MULTIPLE SCLEROSIS JOURNAL | MSJ

Short Report

Ecological impact of isolated cognitive relapses in MS

Riccardo Meli, Luca Roccatagliata, Elisabetta Capello, Nicolò Bruschi, Antonio Uccelli, Gianluigi Mancardi, Matilde Inglese and Matteo Pardini

Multiple Sclerosis Journal

1–4

DOI: 10.1177/1352458518813722

Abstract: Isolated cognitive relapses (ICRs) are transient deficits in cognitive performance that are the only presentation of a multiple sclerosis (MS) relapse. Here, we evaluated the impact of ICRs on cognitive difficulties in daily activities (assessed with the Multiple Sclerosis Neuropsychological Screening Questionnaire, Informant Version (MSNQ-I)) to characterize ICRs' clinical relevance. We used 2-year-long retrospective data to compare 15 relapsing-remitting MS (RRMS) patients with ICRs with 57 RRMS patients presenting an asymptomatic gadolinium enhancing lesion (and no-ICRs). ICRs were associated not only with neuropsychological performance decline but also with an increase in the daily cognitive difficulties. These findings support the ecological relevance of ICRs.

Keywords: Relapses, cognition, quality of life

Date received: 20 August 2018; revised: 17 October 2018; accepted: 25 October 2018

Correspondence to:
M Pardini
Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics and Maternal and Child Health, University of Genoa, Largo Daneo 3, 16143 Genoa, Italy.
matteo.pardini@unige.it

Riccardo Meli
Elisabetta Capello
Nicolò Bruschi
Antonio Uccelli
Gianluigi Mancardi
Matteo Pardini
Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics and Maternal and Child Health, University of Genoa, Genoa, Italy/IRCCS Ospedale Policlinico San Martino, Genoa, Italy

Luca Roccatagliata
IRCCS Ospedale Policlinico San Martino, Genoa, Italy/Department of Health Sciences, University of Genoa, Genoa, Italy

Matilde Inglese
Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics and Maternal and Child Health, University of Genoa, Genoa, Italy/IRCCS Ospedale Policlinico San Martino, Genoa, Italy/Departments of Neurology, Radiology and Neuroscience, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Introduction

Transient cognitive deficits have been shown to be present during multiple sclerosis (MS) relapses, both associated with other sensory-motor symptoms[1,2] or as their only presentation (i.e. isolated cognitive relapses (ICRs)).[1,3]

ICRs have been shown to be associated with long-term cognitive decline in MS, thus hinting to their usefulness to recognize patients at risk to develop neuropsychological impairments.[3] Previous work suggests that ICRs are independent from increases in fatigue levels and depression and are not associated with self-report changes in daily activities.

Here, to better define the ecological validity of ICRs, we evaluated their impact on an informant-based measure of cognitive decline, the MS Neuropsychological Screening Questionnaire, Informant Version (MSNSQ-I).[4] The MSNSQ-I probes the impact of cognitive deficits on daily functioning and has been shown to correlate well with cognitive performance.[5] An association between ICRs and MSNSQ-I changes could be an useful approach to screen for ICRs in the MS population and could allow to evaluate the impact of ICRs on daily activities.[4]

Methods

Patients

In this retrospective study, we evaluated all relapsing-remitting MS (RRMS) patients enrolled in our center during routine clinical care between 2009 and 2017 with the following characteristics: (1) Expanded Disability Status Scale (EDSS) < 6.0; (2) at least one gadolinium enhancing lesion (gad+) at a brain magnetic resonance imaging (MRI) scan; (3) at least three longitudinal neuropsychological evaluations (described below), one of those performed in the year preceding the gad+ scan (t0), and the others in the month (t1) and the year (t2) following the gad+ scan; (4) no changes in EDSS score or therapy with corticosteroids between t0 and t2; (5) at least 8 years of formal education; and (6) normal baseline Symbol Digit Modalities Test (SDMT) performance. The presence of a gad+ lesion was defined as any area characterized by increased signal on T1 sequences obtained by contrast injection, with respect to the same location on pre-contrast T1 weighted images, that could not be considered due to small vascular structures. Subjects gave written consent to all procedures, which were approved by the ethics committee.

Table 1. Demographic, clinical, and cognitive data for the isolated cognitive relapse (ICR) and no-ICR groups.

	ICR	no-ICR	ICR versus no-ICR
No. of subjects	15	57	–
Age (years)	43.3 ± 3.8	42.6 ± 3.5	$p=0.530$
Gender (female/male)	10/5	42/15	$p=0.529$
Education (years)	12.9 ± 4.0	13.4 ± 3.9	$p=0.530$
EDSS, median (range)	2.0 (1–4)	2.0 (1–4)	$p=0.792$
SDMT scores			
T0	51.9 ± 3.8	51.3 ± 3.7	$p=0.612$
T1	43.0 ± 3.5	52.5 ± 3.4	$p=0.001$
T2	47.6 ± 3.2	52.9 ± 3.1	$p=0.010$
MSNQ-I scores			
T0	15.7 ± 2.2	15.4 ± 2.8	$p=0.728$
T1	24.1 ± 3.5	14.1 ± 2.0	$p=0.001$
T2	18.3 ± 3.0	14.5 ± 1.9	$p=0.013$
MSNQ-S scores			
T0	15.0 ± 2.3	14.1 ± 3.6	$p=0.421$
T1	15.3 ± 3.4	14.5 ± 3.3	$p=0.289$
T2	14.6 ± 3.6	15.3 ± 3.6	$p=0.514$
HADS-D scores			
T0	1.5 ± 0.8	1.7 ± 0.5	$p=0.326$
T1	1.3 ± 0.6	1.5 ± 0.7	$p=0.361$
T2	1.4 ± 0.8	1.3 ± 0.6	$p=0.622$

ICR: isolated cognitive relapse; EDSS: Expanded Disability Status Scale; SDMT: Symbol Digit Modalities Test; MSNQ: Multiple Sclerosis Neuropsychological Screening Questionnaire (Informant Version (MSNQ-I); Self-report Version (MSNQ-S)); HADS-D: Hospital Anxiety and Depression Scale, Depression Score.

Neuropsychological protocol and ICR definition

The following tests were collected at all time points: SDMT[6] (higher scores represent a better performance), Informant and Self-report Versions of the MSNQ (MSNQ-I and MSNQ-S;[7] the MSNQ evaluates the impact of cognitive deficits on daily functioning; higher scores represent a worse performance),[4] and Hospital Anxiety and Depression Scale (HADS).[8] In our sample of otherwise asymptomatic MS patients presenting with a gad+ lesion at a routine brain MRI scan, ICRs were defined as the presence at the time of the MRI of a SDMT score lower of at least 4 points compared to SDMT evaluations at and both t0 and t2.[3] A 4-point SDMT decline has been associated with clinically relevant outcomes such as change in employment status.[6]

Statistics. ICR and no-ICR group comparisons at the three time points were performed using repeated measures analyses of covariance (ANCOVAs; Time (t0 vs t1 vs t2) versus Group (ICRs vs no-ICRs), controlling for age and education) independently for SDMT, MSNQ-I, MSNQ-S, and HADS-D. Statistical significance was set at $p=0.05$.

Results

Patient population

Demographic, clinical, and cognitive variables are reported in Table 1. In total, 72 RRMS subjects were included in the study, 15 presenting with and 57 without an ICRs (ICR and no-ICR groups, respectively). Of these, 15 patients were previously reported (3 in the ICRs+ group) in a previous study on the definition of ICRs.[3] There were no significant differences between the two groups in demographics or baseline cognitive evaluations (Table 1). No subjects were treated with corticosteroids.

SDMT and MSNQ-I

There were significant Time ($F=41.9$, $p=0.001$) and Group × Time interaction ($F=38.1$, $p=0.001$) effects on both SDMT (Time: $F=41.9$, $p=0.001$; Group × Time: $F=38.1$, $p=0.001$) and MSNQ-I scores (Time: $F=9.1$, $p=0.001$; Group × Time: $F=10.2$, $p=0.001$). In the ICR group, SDMT and MSNQ-I scores at t1 showed a significantly lower cognitive performance (i.e. lower SDMT and higher

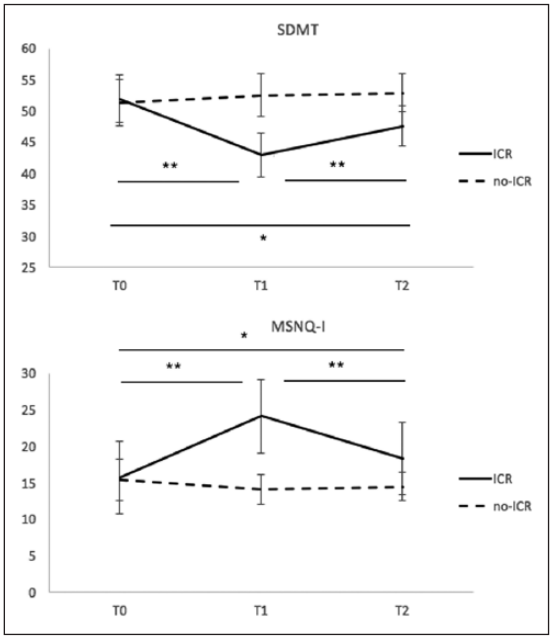

Figure 1. SDMT (upper panel) and MSNQ-I (lower panel) scores in ICR and no-ICR subjects with post hoc paired samples contrasts *p* values.
*$p < 0.05$; **$p < 0.001$.

MSNQ-I scores) compared to all other time points (Figure 1), while no significant difference was observed for both measures in the no-ICR group across time points.

MSNQ-S and HADS-D

There were no significant main effects or interactions on MSNQ-S and HADS-D scores in our population.

Discussion

Here, we showed that during ICRs, not only there is a reduction of objective cognitive performance (SDMT scores) but also that this change in cognition is detectable by an informant and it is associated with changes in daily functioning (MSNQ-I scores), without a change in self-evaluated cognitive abilities.[5,9] This observation confirms the ecological validity of ICRs and strengthens our hypothesis that the associated change in cognition is relevant for daily activities. Indeed, the parallel change over time of both SDMT and MSNQ-I supports our previous proposal of ICR inclusion among the acknowledged MS relapse presentations.

From a methodological point of view, our results suggest that the MSNQ-I represents a time-convenient tool to assess ICRs in the clinical setting and potentially also at home. The inability of patient self-report measures to capture ICRs is in line with both validation studies of MSNQ and our previous work.[3] This confirms that self-evaluation instruments are not suitable to capture MS cognitive impairment.

These results suggest that ICR evaluation and neuropsychological assessment should be more widely used in MS clinical practice. Indeed, the presence of cognitive deficits is associated with a worse overall prognosis in MS, and cognitive decline can be present in those subjects with an otherwise stable disease as assessed with "no evidence of disease activity" criteria.[10]

Caution is needed in the interpretation of our findings, given the retrospective nature of the study as well as the sample size that however depends on the rigid criteria we used to define ICRs. Moreover, in this study, cognitive decline was defined using the SDMT only; future studies focusing on the impact of IRCs on other cognitive tests are warranted.

Despite these limitations, the data presented here point to the relevance of informant-based measures to assess ICRs as well as to the ecological validity of the ICR construct. Future studies are warranted to confirm these observations in a larger MS sample.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: R.M., L.R., E.C., N.B. do not report any conflicting interests. A.U. as received consulting honoraria and/or speaker fees and basic science study grants from Biogen Idec; consulting honoraria and/or speaker fees from Genzyme, Roche, Sanofi Aventis, and Teva; consulting honoraria and/or speaker fees and a basic science study grant from Novartis; consulting honoraria and/or speaker fees and a basic science study grant from Merck Serono. G.M. has received honoraria for lecturing, travel expenses for attending meetings, and financial support for research from Bayer Schering, Biogen Idec, Sanofi Aventis, Teva, Genzyme, and Merck Serono. M.I. has received research grants from the NIH, NMSS, Novartis, and Teva Neuroscience. M.P. receives research support from Novartis and received honoraria from Merck and Novartis.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work has been partially supported by a research prize sponsored by Novartis.

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