteria and indicate for the first time a predictive value of cognitive impairment, assessed through standardized and validated neuropsychological tools. Regarding treatment with disease-modifying drugs which, in clinical trials, has been associated with a delay in clinical conversion to MS,[17–19,24] according to the Italian regulatory agency directives, none of our patients with CIS had received such treatment before conversion.

Previous studies showed the presence of cognitive impairment in the early stages of disease,[5,9,25] with different prevalence estimates depending on different definitions. For instance, a study on probable MS patients found that 94% of these had a score of one SD below the mean of normal controls in at least one of the tests administered and 54% exhibited discrete cognitive impairment.[5] However, using more restrictive definitions, such as a Z-score below 1.5 on at least one test[25] or a score below the fifth percentile for controls on at least three tests,[9] the proportion of cognitively impaired patients was 49 and 27%.

In this study, the proportion of patients with cognitive impairment ranged from 14 to 25%. Only the more restrictive definition, however, that presumably indicates a more significant degree of cognitive impairment, was able to discriminate patients who converted to CDMS, whose time to conversion was significantly reduced. Therefore, this stringent definition seems to be the most meaningful from a clinical perspective. Moreover, in the multivariate analysis, the HR associated with the presence of significant cognitive impairment was of the same magnitude of that associated to MRI features. As in everyday clinical practice, in our study we performed only the conventional MRI and did not assess the possible role of brain tissue damage as assessed by new quantitative metrics.[26] In this regard, we hypothesize that cognitive impairment may represent a sensitive marker of more severe changes within the lesions or more disseminated damage in the normal-appearing brain tissue, that is not revealed by conventional MRI. It is probable that quantitative MRI techniques could better reveal the relationships between cognitive impairment and brain tissue damage. Indeed, MS-related cognitive impairment has been consistently associated with brain atrophy,[27] which in turn has been documented in the incipient phases of MS.[28,29] In particular, cortical atrophy seems to be among the major contributors to cognitive impairment in the earliest disease stages.[30]

On the whole, our findings suggest that among clinical variables, cognitive impairment can serve as an early, sensitive marker of short-term disease evolution in patients with CIS. On the other hand, in patients with established disease, cognitive impairment can have a dramatic impact on several aspects of quality of life, independently of the degree of physical disability, affecting the ability to maintain employment, daily living activities, and social participation.[31,32]

Moreover, cognitive impairment can also limit the capacity of the patient to adhere to treatment regimens and to benefit from inpatient rehabilitation.[33] Therefore, the early identification of MS-related cognitive impairment may provide opportunities for early intervention in order to improve the overall prognosis of the disease.

Disclosure

The authors have nothing to disclose.

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