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Journal of the Neurological Sciences 245 (2006) 67 – 72

Journal of the Neurological Sciences

www.elsevier.com/locate/jns

Predicting neuropsychological abnormalities in multiple sclerosis

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Received 12 March 2005; received in revised form 25 May 2005; accepted 25 May 2005
Available online 19 April 2006

Abstract

Multiple Sclerosis (MS) is associated with MRI signal alteration and neuropsychological (NP) dysfunction. Screening tools have been developed to identify patients at high risk for these neurological complications of MS. One such measure, the Multiple Sclerosis Neuropsychological Screening Questionnaire (MSNQ), has well-established reliability and predictive validity. In this article, we report on the accumulated findings derived from 162 consecutive research participants and MS clinic attendees. Our data show significant correlation between both patient- and informant-report MSNQ and NP impairment. As shown previously, larger, and more significant correlations are found between informant-report MSNQs than with patient-report MSNQs. In addition, we find that the MSNQ predicts follow-up NP testing 51 weeks after baseline with a similar degree of association. Finally, the MSNQ is correlated with MRI measures of whole-brain lesion burden and atrophy, secondary progressive course, and vocational disability. We conclude that the MSNQ is reliable and valid for detecting neuropsychological and neuropsychiatric complications of MS.

Keywords: Multiple sclerosis; MRI; Neuropsychological testing; Screening

1. Introduction

Neuropsychological (NP) dysfunction is a significant source of caregiver distress [1], vocational disability [2], and poor quality of life [3] in MS patients. Because cognitive defects are subtle in some patients, NP testing is necessary for reliable quanitification and detailed clinical analysis. Psychometric tests permit good characterization of the cognitive [4–6] and psychiatric [7–12] sequelae of MS. Impediments to the routine clinical application of NP testing include high cost and inconsistency in third-party reimbursements. We believe that NP testing can be applied in a routine, cost-effective manner, provided that centers use brief examination techniques and screen for impaired patients.

By screening, we refer to a brief, low-cost test applied to members of a defined population for the purpose of identifying individuals who will benefit by further evaluation or treatment. Thus, screening for NP impairment should not be confused with NP testing itself, and it cannot replace a clinical evaluation. With this in mind, we developed the MS Neuropsychological Screening Questionnaire (MSNQ), an office-based measure of cognitive and neuropsychiatric dysfunction. The MSNQ is a 15-item questionnaire available in patient self-report and informant-report formats. Its reliability and validity are well established [13,14].

In the present study, we analyze data derived from a large MS sample and explored for the first time relationships between the MSNQ and disease course, MRI, neuropsychiatric symptoms, follow-up NP testing, and vocational disability.

2. Methods

2.1. Subjects

The data were derived from a sample of 162 patients (mean ± S.D. in years for age and education 43.4 ± 8.6 and

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doi:10.1016/j.jns.2005.05.020

14.5±2.3, respectively) with clinically definite MS [15]. The participants were either consecutive clinical referrals or volunteers for research projects investigating the psychometric properties of the MSNQ [13,14] and NP phenomena in MS [16–18]. There were 121 (75%) women and 149 (92%) Caucasians. Disease course frequencies were as follows: 119 relapsing-remitting (RR), 34 secondary progressive (SP), 2 relapsing progressive, 7 primary progressive (PP) [19].

Available for comparison were data from 49 healthy volunteers (age=43.6±9.1; education=15.1±2.0) matched to patients on age, education, gender, and race (one-way ANOVA and chi-square tests not significant). For research participants, informed consent was obtained per institutional review board requirements. Exclusion criteria were (a) current/past medical or psychiatric disorder (including major depressive disorder and bipolar disorder [20]) other than MS that could affect cognitive function, (b) substance abuse, (c) neurological impairment that may interfere with psychometric testing, (d) MS relapse or corticosteroid pulse within the past 6 weeks.

A sub-sample of 48 patients underwent follow-up NP evaluation, allowing us to determine how well the MSNQ predicts future NP testing. The mean test–retest interval was 364.0 (S.D.=424.3) days. Demographic and clinical characteristics were as follows: age=44.6±8.3, education=15.0±2.3, 38 (79%) female, 45 (94%) Caucasian, course=(38 RR, 6 SP, 3 PP).

2.2. Procedures

Neuropsychological evaluations were prescribed for consecutive clinical patients or were included in research protocols. Prior to testing (see below), each patient completed the self-report version of the MSNQ, in accordance with standardized directions [13]. In brief, after being presented with the questionnaire, each patient was instructed to read the directions and invited to pose questions about the material. The informant-report forms were completed by a single designated family member or friend in a separate room. In accordance with previous research [14], MSNQ scores were considered positive if self-report scores were greater than 23 and informant-report scores were greater than 22.

We employed memory and processing speed tests based on the Minimal Assessment of Cognitive Function in MS battery [21]. Processing speed and working memory were assessed with Rao's adaptations [22] of the Paced Auditory Serial Addition Test (PASAT) [23] and the Symbol Digit Modalities Test (SDMT) [24]. Auditory/verbal learning and memory were evaluated by the total learning and delayed recall indices from the California Verbal Learning Test (CVLT-II) [25]. Analogous measures from the Brief Visuospatial Memory Test—Revised (BVMT-R) [26] were used to assess visual/spatial learning and memory. These tests were available in 161 patients.

Based on patient self- and informant-reports, each participant was categorized at the time of initial screening as employed full time ($n=44$) or disabled ($n=50$). The latter designation necessitated report of being unemployed and having objective evidence of disability (e.g., formal reduction in duties or rank, receipt of disability benefits, prolonged medical leave). The remainder of the sample could not be classified because of either ambiguous reports (e.g., claimed disability without benefits) or unemployment for other reasons (e.g., homemaker, early retirement).

Depression was quantified with the Beck Depression Inventory—Fast Screen (BDI-FS) [27], recently validated in MS [28]. Behavior disorder was measured with the Neuropsychiatric Inventory [29], an informant-based structured interview. The NPI assesses the frequency and severity of delusions, hallucinations, aggression, depression, anxiety, euphoria, apathy, disinhibition, lability, aberrant motor behaviors. It also measures the degree of reported caregiver distress. For this study, we considered two general indicators, total pathology index and caregiver distress index.

Twenty-seven patients underwent a single MRI brain scan using a 1.5-T General Electric Signa 4x/Lx, Milwaukee, WI scanner. For each scan, T2-weighted image (WI), 3D-SPGR T1-WI, conventional spin-echo (CSE) T1-WI and FLAIR images were obtained. The axial dual spin-echo sequence was acquired with TE 30/90, TR 3000, NEX 1, ETL 14, FOV 24×18, matrix 192×256, 5 mm slice thickness (th) with total of 28 slices, no gap and scan time 2:44 min. The axial 3D-SPGR T1-WI scans were acquired with FOV 24×18, matrix 192×256, 2.5 mm th, 70 slices, no gap, TE 7, TR 24, NEX 1, FLIP 30, scan time 4:19 min. The axial CSE T1-WI were obtained with FOV 24×18, matrix 192×256, 28 slices, 5 mm th, no gap, TE 9, TR 600, NEX 2, scan time 2:56 min. The axial FLAIR was obtained with FOV 24×24, matrix192×256, 28 slices, 5 mm th, no gap, TE 128, TI 2000, TR 8002, ETL 22, NEX 1, scan time 3:44 min. Patients and controls were positioned in the magnet according to commonly accepted international guidelines [30].

Image analysis was performed at the Buffalo Neuroimaging Analysis Center, Department of Neurology, University at Buffalo, Buffalo, NY. The image operators were blinded to the patient's clinical and MSNQ status and the analysis was performed on a Gentoo GNU/Linux workstation (Kernel Version 2.6.7; Gentoo Technologies, Inc. Boston, MA, USA). We estimated brain atrophy on 3D-SPGR T1-WI utilizing a modified version of FMRIB's SIENAX [31] cross-sectional segmentation tool called Hybrid SIENAX [32]. First, we applied JIM BrainFinder tool [33] to remove all non-brain, non-CSF tissue from the image volume. Then, 3D constrained morphological erosion was applied to this "deskulled" image to generate an estimate of the skull boundary [34]. Subsequently, the deskulled brain and the skull images were registered to a standard brain map, using the skull as a scaling constraint, in order to determine a subject-specific normalization factor.

Table 1
Classification of MS and normal control subjects by MSNQ score

	MS	NC	
Patient Report			
MSNQ negative	71	46	117
MSNQ positive	91	3	94
	162	49	211
Informant Report			
MSNQ negative	63	36	99
MSNQ positive	84	4	88
	147	40	187

MSNQ=MS Neuropsychological Screening Questionnaire, MS=multiple sclerosis, NC=normal control.

The tissue segmentation was performed with the FAST automated image segmentation tool [35] using a 3D three tissue class model with K-means segmentation for estimation of initial intensity parameters and individual tissue volumes. White matter (WM), gray matter (GM), and cerebrospinal fluid (CSF) volumes were obtained. Brain parenchymal fraction (BPF) was calculated as follows:

$$\mathrm{BPF} = \frac{\mathrm{GM} + \mathrm{WM}}{\mathrm{GM} + \mathrm{WM} + \mathrm{CSF}}$$

The Hybrid SIENAX method is a fully automated brain segmentation method. In a previous study using the same type sequence, the scan–rescan variability was 0.1% for BPF [32].

Lesion volumes (LVs) were calculated using a reliable semi-automated local thresholding technique for lesion segmentation [36–38]. Lesions were delineated as ROIs and the volume was simply calculated for each sequence by multiplying the total ROI area by the slice thickness. The results were expressed in milliliters. T2 lesions were outlined on FLAIR images on each axial slice (T2-weighted scans were always used to increase confidence in lesion detection). The mean COV for T2-LV was 1.1% for intra-observer reproducibility and 1.5% for inter-observer reproducibility. T1 hypointense lesions were defined as any region visible on the T1-weighted sequence with low signal intensity between those of the CSF and GM and corresponding to a region of high signal intensity on the FLAIR image. The mean COV for T1-LV was 2.5% for inter-observer and 3.2% for intra-observer reproducibility.

2.3. Statistical analyses

Group comparisons (diagnosis, course, vocational status) were compared by one-way analysis of variance (ANOVA) and chi-square tests. Correlations were calculated using the Pearson method. Throughout, $p<.05$ was the threshold for statistical significance.

3. Results

Table 1 shows the classification of MS patients and normal controls by MSNQ. It can be seen that the patient self-report form correctly classified 65% of cases and the informant-report form 53%. Specificity was high for both forms (self-report 0.94, informant 0.90), indicating that positive MSNQs were rare in normal controls. The sensitivity of the MSNQ (self-report 0.56, informant 0.43) was much lower, as expected, reflecting the frequency of NP impairment in MS which is roughly 50% [39].

Patient-report MSNQs did not differ significantly between RR and SP patients, but SP patients had significantly higher informant-report scores (27.4±13.0 vs. 20.1±11.8) than RR patients ($p=0.004$).

Correlations are reported in Table 2. Excepting BDI-FS, there were higher correlations between NP and MRI scales

Table 2
Correlations between MSNQ and neuropsychological variables

	Correlation with MSNQ patient self-report form		Correlation with MSNQ informant-report form	
	Baseline	Follow-up	Baseline	Follow-up
CVLT-II Total Learning	−0.19*	ns	−0.49***	−0.48**
CVLT-II Delayed Recall	−0.24**	ns	−0.50***	−0.34*
BVMT-R Total Learning	−0.23**	ns	−0.46***	−0.46**
BVMT-R Delayed Recall	−0.24**	ns	−0.48***	−0.36*
PASAT	−0.30***	−0.31*	−0.46***	−0.61***
Symbol Digit Modalities Test	−0.27**	−0.34*	−0.55***	−0.65***
Beck Depression Inventory Fast Screen	0.56***	0.48**	ns	ns
NPI Total Index	0.27**	–	0.50***	–
NPI Caregiver Distress Index	0.26**	–	0.53***	–
T2 Lesion Volume	ns	–	0.46*	–
T1 Lesion Volume	ns	–	0.52**	–
BPF	ns	–	−0.52**	–

CVLT-II=California Verbal Learning Test, 2nd ed. BVMT-R=Brief Visuospatial Memory Test—Revised. NPI=Neuropsychiatric Inventory. BPF=Brain Parenchymal Fraction.
ns=not statistically significant; – signifies not enough subjects for analysis.
* $p<.05$.
** $p<.01$.
*** $p<.001$.

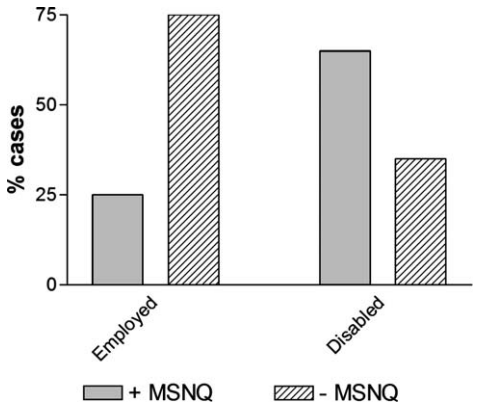

Fig. 1. Employed vs. Disabled MS patients categorized by positive/negative MSNQ. There is a significantly higher proportion of negative MSNQs among employed patients. In contrast, we find a high proportion of positive MSNQs among disabled patients.

with informant-report compared to self-report MSNQs. Correlations between cognitive tests and informant-report MSNQ ranged from −0.46 ($p<0.001$) for BVMT-R Total Learning to −0.55 ($p<0.001$) for SDMT. Informant reports were also strongly correlated with neuropsychiatric symptoms ($r=0.50$, $p<0.001$), and caregiver distress caused by neuropsychiatric symptoms ($r=0.53$, $p<0.001$), as measured by the NPI. In contrast, BDI-FS was significantly correlated only with self-report MSNQ ($r=0.56$, $p<0.001$).

A similar pattern of correlation coefficients was found upon examination of follow-up NP testing data. As the sample was smaller, there was less statistical power—only PASAT, SDMT and BDI-FS were significantly correlated with self-report MSNQ. Correlations between cognitive tests and informant-report MSNQs were very similar to baseline results. Again, there was no association between informant-report MSNQ and BDI-FS. Correlations with cognitive measures ranged from −0.34 ($p<0.05$) for CVLT-II Delayed Recall to −0.65 ($p<0.001$) for SDMT.

Likewise, MRI measures were correlated with informant- but not self-report MSNQs (Table 2). Informant-report MSNQ with MRI correlations ranged from 0.46 for T2-LV ($p<0.05$) to 0.52 for both T1-LV and BPF ($p<0.01$).

Informants of disabled patients observed greater neuropsychological impairment in patients, as demonstrated by higher informant-report MSNQ scores (28.5±12.2 vs. 15.7±10.0), than did informants of employed patients ($p<0.001$). Of the 40 patients classified as unemployed/disabled, 65% had abnormal informant-report MSNQs. In contrast, only 25% of MSNQs from employed patients were positive (Fig. 1). The difference in proportion of abnormal MSNQs between disabled and employed patients was statistically significant (Pearson Chi-Square=14.3, $p<0.001$).

4. Discussion

The current data expand upon previous work with the MSNQ which showed that it has good internal consistency [13], test–retest reliability [14], and predictive validity [13,14]. In this study, the psychometric aspects of the MSNQ were further supported. While both self- and informant-report MSNQs were correlated with cognitive impairment, higher correlations were found for the informant-report form. In contrast, depression ratings showed the opposite relationship. In this study, we also found that MSNQ to be associated with (a) SP course, (b) MRI measures of lesion burden and brain atrophy, (c) follow-up NP testing approximately 1 year after baseline, and (d) vocational status. Thus, the present findings extend the clinical validity of the MSNQ.

It is important to emphasize that elevated scores on the patient self-report and informant-report forms of the MSNQ have very different implications. It is well established that cognitive complaints are associated with symptoms of depressive disorder [40,41]. Previously [14], we found that self-report MSNQs have acceptable [sensitivity=.80, specificity=.68, PPV=.73, NPV=.75] predictive power provided that cases are defined as cognitively impaired or depressed, in accordance with the BDI-FS test manual [27]. As shown here, we again find that self-report MSNQs are modestly correlated with cognitive function, but strongly correlated with BDI-FS. The opposite is true of the informant-report form, which is consistently correlated with cognitive impairment. In addition, we now find that the informant-report form is also correlated with SP course, neuropsychiatric symptoms, MRI pathology, and vocational disability.

MS-associated cognitive and emotional disorders have been recognized for well over a century [42] and they remain a significant source of caregiver distress [1] and vocational disability [2]. Studies suggest that cognitive impairment may be the most significant clinical domain for predicting vocational disability [2,43]. Thus, it is important that such impairment be detected early so that remedial strategies [12,44] and medication [45] can be brought to bear on the problem. The MSNQ can be used to alert clinicians to the potential for pathology in a range of areas, including but not limited to cognitive impairment. In this way, the significant correlation with NPI is important. Neuropsychiatric disorders are common in MS [9,11,18,46], and increasingly, an association between brain atrophy and both mood disorder [47] and euphoria sclerotica [18] is recognized in the literature.

We also found that the MSNQ shows reasonable association with vocational disability. We separated patients employed full-time from those with objective evidence of vocational disability (e.g., USA Social Security Disability benefits). Informants from the latter group generated significantly higher MSNQ scores than their employed counterparts. Chi-square test showed that the frequency of positive MSNQ is significantly greater in the disabled group. Thus, we find that the MSNQ may be able to target those patients who are not only cognitively impaired, but who also face personality/behavior changes and vocational disability.

A primary caveat in this study is the reliance on informant report for both the MSNQ and NPI. Indeed, another interpretation of the data might be that patient self-reports (MSNQ, BDI-FS) correlate with one another, as do informant-reports (MSNQ, NPI). While the correlations between cognitive testing and MSNQ scores are not affected by this potential bias, nevertheless, future work would benefit from confirmation of these reported associations via other forms of observation, such as blind ratings of social behavior in a laboratory setting.

In summary, the MSNQ is a brief questionnaire that identifies with reasonable accuracy patients who are likely to have some form of neuropsychological or neuropsychiatric compromise. Elevated patient MSNQ scores signify cognitive impairment or depression, whereas informant reports are correlated with multiple MRI measures of cerebral pathology, cognitive impairment, and neuropsychiatric disorder. This test is inexpensive to implement, and it obviates the technical and professional components of NP screening. Translated versions are in the process of validation. Because some misclassifications (especially false positives) occur, a positive screen should be followed by formal NP testing.

Acknowledgements

The authors recognize the contributions of Darcey Cox, PhD, Laetitia Thompson, PhD, and Fred Foley, PhD, who provided some data used in this report. Some of the data were collected with assistance of an unrestricted educational grant from Biogen Idec.

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