



Cognition in MS as a Marker of Disability Progression: Observations from Real Life

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Introduction

Multiple sclerosis (MS) is a chronic demyelinating disease of the CNS. Cognitive impairment varies across the lifespan and has a profound effect on instrumental activities of daily living. It can occur in the early stages of MS, even in the absence of other neurological deficits [1]. The prevalence of cognitive impairment in adults with MS ranges from 34% to 65%, varying by research setting and disease course [2,3]. Patients with MS with cognitive impairment have lower employment rates, engage in fewer social activities, and are at a greater risk of developing comorbid psychiatric illnesses [1], underlining the clinical and socioeconomic significance of cognitive impairment as a relevant marker of disease severity [4].

Despite all that is known about cognitive impairment in MS and its impact on individuals with MS and their families, cognitive function is still not openly discussed, routinely assessed, or optimally treated in clinical practice [5]. Ample evidence supports early and repeated cognitive assessments and personalized treatments in MS. However, significant barriers prevent the access to neuropsychological testing and rehabilitation. Furthermore, compared to cognitive impairment, physical deficits result to be often privileged by clinicians and overweighed by EDSS [6] in the evaluation of disability progression; cognitive deterioration is seldom considered as a main justification for change of the disease-modifying drug. Finally, cognitive rehabilitation in MS has proven to be effective by many well conducted randomized clinical trials (RCT) [7,8], although –in practice– MS patients with cognitive impairments rarely undergo appropriate cognitive trainings [9].

The aim of this study was to investigate, in a limited sample of Italian professionals, how was the prescription of

neuropsychological assessment conducted in their clinical practice and if they considered it relevant for therapeutical decisions. Furthermore questions about the use of cognitive rehabilitation were asked.

Methods

A group of expert clinicians belonging to the most relevant MS Centres of Lombardia, a region of northern Italy with the same sanitary regulation, were asked to meet twice. They had to be provided with a neuropsychologist dedicated, at least in part, to MS. Seven neuropsychologists and six neurologists belonging to five different MS Centres met twice in May and June 2022. In particular they belong to MS Centre of Brescia Hospital, Milano San Raffaele Hospital, Milano Policlinico Hospital, Legnano Hospital and Como Hospital.

In the first meeting, after a formal presentation (made by FM, a neurologist and CS, a neuropsychologist) of the literature regarding recent advances on cognitive deficits of MS patients, their clinical aspects and on evidences about the effects of cognitive rehabilitation, a consensus was reached by all the participants about the main questions to be addressed by participants. The questions were related to a quantification of the use of cognitive evaluation and cognitive interventions on MS patients afferent to these centres, performed in a 18 month period before the meeting. All the questions proposed were accepted and each neurologist/neuropsychologist of the same Centre was asked to provide answers to be discussed on the next meeting. In the second meeting a pooling of the numerical results was done, a written report for non numerical answers was done (i.e. organization of the activity of both the neurologist and the neuropsychologist, timing and reimbursement of cognitive evaluations and rehabilitations for in and out patients)

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and all the suggestions made by all the participants, in order to improve the neuropsychological evaluation and treatment of patients, were formalized. The following questions were made to the participants, who were asked to answer:

1. How many visits did you do on MS patients in your Centre from January 2021 to June 2022 and which was their MS subtype?
2. How many of them were newly diagnosed patients?
3. How many of the visited patients were submitted to a neuropsychological evaluation in this time range?
4. How many of them had a previous neuropsychological evaluation to be compared with the present one?
5. How many of these were submitted to cognitive rehabilitation? What was the setting (in vs. out patients setting)?
6. Are the neurologists and the neuropsychologists dedicated to MS only or to other pathologies? If to other pathologies what is the mean amount of hours per week dedicated to MS?
7. Which are, in your opinion, the best neuropsychological tests to be used in clinical practice in MS patients?
8. Which were the instruments used and how long lasted cognitive rehabilitation?

Results

In the 18 month period examined, the total number of MS visits was 2565 in Brescia, 2600 in Milan San Raffaele, 500 in Milan Policlinico, 450 in Legnano and 350 in Como Centres (mean 1239, range 350-2600). Data on MS subtypes are shown in Table 1, showing a prevalence in relapsing remitting (RR) MS subtype, compared to primary progressive (PP), secondary progressive (SP) subtypes or clinically isolated syndromes (CIS). The mean number of newly diagnosed MS patients in this time course resulted 46 (range 10-130).

Table 1: Characteristics of MS populations in different MS Centres in 18 months (from January 2021 to June 2022).

	Brescia	Milan San Raffaele	Milan Policlinico	Legnano	Como	Mean
MS patients	2565	2600	500	450	350	1239
Relapsing MS	1946	1820	360	228	264	923
Primary progressive MS	204	182	44	47	17	99
Secondary progressive MS	347	520	78	23	21	198
Clinically isolated Syndrome	0	78	20	6	18	24
Newly diagnosed MS	29	130	42	10	18	46
Patients with Neuropsychological evaluation	80	31	32	10	69	44
Patients with previous Neuropsychological evaluation	30	10	0	4	28	14,4

In the same period the number of patients evaluated by neuropsychologists was 80 in Brescia, 31 in Milan San Raffaele, 32 in Milan Policlinico, 10 in Legnano and 69 in Como MS Centres (mean 44; range 10-80). A minority (72) of the whole sample of MS patients resulted to have a previous cognitive evaluation for comparison (mean 14,4; range 0-30). In 22 out

of these 72 cases, the repeated neuropsychological evaluation showed a cognitive worsening (defined as a worsening of the corrected score in at least one test in the battery used for evaluation). In particular 12/30 worsening patients were found in Brescia, 4/10 in Milan San Raffaele, 5/28 in Como and 1/4 in Legnano Centres. Milan Policlinico Centre did not repeat cognitive evaluations in any patient during this time course and was not able to compare previous cognitive status. In the whole patients' population considered 10 patients only had a baseline (intended as a cognitive evaluation performed close to the diagnosis of MS) cognitive evaluation. Results on cognitive rehabilitation showed that cognitive rehabilitation was practiced in two MS centres only. In Brescia Centre 25 patients were treated as out-patients for a duration of three months twice a week; in San Raffaele Centre only 6 out-patients were treated for a 10 weeks mean duration with weekly sessions and 13 in-patients (admitted in a Rehabilitation Unit for physical rehabilitation) were also treated with daily sessions for the whole duration of their stay in the rehabilitation Unit. In the other centres cognitive rehabilitation was not done for several reasons, i.e. insufficient availability of neuropsychologist, lack of reimbursement of cognitive rehabilitation by Health Care System to Neurology units, problems in organization for patients who still work. Only two neurologists (Brescia and Milan Policlinico) did change the disease modifying therapy, on the basis of a documented cognitive worsening alone, without a change in MRI or other Functional scales of the EDSS.

In each of the five MS centres all the neurologists resulted to be regularly hired by the Hospital; on the other hand all the neuropsychologists were not under public employment contract, but were freelance. While neurologists were specifically dedicated to MS patients, neuropsychologists were also employed in other pathologies, mainly dementia or post stroke cognitive deficits. Hours per week specifically dedicated by each neuropsychologist to MS patients resulted to be 10 in Brescia, 20 in Milan San Raffaele, 2 in Milan Policlinico, 2 in Legnano and 8 in Como Centres. Como and Milan San Raffaele centres had the greater available neuropsychologist's time for MS patients (one and a half hour/patient for Milano San Raffaele and Como); 15'/patients for Brescia and 20'/patient for Milano Policlinico and Legnano Centres. All the centres had one available Neuropsychologist, except Milano San Raffaele and Brescia Centres who had three and two respectively.

In all the MS Centres neuropsychological evaluations were not synchronous with neurological evaluations, but were performed days/months after the visit (depending on the waiting time of the neuropsychologist). Results of neuropsychological evaluations were returned to the neurologist in different times: a week after testing in Brescia Centre, in the remaining cases tests' results were given directly to the patient, who was in charge of returning the report to the neurologist at the following scheduled visit.

Neuropsychological tests used by each centre are reported in Table 2, showing good agreement about the Rao Brief Repeatable Battery (BRB) across Centres and other tests, including fatigue or depression questionnaires [see tests' References from 10 to 31]. Older patients, in San Raffaele

Table 2: Neuropsychological tests used by each Centre.

Spedali Civili BS	S. Raffaele Milano	Ospedale Valduce Como	Legnano	Policlinico Milano
	Under 52 years old patients:			
	- The Rao's Brief Repeatable Battery (RAO) ¹⁰			
- The Rao's Brief Repeatable Battery (RAO) ¹⁰	- Short story ¹⁴			
- Wisconsin Card Sorting Test (WCST) ¹¹	- Token Test ²¹			
- The Delis–Kaplan Executive Function System (D-KEFS) ¹²	- Verbal Fluency test ¹⁷			
- MMSE ¹³	- Benton Test ²²			
- Short story ¹⁴	- Stroop Test Short Version ²³			
- Rey's Complex Figure Test ¹⁵	- Wisconsin Card Sorting Test WCST ¹¹	- The Rao's Brief Repeatable Battery RAO ¹⁰	- The Rao's Brief Repeatable Battery RAO ¹⁰	- The Rao's Brief Repeatable Battery RAO ¹⁰
- Trail Making Test (TMT) ¹⁶	- The Delis–Kaplan Executive Function System D-KEFS ¹²	- Stroop Test Short Version ²³	- MMSE ¹³	- Beck depression inventory–II BDI-II ¹⁹
- Verbal Fluency test ¹⁷	- Digit Span ²⁴	- Wisconsin Card Sorting Test WCST ¹¹	- Memoria di prosa ²¹	- Beck depression inventory–II BDI-II ¹⁹
- *Aachen Aphasia Test (AAT) ¹⁸	- MMSE ¹³	- Beck depression inventory–II BDI-II ¹⁹	- Trail Making Test (TMT) ¹⁶	- Measuring the functional impact of fatigue (MFIS) ³¹
- Beck depression inventory–II (BDI-II) ¹⁹	- Token Test ²¹	- The fatigue severity scale ³¹	- Test dei giudizi verbali ²¹	
	- Attention Matrices Test ²⁵		- Test delle stime cognitive ²¹	
	- Rey's Complex Figure Test ⁶		- Boston Naming Test ³⁰	
	- Rey auditory-verbal learning test ²⁶		- Verbal Fluency test ¹⁷	
	- Verbal Fluency test ¹⁷			
	- Standard progressive matrices (Raven SPM) ²⁷			
	- Clock Drawing Test ²⁹			
	- Symbol digit modalities test (SDMT) ²⁸			

*Only in case of language disturbances.

Centre, were evaluated with different instruments, usually used for dementia. BICAMS [32] and MACFIMS [33] were not currently used by any of the neuropsychologists. Regarding the limited use of worsened cognition as a marker of disability progression leading to possible change in therapies, the majority of the neurologists considered a problem the paucity of data on the efficacy of DMT in limiting the progression of cognitive deficits and the fact that there is no agreement on when a change in cognitive performance can be considered indicative of a clinical worsening of disability.

Following a discussion on the results of this survey, the suggestions provided by neurologists and neuropsychologists in order to better include cognitive deficits in definition of disability were the following:

1. Improve the availability of neuropsychological personnel for MS population of patients in order to improve cognitive evaluation and rehabilitation of patients. A dedicated psychologist for MS patients should be ideal
2. Prescribe all the patients a baseline neuropsychological evaluation by using a sufficiently complete tests battery. This evaluation should be done within a six month period from the diagnosis. This baseline evaluation should be used as a comparator with the following evaluations. The most frequently used BRB battery should be associated with a test examining executive functions. If time consuming an option would be a wider use of BICAMS in clinical practice.
3. Prescribe follow up evaluations regularly: repeat the same evaluation after one year if a deficit in any of the baseline test was present, after two years if all the tests resulted normal. Proceed at least with two years intervals in the follow up and use alternative forms of the tests to avoid learning.

4. Only for patients with long lasting normality of evaluations (proposed 5 years stability in cognitive evaluation) a five year interval should be considered with extended testing, but short screening tests (SDMT) is yearly advisable.
5. Frequent interaction between neuropsychologist and neurologist should be ensured in order to facilitate the consideration of cognitive worsening as a measure of disability progression. This may be better organized if the psychologist can examine patients within the MS Centre and directly communicate to the neurologist tests' scores.
6. In case of cognitive worsening in one or two functions, neuropsychological rehabilitation should be prescribed for at least three months, in case of function specific cognitive training. If the subsequent evaluation at the end of the training shows an amelioration of the deficit, no other actions are needed and regular annual follow up is prescribed. If a worsening evaluation or the profile is unchanged this should be considered as a possible indication of cognitive progression that may merit a therapeutic change
7. Regarding EDSS score, a change in FS cerebral function would be advisable. In order to avoid subjective evaluations of patient's cognition, one option could be incorporating objective results of neuropsychological testing into this score. This could be done after more research will be done on the validation of this procedure (i.e. number of SD below norms in each test or number of impaired tests corresponding to different EDSS Functional Scores in cognition).

Discussion

Our retrospective study investigated, in five MS Centres of Lombardy (Italy), to what extent MS patients underwent

cognitive evaluation, how it helped clinical decisions in clinical practice and how often and with which procedures cognitive rehabilitation was conducted. These data come from a relatively small and homogeneous territory of Italy, from a social and welfare point of view in which, however, the figure of the neuropsychologist is present in every MS Centre. Despite this, results generally show limited prescriptions of cognitive evaluations in patients and an infrequent repetition of cognitive assessment in MS population. The small number of the repeated assessments causes the impossibility of an identification of cognitive deterioration on a large scale. This necessarily implies that there is a strong limitation to the use of cognitive impairment as an indicator of disability progression in clinical practice. Consequently, the decision of a therapeutic change based on the progression of cognitive disability only, resulted to be very rare in these patients' population, thus limiting the potential therapeutic action of clinicians on disease progression.

Evidences from clinical trials clearly show that disease-modifying treatments (DMTs) are the gold standard in MS therapy, although their benefits are usually measured on diverse outcomes including annualized relapse rate (ARR), neurologic disability measured by the EDSS, or MRI metrics of disease burden, with escalation therapies having a greater impact on disability worsening, lesion activity, and load than platform therapies [34]. Unfortunately, published data on the effects of DMTs on cognition [35] in patients with MS, are less numerous. Although it is worth noting that available single studies hints toward an overall beneficial effect on cognitive functioning for a range of DMTs [36, 37] and a recent meta-analysis shows greater impact of monoclonal antibodies and natalizumab over platform and oral therapies on improvement in SDMT over a decade follow up [38]. These data should support the clinicians in the decision about the usefulness of an escalation therapy also in cases of a well documented isolated cognitive worsening in MS patients, particularly if not susceptible of improvement with appropriate cognitive training and rehabilitation. From our survey, cognitive rehabilitation resulted to be infrequently used in MS patients as well; variable durations and settings (in or out-patient setting) for cognitive rehabilitation across centres was also observed. Literature on the efficacy of rehabilitation in MS cognitive impairment is encouraging: several studies clearly show evidence based data on the effectiveness of several techniques, ranging from PC assisted, to neuromodulation associated rehabilitation and aerobic training [39,40,41]. These data should be used in clinical practice and a greater utilization of cognitive rehabilitation procedures would be advisable.

In this retrospective study, conducted on a small territory of north Italy with the same health care system, neurologists were all dedicated to MS care and neuropsychologists all showed expertise about the appropriate tests to be used in MS patients and their interpretation. Though, very few patients resulted to have received a regular cognitive assessment, allowing appropriate monitoring of cognitive deterioration over time. The main obstacle to a correct use of cognitive data in general disability evaluation of MS patients was considered to be the

lack of resources and the insufficient integration between neuropsychological and neurological activity at the single patient's level. Although these results are not generalizable to the entire MS population, they are interesting as they give, at least in part, an explanation to the low consideration of cognitive impairment of MS patients in clinical practice. The lack of psychological resources seems to be relevant, as – despite consensus on the issue- without more availability of neuropsychologists, it would be challenging to provide better cognitive care to MS patients. A different organization of each visit in clinical practice, with the possibility for MS patients to be submitted to both neuropsychological testing and neurological exam in the same occasion, is also advisable. This could allow a better interaction between neurologist and neuropsychologist, similarly to what happens in the case of other neurological condition for which cognitive assessment is an integral part of neurological objectivity (i.e. dementia, extrapyramidal disorders). Furthermore, given the widespread use of EDSS and its scarce sensitivity to cognitive domain, a more standardized grading of FS Cerebral Function in the EDSS would be useful. In our sample of neurologists and neuropsychologists BRB was the most frequently used tests' battery. Surprisingly BICAMS and MACFIMS were not. This may be due to the more long lasting use of BRB in Italy; furthermore whereas BICAMS is sensitive and requires short time to be administered, MACFIMS, which is more complete and explores more functions, requires time. Probably a better integration between BICAMS, BRB as well as SDMT -as a screening test-, would allow greater prescription of cognitive testing. Rehabilitative procedures should also be implemented in MS patients, on the basis of the clinical evidences. This could be done by uniform reimbursement of outpatient rehabilitative services, not limiting this to in patients, as frequently happens. MS patients are often young and still working persons, so that out patients or home based procedures could be better suited for them. Although results of this retrospective survey are not generalizable to the whole MS Italian population, the social homogeneity of the geographical territory examined suggests that, at least in north Italy, these findings are reasonably replicable.

Administrative decision about health care system and organization within MS Centres could take in consideration the present data, in order to customize a better clinical care of patients by implementing regular and repeated cognitive evaluations in MS patients, more frequently prescribed cognitive rehabilitation and greater integration between neurologists and neuropsychologists. MS as a disease entity, is not only focal inflammation, relapses and focal MRI activity, but a more diffuse smouldering pathological process that affects the entire CNS and cognitive deficits are sensitive measures of this process. We therefore need to go beyond the concept of no evident disease activity (NEDA) or relapse associated worsening (RAW), but focus on other pathological processes in order to delay or prevent the slow loss of neurological function in people with MS [42].

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