The Comparison of Information Processing Speed in the Symbol Digit Modalities Test and Paced Auditory Serial Addition Test in Relapse-Remitting Multiple Sclerosis Patients

Mahdieh Azin

Neuroscience Research Center, Institute of Neuropharmacology, Kerman University of Medical Sciences, Kerman, IR Iran

Tel: +98 913 290 8035 Email: mahdieh.azin@collegian.kmu.ac.ir

Nasser Zangiabadi (Corresponding author)

Neuroscience Research Center, Institute of Neuropharmacology, Kerman University of Medical Sciences, Kerman, IR Iran

Tell: +98-021 82483250 Email: nzangiabadi1@gmail.com

Farhad Iranmanesh

Neurology Research Center, Kerman University of Medical Sciences, Kerman, IR Iran

Tel: +98 913 191 4290 Email: fpp_farhad@yahoo.com

Mohammad Reza Baneshi

Research Center for Modeling in Health, Institute for Futures Studies in Health, Kerman University of Medical Sciences, Kerman, IR Iran

Tel: +98 913 442 3948 Email: m_baneshi@kmu.ac.ir

Abstract

Introduction: We compared the sensitivity of Symbol Digit Modalities Test (SDMT) and Paced Auditory Serial Addition Test (PASAT) related to assessment of information processing speed in relapsing-remitting (RR) MS patients with mild disabilities, and their correlation with upper and lower motor functions.

Materials and Methods: Thirty-eight RR MS patients and 38 age, gender, and education level-matched healthy subjects participated in this study. Examination procedures included: PASAT, SDMT, Timed 25-Foot Walk (T25FW) and Nine Hole Peg Test (9HPT). Data analysis was performed by receiver-operating characteristic (ROC) analysis, Pearson correlation and independent t test.

Results: Information processing speed was significantly different between MS patients and healthy subjects (for SDMT: p=0.001; for PASAT: p=0.03). SDMToral had the highest sensitivity (98.4%) and specificity (93%) among tests for classifying cognitively impaired MS patients. SDMT oral scores correlated significantly with scores of T25FW and 9HPT. PASAT and SDMT written scores did not correlate with scores of T25FW and 9HPT.

Conclusions: We suggest that SDMT oral be used in neurologic examination in order to assess cognitive impairment in MS patients with mild disability, because it correlates strongly with ambulation and manual functions, and because it has greater sensitivity.

Keywords: Multiple Sclerosis, Information Processing Speed, Symbol Digit Modalities Test, Paced Auditory Serial Addition Test

1. Introduction

Multiple sclerosis is an autoimmune inflammatory demyelinating disease that damages myelin in the white and gray matter of the central nervous system (Frohman et al, 2006). RR subtype is more frequent than the other forms of MS. The mean age of MS onset is 29 years, when a person has the most amount of social activities (Lublin & Miller, 2008).

Cognitive dysfunction is one of the most common symptoms of MS. Information processing speed in RR MS patients is impaired more than the other cognitive functions (Demaree et al, 1999; Nocentini et al, 2006). Due to the influence of cognitive impairment on daily life, social functioning (Amato et al, 1995) and professional work (Beatty et al, 1995), evaluation of cognitive deficits is the early stages of the disease are very important. PASAT can assess auditory processing speed, working memory and calculation ability. SDMT can evaluate visual processing speed and working memory (Benedict et al, 2002; Benedict et al, 2008). At the moment, both PASAT and SDMT are used for the evaluation of the information processing speed in MS patients. The PASAT is included in the Multiple Sclerosis Functional Composite (MSFC) measure, which is commonly used in clinical settings to monitor neurologic status.

There is controversy about replacing PASAT in the MSFC with other, more sensitive tests. Some studies proposed not to substitute PASAT in the MSFC with SDMT (Brochet et al, 2008), but other studies show that although both tests are valid, SDMT was nevertheless preferred (Drake et al, 2010). Therefore, it would be of interest to compare both PASAT and SDMT, in order to determine which of these information processing speed tests are more useful.

The main aim of our study was to compare the sensitivity and specificity of SDMT oral, SDMT written and PASAT in MS patients with mild disability. Also, we determined the correlation of the information processing speed with upper and lower motor functions.

2. Methods

2.1 Participants

In this study, 38 RR MS patients (male: 26.3%, mean age: 30.1± 6.8 years) from the Kerman/Iran multiple sclerosis society invited to participate from January to June 2013. Also, 38 age, gender, and education level-matched healthy subjects were participated in this study.

The diagnosis of MS was based on the McDonald criteria (Polman et al, 2011), and disability was estimated according to the Kurtzke Expanded Disability Status Scale (EDSS) (Kurtzke, 1983). The mental status of patients was assessed by means of a Mini-Mental State Examination (MMSE) (Folstein et al, 1975). Patients with MMSE score < 26, EDSS > 3, pregnancy, recent relapse, other neurological diseases (stroke, seizure, etc.), history of head trauma, chronic psychiatric disorder, or severe visual deficiency, as well as those who had received corticosteroids during the three months prior to the study, were excluded from our study.

This study was approved by the Ethics Committee of Kerman University of Medical Sciences, and all of the patients gave signed written informed consents before taking part in the study.

2.2 Procedure

A postgraduate student at the Kerman Neuroscience Research Centre carried out the assessments.

Fatigue and depression were evaluated by the Fatigue Severity Scale (FSS) questionnaire (Krupp et al, 1989) and Beck Depression Inventory-II (BDI-II) (Ghassemzadeh et al, 2005) respectively.

The tests for the MS patients started with MSFC, which is a quantitative instrument that evaluates three clinical dimensions of MS: leg/ambulation, arm and cognitive function (Fischer et al, 1999).

The first component of MSFC involved two trials of T25FW, followed up by two trials of 9HPT for dominant and non-dominant hands, and ending with the PASAT-3" version, in accordance with the manual of the National MS Society's Clinical Outcomes Assessment Task Force (Fischer et al, 1999). At the end of the session, the SDMT was performed in both oral and written forms.

In the T25FW test, patients walked 25 feet (7.62 meters) twice as quickly as possible in a safe mode. We recorded the mean time in seconds spent by patients to complete two trials (Rudick et al. 2002). The 9HPT consisted of 4 trials and evaluated upper extremity motor functions. During the two consecutive trials, the dominant hand was tested, then immediately the non-dominant hand was tested twice. The required time to move nine pegs from a container into nine holes on a peg board, then return them to the container, was measured (Mathiowetz et al, 1985). For statistical analysis, means of 4 trials were calculated. PASAT is an important component of both MSFC (Fischer et al, 1999) and minimal assessment of cognitive function in MS (MACFIMS) (Benedict et al. 2002). In this test, the patients listened to 61 audio taped single digits every 3 seconds and added each new digit to the previous one. The number of total correct sums was recorded (Rudick et al, 2002). SDMT is a sub-component of MSFC; it presented a key consisting of nine symbols, each paired with a number, at the top of a paper. Below the key, there was a series of unpaired symbols that the patients were asked first to articulate, and then write the numbers associated with each of the symbols as fast as possible in 90 seconds. The total number of correct responses was recorded (Benedict et al, 2002).

2.3 Statistical Analysis

An independent t test was used to explore statistically significant differences in the performance of SDMT oral, SDMT written and PASAT between MS patients and healthy subjects. The Z score of SDMToral, SDMT written and PASAT of patients was calculated in relation to mean and standard deviation (SD) of healthy subjects. Impairment in SDMToral, SDMT written and PASAT was defined as score ≤ -1.5 SD of matched healthy subjects (Eshaghi et al, 2012). Afterwards, MS patients were classified into two groups – impaired and normal – according to the information processing speed. ROC analysis was then conducted in order to compare sensitivity and specificity of SDMT oral, SDMT written and PASAT in MS patients with mild disability, and to determine the appropriate cut-off score. Area under the ROC curve rate was 0.5 to 1. Values 0.5 and 1 indicate poor and perfect tests respectively for classification of impaired patients from healthy subjects. A Pearson correlation test was used to assess the relationship between three tests of information processing speed and upper and lower motor functions, fatigue scale, depression score and disease duration.

Data analysis was performed by SPSS17. The level <0.05 was regarded as a significant effect.

3. Results

There were no significant differences in the gender, age and educational level between the two experimental groups (Table 1).

Table 2 illustrates that the scores of the three tests related to information processing speed in MS patients showed a significant decrease compared to healthy subjects.

Among 38 patients, 8 MS patients showed information processing speed impairment in all three tests (SDMT oral, SDMT written and PASAT), 5 patients showed impairment only in SDMT oral & written, and the other 5 patients showed impairment only in PASAT, based on ≤ -1.5 SD of healthy subjects. Thus, there were 34.2 % of patients with visual and auditory information processing speed deficits.

The ROC curves graph for data of SDMT oral, SDMT written and PASAT is shown in Figure 1.

The area under the ROC curve (AUC) with respect to SDMT oral, SDMT written and PASAT was 0.987, 0.945 and 0.766 respectively. There was a significant difference between the AUC of all the three tests. Thus, SDMT oral had the highest value of the AUC, and was the best diagnostic criteria to differentiate impaired MS patients with mild disability from healthy subjects in terms of information processing speed.

Maximum sensitivity (98.4%) and specificity (93%) on SDMT oral was attained with a cut-off score of 41.5. Considering this cut-off point, there were 34.2 % patients with processing speed impairment in SDMT oral performance. Z-score of this cut-off was -1.53, based on SD of healthy subjects, and classification accuracy of SDMT oral was 100% with this cut-off point.

Maximum sensitivity (93.4%) and specificity (93%) on SDMT written was attained with a cut-off score of 40.5. Considering this cut-off point, the classification accuracy of this test was 97.4%, and 36.8 % patients had information processing speed impairment.

Maximum sensitivity (93.4%) and specificity (46.2%) on PASAT was attained with a cut-off score of 36.5. With this cut-off score, there were 23.7% processing speed impaired patients, and 89.5% patients were classified correctly.

Correlation analysis showed that the SDMT oral score correlated negatively with upper motor function and ambulation. Increases in the SDMT oral score were correlated with decreases in the time needed for the completion of 9HPT and T25FW. There was no correlation between the SDMT oral score and fatigue and depression scores or disease duration (Table 3). Table 3 showed that the SDMT written score was not correlated with upper motor function or ambulation. Also, the SDMT written score did not correlate with the fatigue and depression scores, or with the disease duration. There was no association between the PASAT score and the other listed variables.

4. Discussion

The results of our study showed that information processing speed declined in MS patients with mild disability in comparison to healthy subjects, and 34.2 % of patients were impaired in visual and auditory information processing speed. Also, our study showed that SDMT oral had the highest values for AUC, sensitivity and classification accuracy. Our findings showed that the SDMT oral correlated significantly with ambulation and manual dexterity.

Because of the importance of the speed of information processing in MS patients, several studies were conducted to compare the different instruments of information processing speed in various subtypes of MS (Benedict et al, 2008; Brochet et al, 2008; Drake et al, 2010; Eshaghi et al, 2012; Parmenter et al, 2007). Brochet et al. were the first to propose that SDMT might be a viable alternative to PASAT. The authors compared MSFC, incorporating SDMT with PASAT in a sample of 46 patients over five years. In this study, they concluded not to substitute PASAT with SDMT in MSFC, but rather, to consider SDMT as a complementary approach to evaluate the MS disease (Brochet et al, 2008).

In this regard, the primary objective of this study was to explore two tests related to information processing speed, from different aspects, in RR MS patients with mild disabilities.

Our findings with regard to 38 mildly disabled MS patients showed that 34.2 % of the patients were impaired in information processing speed. Another study on 291 MS patients in the USA showed that 51.9% of the MS patients were impaired in SDMT oral performance and 27.4% of the MS patients were impaired in PASAT performance, based on Z-score < -1.5 SD in healthy subjects (Benedict et al, 2006). The difference between the number of impaired patients this study could be explained by the fact that Benedict et al. assessed all four types of MS patients, but in the present study, only RR MS patients with mild disability were assessed.

Consistent with our findings showing that SDMT oral had the highest levels of sensitivity, specificity and classification accuracy, previous research on RR and secondary progressive MS patients in Iran revealed that among the cognitive tests related to MACFIMS, the maximum levels of AUC and sensitivity belong to SDMT oral (Eshaghi et al, 2012). Another study in France on 57 RR MS patients in early-stage disease demonstrated that among the five tests (Selective Reminding Test, the Wechsler Adult Intelligence Scale-Revised, the Stroop Test , PASAT and SDMT oral), SDMT oral was the best test for identifying cognitively impaired MS patients in early-stage disease (Deloire et al, 2006). In our research, we suggest the cut-off score of 41.5 for SDMT oral for classifying patients into two groups: impaired and normal. In their study, Parmenter suggested a cut-off score of 55 for SDMT oral, in which maximum sensitivity and specificity were 82% and 60% respectively (Parmenter et al, 2007).

In our study, only SDMT oral correlated with ambulation and manual functions. In their research on 400 MS patients, Drake et al. demonstrated that both SDMT oral and PASAT correlated with ambulation and manual functions; however, correlation of SDMT oral was stronger than PASAT (Drake et al, 2010). A 5-year follow-up longitudinal study on 46 MS patients revealed that there was significant correlation between SDMT oral Z-score and EDSS, but no correlation between PASAT Z-score and EDSS (Brochet et al, 2008). In our study, correlation of cognitive performance with fatigue, depression and duration of disease was not seen. Also, Drake and colleagues show that SDMT oral and PASAT both correlated weakly with fatigue and depression scores in

MS patients (Drake et al, 2010).

5. Conclusion

With due attention to our findings we suggest that SDMT oral can be used in MS patients with mild disability to screen impaired patients in terms of information processing speed, because of the following: 1) this test has high sensitivity and specificity and good classification accuracy; 2) this test correlates well with ambulation and manual functions; 3) this test was administered and scored in less than five minutes, and patients can easily tolerate it and participate with little stress.

Acknowledgements

We would like to thank MS patients and healthy subjects who participated in this study and the staff of the MS Society of Kerman. This work was supported by funds from the Kerman Neuroscience Research Center, Kerman, Iran.

References

Amato, M.P., Ponziani, G., Pracucci, G., Bracco, L., Siracusa, G., Amaducci, L. (1995). Cognitive impairment in early-onset multiple sclerosis. Pattern, predictors, and impact on everyday life in a 4-year follow-up. *Arch Neurol*;52(2):168-172. PMID:7848126 [PubMed - indexed for MEDLINE]

Beatty, W.W., Blanco, C.R., Wilbanks, S.L., Paul, R.H., Hames, K.A. (1995). Demographic, clinical, and cognitive characteristics of multiple sclerosis patients who continue to work. *Neurorehabilitation and Neural Repair*;9:167-73.

Benedict, R.H., Fischer, J.S., Archibald, C.J., Arnett, P.A., Beatty, W.W., Bobholz, J., et al. (2002). Minimal neuropsychological assessment of MS patients: a consensus approach. *Clin Neuropsychol*;16(3):381-97. PMID: 12607150 [PubMed - indexed for MEDLINE]

Benedict, R.H., Cookfair, D., Gavett, R., Gunther, M., Munschauer, F., Garg, N., et al. (2006). Validity of the minimal assessment of cognitive function in multiple sclerosis (MACFIMS). *J Int Neuropsychol Soc*;12(5):549-58. PMID:16981607 [PubMed - indexed for MEDLINE]

Benedict, R., Duquin, J., Jurgensen, S., Rudick, R., Feitcher, J., Munschauer, F., et al. (2008). Repeated assessment of neuropsychological deficits in multiple sclerosis using the Symbol Digit Modalities Test and the MS Neuropsychological Screening Questionnaire. *Multiple Sclerosis*;14(7):940-6. PMID:18573822 [PubMed - indexed for MEDLINE]

Brochet, B., Deloire, M.S, Bonnet, M., Salort-Campana, E., Ouallet, J.C., Petry, K.G., et al. (2008). Should SDMT substitute for PASAT in MSFC? A 5-year longitudinal study. *Mult Scler*;14(9):1242-9. PMID:18653737 [PubMed - indexed for MEDLINE]

Demaree HA, DeLuca J, Gaudino EA, Diamond BJ. (1999). Speed of information processing as a key deficit in multiple sclerosis: implications for rehabilitation. *J Neurol Neurosurg Psychiatry*;67(5):661-3. PMID:10519876 [PubMed - indexed for MEDLINE]

Deloire, M.S., Bonnet, M., Salort, E., Arimone, Y., Boudineau, M., Petry, K., et al. (2006). How to detect cognitive dysfunction at early stages of multiple sclerosis?. *Multiple sclerosis*;12(4):445-52. PMID: 16900758 [PubMed - indexed for MEDLINE]

Drake, A.S., Weinstock-Guttman, B., Morrow, S.A., Hojnacki, D., Munschauer, F.E., Benedict, R.H. (2010). Psychometrics and normative data for the Multiple Sclerosis Functional Composite: replacing the PASAT with the Symbol Digit Modalities Test. *Mult Scler*;16(2):228-37. PMID:20028710 [PubMed - indexed for MEDLINE]

Eshaghi, A., Riyahi-Alam, S., Roostaei, T., Haeri, G., Aghsaei, A., Aidi, M.R., et al. (2012). Validity and reliability of a Persian translation of the Minimal Assessment of Cognitive Function in Multiple Sclerosis (MACFIMS). *Clin Neuropsychol*;26(6):975-984. PMID: 22681459 [PubMed - indexed for MEDLINE]

Fischer, J.S., Rudick, R.A., Cutter, G.R., Reingold, S.C. (1999). The Multiple Sclerosis Functional Composite Measure (MSFC): an integrated approach to MS clinical outcome assessment. National MS Society Clinical Outcomes Assessment Task Force. *Mult Scler*;5(4):244-250. PMID: 10467383 [PubMed - indexed for MEDLINE]

Folstein, M.F., Folstein, S.E., McHugh, P.R. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*;12(3):189-98. PMID:1202204 [PubMed - indexed for MEDLINE]

Frohman, E.M., Racke, M.K., Raine, C.S. (2006). Multiple sclerosis--the plaque and its pathogenesis. *N Engl J Med*;354(9):942-55. PMID:16510748 [PubMed - indexed for MEDLINE]

Ghassemzadeh, H., Mojtabai, R., Karamghadiri, N., Ebrahimkhani, N. (2005). Psychometric properties of a Persian-language version of the Beck Depression Inventory--Second edition: BDI-II-PERSIAN. *Depress Anxiety*;21(4):185-192. PMID: 16075452 [PubMed - indexed for MEDLINE]

Kurtzke, J.F. (1983). Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology*;33(11):1444-52. PMID:6685237 [PubMed - indexed for MEDLINE]

Krupp, L.B., LaRocca, N.G., Muir-Nash, J., Steinberg, A.D. (1989). The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol*;46(10):1121-3. PMID: 2803071 [PubMed - indexed for MEDLINE]

Lublin, F.D,, Miller, A.E. (2008). Multiple sclerosis and other inflammatory demyelinating diseases of the central nervous system. In: Bradley WG, editors. Neurology in clinical practice: The neurological disorders. *Butterworth-Heinemann Elsevier*, Pp: 1588-95.

Mathiowetz, V., Weber, K., Kashman, N., Volland, G. (1985). Adult norms for the Nine Hole Peg Test of finger dexterity. *Occupational Therapy Journal of Research*;5:24-38.

Polman, C.H., Reingold, S.C., Banwell, B., Clanet, M., Cohen, J.A., Filippi, M., et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the "McDonald Criteria". *Ann Neurol*. 2011;69(2):292-302. PMID:16283615 [PubMed - indexed for MEDLINE]

Parmenter, B.A., Weinstock-Guttman, B., Garg, N., Munschauer, F., Benedict, R.H. (2007). Screening for cognitive impairment in multiple sclerosis using the Symbol digit Modalities Test. *Mult Scler*;13(1):52-7. PMID: 17294611 [PubMed - indexed for MEDLINE]

Rudick, R.A., Cutter, G., Reingold, S. (2002). The multiple sclerosis functional composite: a new clinical outcome measure for multiple sderosis trials. *Mult Scler*;8(5):359-65. PMID: 12356200 [PubMed - indexed for MEDLINE]

Table 1. Demographic characteristics of healthy subjects and MS patients

Variables	Healthy subjects	MS patients	P value
Male/female; % male	10/28;26.3	10/28;26.3	1.0
Age(years)	29.9±6.8	30.5±7	0.71
Education(years)	13.6±3	14.1±4.2	0.45
Disease duration (months)	-	28.2±27.5	-

Table 2.Comparison between healthy subjects and MS patients in terms of SDMT oral, SDMT written and PASAT scores

Variable	MS Patients	Healthy Subjects	Difference Between Groups
SDMT oral score Mean ± SD	45.97 ± 10.3	52.9 ± 7.4	p=0.001
SDMT written score Mean ± SD	44.2 ± 10.6	51.3 ± 7.4	p=0.001
PASAT score Mean ± SD	45.1 ± 10.7	49.95 ± 7.2	p=0.03

Abbreviations: MS, multiple sclerosis; SDMT, Symbol Digit Modalities Test; PASAT, Paced Auditory Serial Addition Test

Table3. Correlation between scores of tests related to information processing speed, and ambulation, upper motor function, depression and fatigue scores, and duration of disease in MS patients.

Variable	Mean time of T25FW	Mean time of 9HPT	BDI-II	FSS	Disease duration
SDMT oral score	r= -0.5 P= 0.002	r= -0.5 P= 0.005	r= -0.03 P= 0.9	r= -0.2 P= 0.3	r= -0.2 P= 0.3
SDMT written score	r= -0.3 P= 0.07	r= -0.3 P= 0.09	r= -0.07 P= 0.7	r= -0.1 P= 0.5	r= -0.2 P= 0.2
PASAT score	r= -0.04 P= 0.8	r= -0.2 P= 0.2	r= -0.01 P= 0.9	r= -0.01 P= 0.9	r= -0.02 P= 0.9

Abbreviations: MS, multiple sclerosis; SDMT, Symbol Digit Modalities Test; PASAT, Paced Auditory Serial Addition Test; T25FW, Timed 25-Foot Walk; 9HPT, Nine Hole Peg Test; BDI-II, Beck Depression Inventory-II; FSS, Fatigue Severity Scale.

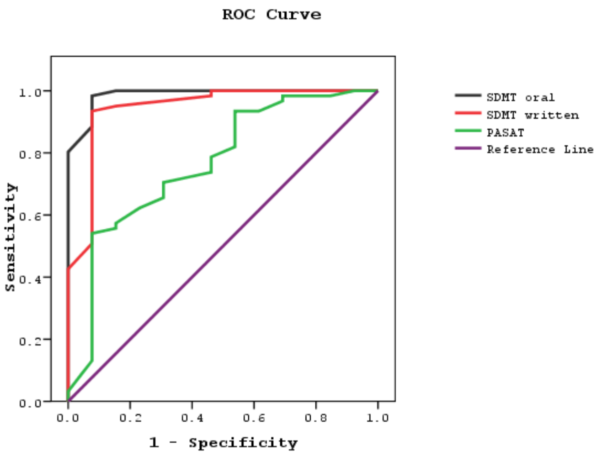

Figure 1. ROC curve for SDMT oral, SDMT written and PASAT