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(Citation)
Multiple Sclerosis and Related Disorders,35:272-275

(Issue Date)
2019-10

(Resource Type)
journal article

(Version)
Accepted Manuscript

(URL)
https://hdl.handle.net/20.500.14094/90006695

Validation of the Guy's Neurological Disability Scale as a screening tool for cognitive impairment in multiple sclerosis

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Key words: GNDS, multiple sclerosis, cognitive impairment, PASAT, SDMT

Word count: 1525
Number of table: 4
Number of figure: 1
Number of reference: 19
Number of supplemental figure: 1
Number of supplemental table: 1

A short summary

Objectives

Cognitive impairment is a common symptom affecting daily activities of the patients with multiple sclerosis (MS). Various cognitive evaluation tests are available, yet most of them are complex and time-consuming to perform in outpatient clinics. In this study, we aimed to validate a Japanese version of the Guy's Neurological Disability Scale (GNDS) as a user-friendly tool to evaluate comprehensive disabilities in MS including cognitive function.

Methods

Questions of the GNDS were translated into Japanese and named GNDS-J. Forty-four patients were examined by the Expanded Disability Status Scale (EDSS), the Paced Auditory Serial Addition Test (PASAT), the Symbol Digit Modalities Test (SDMT), the vitality scale, and the GNDS-J in the same time at remission state.

Results

The GNDS-J scores correlated with the EDSS scores(r=0.61), and inversely correlated with the PASAT2/1(r=-0.56/-0.49) scores and the SDMT scores (r=-0.68), whereas the GNDS-J did not show any correlation with the vitality scale. Furthermore, eleven patients were evaluated over 5 years for changes in these scores. Eight out of 11 patients had exacerbated GNDS, and all of these patients experienced clinical relapse during this period.

Conclusion

The GNDS-J is a valid tool to perform in outpatient clinics, which could provide a comprehensive scale for evaluating symptoms of MS, thus the disease activity by repeated measure.

INTRODUCTION

Cognitive impairment is a frequent symptom in multiple sclerosis (MS) patients[1] and starts from early stage of the disease, where brain atrophy proceeds

throughout the course of MS[2]. Attention and information-processing speed, working memory, verbal and visuospatial memory, and executive functions are the predominantly affected cognitive domain[3]. The Paced-Auditory-Serial-Addition Test (PASAT) and the Symbol-Digit-Modalities Test (SDMT) are internationally recommended for evaluating neuropsychological functions and cognitive impairment in MS[4]. Several neuropsychological assessment batteries have been reported, such as the Minimal Assessment of Cognitive Function in MS (MACFIMS) and the Brief Repeatable Battery of Neuropsychological tests (BRB-N); including both of the PASAT and the SDMT, as well as the Brief International Cognitive Assessment for MS(BICAMS) including the SDMT[5-7], however they are complicated and time consuming, thus not easy to perform for outpatients in each visit. The MACFIMS requires approximately 90 min[8]. The BRB-N administration time is approximately 25–30 minutes[9], and the BICAMS takes 15 minutes[7].

The Expanded Disability Status Scale (EDSS) is a well-devised assessment

tool for evaluating disabilities affecting the daily activities of MS patients. However, non-physical disabilities, including cognitive impairment, are susceptible to multiple biases, and are often difficult to assess. A proper neuropsychological examination is indispensable for assessing these elusive symptoms. For evaluating multidimensional symptoms of MS, Sharrack et al. established a subjective scoring method referred to as the Guy's Neurological Disability Scale (GNDS)[10], and there have been several literature evaluating the validity of the GNDS except for in Asia[11-15]. The GNDS has been translated and used in various languages, and it has been reported good correlations with the scales of mainly physical disabilities, such as the EDSS, the Barthel Index(BI), the Functional Independence Measure (FIM) etc, however its correlations with non-physical disabilities has been merely reported.

Here, we aimed to investigate whether the Japanese version of the GNDS correlates with other parameters evaluating not only physical, but also non-physical functions of MS.

PATIENTS AND METHODS

Patient and controls

Forty-four MS patients fulfilled the McDonald's diagnostic criteria[16] were enrolled in this study. All the patients were evaluated for disabilities while in their remission phase. We could evaluate 11 patients who keep visiting our hospital after 5 years for the changes of each score over years. This research was approved by the ethical committee of Kobe University Hospital.

Disability evaluation examinations

We translated GNDS questions into Japanese for this study, and named it GNDS-J (Supplemental Figure 1). MS patients were evaluated by the PASAT2, the PASAT1, the SDMT, the vitality scale, the EDSS and the GNDS-J. The PASAT examines processing speed as well as working memory by the auditory and verbal

sphere, entitled ‘1’ or ‘2’ represents each paced seconds of examination, and the SDMT examines working memory by the visual and writing sphere. Patients were also evaluated by the vitality scale, a questionnaire method that evaluates depression and apathy: scores range 0-99, higher score indicate greater severity[17]. The GNDS is a questionnaire comprising 12 domains: cognition, mood, vision, speech, swallowing, upper limb function, lower limb function, bladder function, bowel function, sexual function, fatigue, and ‘other’. Each domain score ranges from 0(normal) to 5(complete loss of function or maximal help required) and the total score ranges from 0(no disability) to 60(maximum possible disability). Patients answer yes/no to a few questions in each domain. These examinations were performed on the same day by neurologists at Kobe University Hospital. The PASAT2/1, the SDMT, and the vitality scale formats in Japanese were purchased from Shinkoh Igaku Shuppansha Publishing Company.

Data analyses

Spearman's rank-order correlation tests were performed to evaluate the validity of the GNDS-J, and Fisher's exact test were performed to evaluate the change in the 5-year follow-up. These statistics were calculated using GraphPad Prism 7.0 software. Cronbach's alpha was calculated to assess the reliability of the GNDS-J using R software. Cronbach's alpha is a measure of internal consistency, and the alpha coefficient ranges in value from 0 to 1; the higher the value, the more reliable the generated scale is (0.7 has been demonstrated to be an acceptable reliability coeficient).

RESULTS

GNDS-J scores inversely correlated with cognitive assessment batteries.

Baseline clinical features of the patients are shown in the Table 1. Patients (N=44) were a mean age of 41.4 years (SD 8.8), and 34 (77.3%) were females. The mean score of the EDSS was 3.03 (SD 1.95). Disease modifying treatments when their

data acquired were Interferonβ (17/44, 38.6%), fingolimod (5/44, 11.4%), glatiramer acetate (2/44, 4.6%), and dimethyl fumarate (1/44, 2.3%). Baseline characteristics of each parameter are shown in Table 2. The data of the vitality scale was missed in one patient. The mean of healthy controls of the GNDS-J was calculated from 10 healthy volunteers(female/male 7/3, mean age 34). The GNDS-J score was significantly higher in SPMS (mean 30.3; SD 9.1) than RRMS (mean 9.8; SD 6.5) ($p<0.01$, Wilcoxon rank sum test).

We found that the GNDS-J score inversely correlated with both the PASAT2/1 and the SDMT score (r=-0.56/-0.49, -0.68). The GNDS-J score also correlated with the EDSS score (r=0.61) indicating it reflects multiple symptoms of MS including both physical and non-physical disabilities, whereas the GNDS-J score did not correlate with the vitality scale (Fig1). Of note, no significant difference was found between GNDS-J and disease duration (p=0.23). Cronbach's alpha coefficient calculated with all patient GNDS-J score was 0.78, which was almost equivalent to the original version of the

GNDS (0.79)[10].

Long-term evaluation by GNDS-J sensitively detected disabilities of MS patients

In this study, eleven out of forty-four patients were examined changes in these scores after 5 years, clinical information, and MRI findings based on medical records. We compared 11 followed-up patients and 33 non-followed-up patients where they did not show any statistical difference in age, sex, disease duration, EDSS, PASAT score, SDMT score, GNDS-J score, and etc except for 2 years relapse rate before the initial evaluation that was higher in 11 followed-up patients (Supplemental Table 1). Among these eleven patients, one patient was found to be SPMS over the course, and the remaining ten RRMS patients were included to the assessment. In 5 years, eight out of ten patients showed exacerbation of the GNDS-J score, and all of them experienced clinical relapse during this period, whereas patients whose GNDS-J score had improved or unchanged did not experienced clinical relapse during this period. We employed

Fisher's exact test that exhibited the groups divided by the difference of the GNDS-J score over 5 years (ΔGNDS-J score) are significantly different depending on whether they experienced relapse or not ($p<0.05$) (Table3). However, increase of the EDSS did not always correlate with clinical relapses. These results suggest that the GNDS-J covers comprehensive symptoms of the disease and may be able to reflect disease activity more sensitively than the EDSS.

DISCUSSION

Cognitive impairment often restricts the daily social activities of MS patients, however, objective evaluation of signs is sometimes difficult because patients often express symptoms such as fatigue or mood disturbances that is hard to distinguish from depression or apathy. In this study, we showed that symptoms represented by the GNDS-J correlated with the PASAT and the SDMT scores. We also confirmed that the GNDS-J scores did not correlate with the vitality scale, suggesting that the GNDS-J

scores were less affected by the depression or apathy of patients in our study, hence mainly reflects the cognitive function of MS patients. The correlation between the GNDS and the EDSS was similar as reported[10].

A hallmark of objective response to therapy is the number of gadolinium (Gd)-enhanced legions and new T2WI high intensity lesions identified with MRI[18]. In this study, the patients who showed increase of the GNDS-J score exhibited new MRI lesions over the time where the EDSS score did not always reflect the increase of MRI lesions. This indicates the EDSS score sometimes underestimate disease activity, which can be detected by either MRI scan or the GNDS-J score. (Table 4). Indeed, in the course of 5 years, the GNDS-J exacerbated in many cases, and it seems to reflect disease progression of MS.

Although our study has limitations related to patient number and prospective cohort studies with more subjects are needed, the statistically confirmed results suggest that the GNDS-J reflects physical and cognitive function of Japanese MS patients and

provides convenient tool assessing daily activity changes of multiple sclerosis patients.

It is important for patients to be aware of their symptoms of their own diseases. If the patients care about these subjective questions in the GNDS in daily activities, they could recognize relevant clinical symptoms appropriately. The GNDS-J is a patient-friendly and useful tool to evaluate MS disabilities including cognitive function, moreover it is also expected to be developed into an application tool using smartphones, which has recently been suggested to be reliable in neurodegenerative disease such as Parkinson disease[19].

Acknowledgements:

We thank folks in the Division of Neurology at Kobe University Graduate School of Medicine for their help collecting data. We also thank T. Omori (Clinical & Translational Research Center at Kobe University Hospital) for advice on statistical analysis.

This work was supported by a Grant-in-Aid for Young Scientists from the Japan Society for the Promotion of Science.

Author contributions:

R.A. and N.C. designed research; R.A., N.C. and H.T. performed research; R.A., N.C., H.T., S.K., H.K., F.K. and T.T. analyzed data; N.C. and T.T. supervised the work; and R.A., N.C., H.K., and T.T. wrote the paper.

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Figure 1.

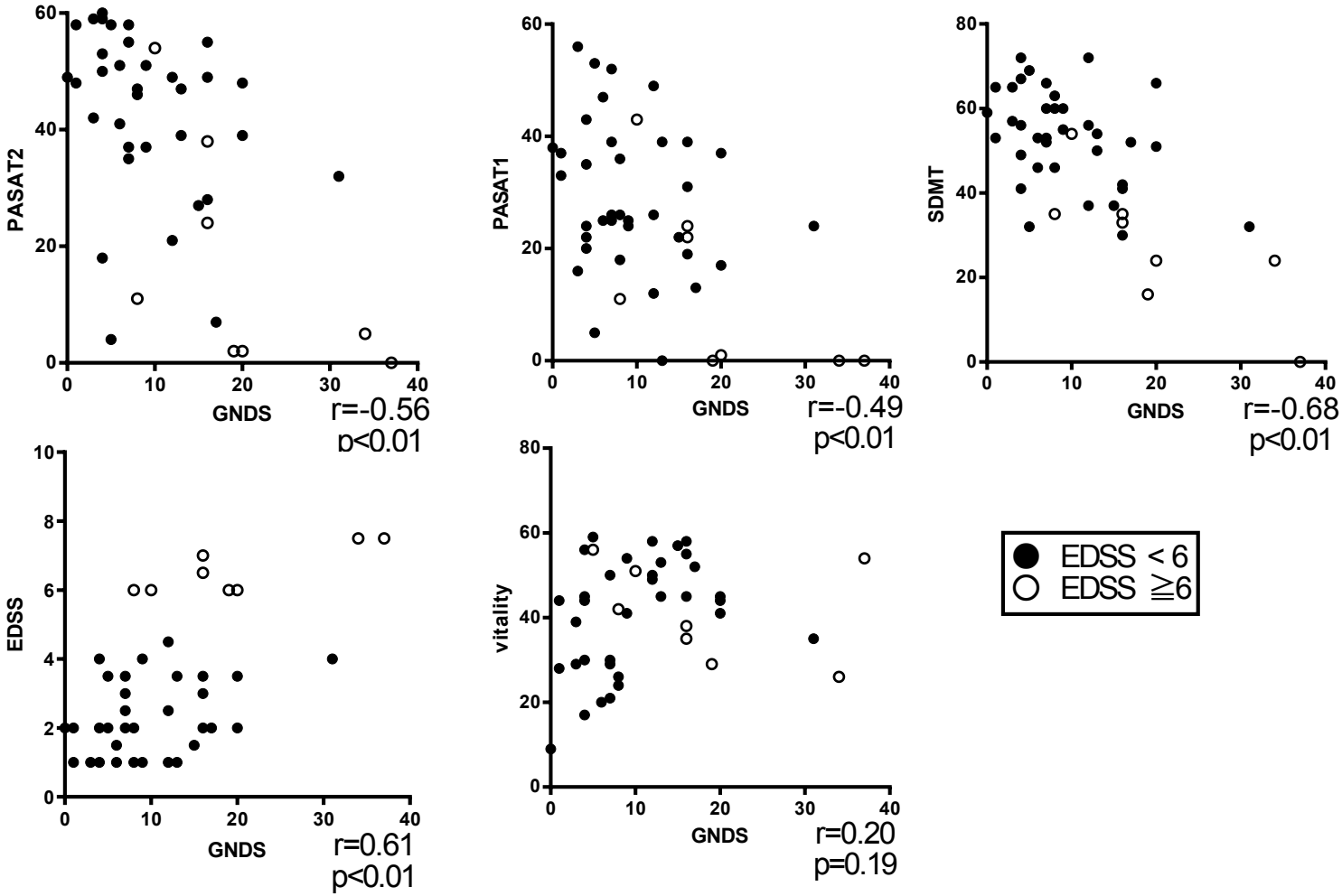
PASAT2
GNDS
r=-0.56
p<0.01
PASAT1
GNDS
r=-0.49
p<0.01
SDMT
GNDS
r=-0.68
p<0.01
EDSS
GNDS
r=0.61
p<0.01
vitality
GNDS
r=0.20
p=0.19
EDSS < 6
EDSS ≧6

Figure legends

Figure1.

Scatter plots of the GNDS-J scores against other (PASAT2, PASAT1, SDMT, EDSS, or vitality) scores. The association of two variables was determined using Spearman's rank-order correlation (r: correlation coefficient, p: strong association was set as $p < 0.05$). The PASAT2, PASAT1, and SDMT scores had an inverse correlation with the GNDS; the EDSS had correlated with the GNDS; and the vitality scale scores did not show any correlation with the GNDS.

GNDS: Guy's Neurological Disability Scale; PASAT: Paced auditory serial addition test;; SDMT: Symbol digit modalities test; EDSS: Expanded disability status scale

Table 1.

The number of patients	44
Sex (Female : Male)	34:10
Age	41.4±8.8
Disease duration (year)	10.9±7.7
ARR	0.51±0.48
EDSS	3.03±1.95
Type of MS (RRMS/SPMS)	41/3
Treatment	
Interferon β	17/44 (38.6%)
Fingolimod	5/44 (11.4%)
Glatiramer acetate	2/44 (4.6%)
Dimethyl Fumarate	1/44 (2.3%)
None	19/44 (43.2%)

Clinical profile of MS patients
The values indicate the number of patients or the value of mean ± standard deviation (SD).

MS: multiple sclerosis; ARR: Annualized relapse rate; EDSS: Expanded disability status scale; RRMS: Relapsing-remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis

Table 2.

	PASAT2	PASAT1	SDMT	Vitality	GNDS-J
Number of patients	44	44	44	43	44
Mean of the score	38.4	26.2	48.6	40.8	11.2
Standard deviation	18.2	15.1	15.7	12.8	8.38
Minimum	0	0	0	9	0
Median	46.0	25.0	52.5	44.0	8.5
Maximum	60	56	72	59	37
Range of score	0-60	0-60	0-110	0-99	0-60
Mean of HC※1	48.1	28.7	64.2	28.6	2.0

Summary of examined tests
Disability-evaluation-scale values collected from MS patients (N=44) in remission are shown.
※1 Data of PASAT2/1, SDMT, and the vitality scale in healty controls were excerpted from the literature 17) .

PASAT: Paced auditory serial addition test; SDMT: Symbol digital modalities test;
GNDS: Guy's neurological disability test; HC: Healthy Controls.

Table 3.

	ΔGNDS-J		
	>0	≦0	Total
Relapse(+)	8	0	8
Relapse(-)	0	2	2
Total	8	2	10

*p=0.022

	ΔEDSS		
	>0	≦0	Total
Relapse(+)	4	4	8
Relapse(-)	0	2	2
Total	4	6	10

p=0.47

The relation between GNDS-J/EDSS change and relapse in 5 years
The contingency table showed the number of patients. Δ means change of the GNDS-J and the EDSS in 5 years. Patients who experienced clinical relapse in these periods are in 'Relapse(+)' , and 'Relapse(-)' indicates relapse-free. The results were analyzed using Fisher's exact test.

Table 4.

Pt	age	sex	EDSS		ΔEDSS	GNDS-J		ΔGNDS-J	t2		Δt2	Relapse /5yrs	DMT	
			Base line	5years after		Base line	5years after		Base line	5years after			Base line	5years after
1	42	F	2	4.5	2.5	0	10	10	46	49	3	1	IFNβ	DMF
2	27	M	1	1.5	0.5	9	11	2	8	8	0	1	IFNβ	FTY
5	37	F	1	1	0	1	1	0	47	47	0	0	IFNβ	FTY
7	32	F	1	1	0	12	14	2	23	25	2	5	none	FTY
8	42	F	2	6	4	4	17	13	11	14	3	3	IFNβ	FTY
10	42	F	7	7	0	16	18	2	20	21	1	1	none	FTY
12	55	M	4	6	2	9	13	4	6	7	1	1	none	FTY
13	28	F	1	1	0	8	12	4	9	10	1	2	none	none
16	37	M	3.5	3.5	0	20	17	-3	4	NA	NA	0	IFNβ	IFNβ
17	40	F	6	6	0	8	10	2	40	36	-4	1	IFNβ	FTY

Changes of scores in 5 years-follow-up

In the table 'age' represents baseline age of patients.

Pt: patient; F: Female; M:Male; t2:number of T2WI high intensity lesions of MRI; NA: not available ; INFβ: interferon β; DMF: dimethyl fumarate; FTY: fingolimod

Supplemental Table 1.

	Sex (female)	Age (mean)	Duration (mean)	Relapse/2y (mean)	EDSS (mean)	Type (RRMS)	PASAT 2 (mean)	PASAT 1 (mean)	SDMT (mean)	Vitality (mean)	GNDS-J (mean)
11 followed-up Patients	72.7%	39.3	14	1.73	3.27	90.9%	39.4	22.4	51.2	36.4	11.0
33 non-followed-up Patients	78.8%	42.1	9.8	0.79	2.95	93.9%	38.0	27.5	47.8	42.3	11.3
p-value	0.68☆	0.27	0.33	0.005*	0.83	0.73☆	0.98	0.28	0.60	0.17	0.98

The comparison of followed-up and non-followed-up patients.
The p-values were calculated using Pearson's Chi-squared tests for sex and disease type, and Wilcoxon rank sum tests with continuity correction for other items.
☆ Pearson's Chi-squared test, * $p<0.01$, Wilcoxon rank sum tests.