Digit Span and Verbal Fluency Tests in Patients with Mild Cognitive Impairment and Normal Subjects in Thai-Community†

Weerasak Muangpaisan MD, MPhil*,
Somboon Intalapaporn MD*, Prasert Assantachai MD, FRCP*

†*The abstract of this study was presented as a poster at the American Geriatrics Society 2007 Annual Scientific Meeting and was published in J Am Geriatr Soc 2007; 55 (4 Suppl): S105*
** Department of Preventive and Social Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand*

Background: *Far too little attention has been paid to the difference of Digit Span test and category verbal fluency test (CVFT) between normal and mild cognitive impairment (MCI) subjects.*
Objective: *To investigate the difference of Digit Span test and CVFT between normal subjects and patients with MCI and study the influence of age, gender, and education on the task performance.*
Material and Method: *The authors collected data of 77 participants diagnosed with amnestic MCI (from 517 participants screened) and 30 normal subjects aged 50 or over enrolled from communities in Bangkok. The Digit Span test and CVFT (semantic fluency and Controlled word association test for letter fluency) were used to evaluate the subjects.*
Results: *MCI patients had significantly lower digit span score, in both Digits Forward and Digits Backward, poorer performance on semantic fluency for animals and fruits and letter fluency test. The logistic regression model of MCI diagnosis showed that only Digits Backward score was a predictor of MCI diagnosis (OR 0.643 for each increment of 1 digit, p = 0.009, 95% confidence interval 0.462-0.896). The cut-off point of Digit Backward score was 4 and yielded sensitivity of 77% and specificity of 57%. Females had lower scores than males in every test except semantic fluency for fruits. The digit span and semantic fluency scores decreased as age increased but letter fluency increased correspondently with age. The digit span and CVFT scores increased in parallel with the increase of education.*
Conclusion: *MCI patients had poorer performance on the Digit Span and CVFT tests than normal age and education matched subjects. Digits Backward test can predict the MCI diagnosis. Age, gender and education have an impact on the performance of the tests.*

Keywords: *Mild cognitive impairment, Verbal fluency, Digit span, Community, Elderly*

J Med Assoc Thai 2010; 93 (2): 224-30
Full text. e-Journal: *http://www.mat.or.th/journal*

Digit Span and Verbal fluency tests are rapid methods used in an outpatient clinic to assess patients with cognitive problems. Physicians use the category verbal fluency tests (CVFT) to evaluate semantic memory, language and executive function and use the Digit Span test to assess the attention of patients[1-6]. Verbal fluency is typically tested in letter and semantic domains. Differential performance on measures of letter versus semantic fluency has been shown in ageing-related disorders such as Alzheimer's disease (AD)[7]. However, far too little attention has been paid to the difference of Digit Span test and CVFT in MCI subjects from normal population. In addition, there is no normative data of this test in a Thai population and Thai physicians have to use the standard value from Western textbooks, which may not represent the Thai population.

Correspondence to: Muangpaisan W, Department of Preventive and Social Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand. Phone: 0-2419-8388, Fax: 0-2411-5034. E-mail: siwmp@mahidol.ac.th

The purpose of the present study was to investigate the difference of the digit span and CVFT in normal and mild cognitive impaired patients. The present paper will also seek the normal value of these two tests in normal subjects aged 50 and over and patients with mild cognitive impairment and the influence of age, gender and education on the tests.

Material and Method

The present study was carried out at community-based units as part of The Bangkok Longitudinal Study by Siriraj Hospital for the Older Men and Women (BLOSSOM) in Bangkok, Thailand. All patients presenting with a subjective complaint of cognitive decline and intact instrumental activities of daily living (IADLs) were invited to be screened for the study.

The authors excluded patients with Thai version Mental State Examination (TMSE) < 24 and major depression diagnosed by Diagnostic and Statistic Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria[8,9]. Patients with the Thai Geriatric Depression Scale (TGDS) over 12 were not excluded unless they met the DSM-IV criteria for major depression[10], because depressive symptoms can be one of the neuropsychiatric manifestations of MCI[11].

Patients were then assessed for the presence of cognitive and neuropsychiatric symptoms by a geriatrician rater blinded to their TMSE score. Diagnosis of MCI was based on Petersen's criteria, showing impairment on one or more measures of memory, clinician's judgment based on a structure interview by using Clinical Dementia Rating Scale (CDR) 0.5 and Global Deterioration Scale (GDS) 3 with performance in other cognitive domains within normal ranges and no impairment in functional or IADLs[12-14].

The normal subjects were classified by basing on 1) TMSE $\geq$ 24 2) no impairment in activities of daily living (ADLs) 3) no diagnosis of major medical, neurological or psychiatric illness 4) no history of head injury and substance abuse 5) no evidence of dementia or memory impairment on assessment.

The authors collected medical history, baseline characteristics, functional assessment, physical examination, blood test and cognitive tests. The authors used the Digit Span test (Forward and Backward), semantic fluency (animal and fruit naming) and Controlled oral word association test (COWAT) for letter fluency (words starting with letter Koh and letter Soh in Thai).

The two parts of Digit Span- Digits Forward and Digits Backward-were administered separately. The digits were given at the rate of one per second. In Digits Forwards, the patient was to repeat the digits, while in Digits Backward the patient was to reverse the digits. Two attempts were administered at each level. When a patient failed at both attempts at the one level, the test ceased. Score 2 was given if the patients passed both tests, score 1 was given if the patients passed one trial and score 0 was given if they failed both attempts.

Category fluency tests were instructed by asking the participants to generate as many names of animals that they could think of in one minute. Then the participants were asked to generate names of fruits in another one minute. After that, the COWAT was administered by asking the participants to generate as many words as they could think of starting with particular letters, excluding proper nouns, numbers, and the same word with a different suffix. In the present study, the authors chose letter Koh (for one minute) and letter Soh (for another 1 minute).

Statistical analyses were performed using SPSS for Windows (SPSS 10). P-value less than 0.05 was considered statistically significant. Independent-samples t-test was used to compare means of the two groups and logistic regression was used to assess the tests to predict the likelihood in the diagnosis of MCI. The present study was approved by the local ethic committee and informed consent was given by every subject.

Results

Of the 517 participants screened, there were 77 patients diagnosed amnestic MCI based on Petersen's criteria. Thirty normal subjects were selected for more neuropsychological tests and for the comparison. Of the MCI subjects, 68% were single domain amnestic MCI and 32% were multiple domain amnestic MCI. The baseline characteristics are summarized in Table 1. There was no difference in mean age, educational level, male: female ratio and APOE status.

The TMSE was significantly lower in MCI compared to normal subjects and the TGDS and ADAS-cog scores were significantly higher in MCI patients.

Compared to normal subjects, MCI patients had significantly lower digit span score, in both Digits Forward and Digits Backward, poorer performance on semantic fluency for animals and fruits. The letter fluency test showed significantly lower scores in MCI

Table 1. Clinical characteristics of normal subjects and MCI patients

Characteristic	Normal (n = 30)	MCI (n = 77)	p-value
Age, mean ± SD (years)	63.7 ± 7.3	66.3 ± 7.9	0.127
Education, mean ± SD (years)	6.7 ± 3.2	6.1 ± 3.3	0.368
Male: female ratio	25%	35%	0.518
Duration of symptoms, mean ± SD (years)	-	2.8 ± 1.1	
Type of MCI (number, %)			
Single domain amnestic MCI	-	52 (68%)	
Multiple domain amnestic MCI	-	25 (32%)	
TMSE	28.1 ± 1.8	26.5 ± 1.6	<0.001
TGDS	7.0 ± 5.6	12.1 ± 5.9	<0.001
ADAS-cog	6.7 ± 2.8	9.7 ± 4.1	<0.001
APOE epsilon-4 +ve (heterogenous/homogenous)	10 (33%)	19 (26%)	0.454

SD = standard deviation, MCI = Mild cognitive impairment, TMSE = Thai mental state examination, TGDS = Thai geriatric depression scale, ADAS-cog = The Alzheimer's disease assessment scale-cognitive subscale, APOE = Apolipoprotein E

Table 2. Comparison of means of the digit span test and CVFT of normal and MCI subjects by Independent sample t-test

Measures	Normal	MCI	Mean dif	95% CI	p-value
Digits Forward score	11.9 ± 1.8	10.6 ± 1.8	1.30	0.52-2.08	0.001
Digits Backward score	5.3 ± 2.1	3.9 ± 1.3	1.41	0.59-2.24	0.001
Semantic fluency					
Fluency for animals	17.3 ± 6.4	14.6 ± 5.0	2.71	0.37-5.04	0.024
Fluency for fruits	15.8 ± 3.7	13.1 ± 4.1	2.68	0.94-4.41	0.003
Letter Fluency					
Letter Koh (Thai alphabet)	9.7 ± 6.0	6.1 ± 4.4	3.18	0.69-5.67	0.014
Letter Soh (Thai alphabet)	10.0 ± 5.8	6.4 ± 4.2	3.54	1.52-5.55	0.001

compared to normal subjects. Table 2 summarizes the comparison of digit span and CVFT between the two groups.

Females had poorer scores than males in every test of Digit Span and CVFT except semantic fluency for fruits. Comparing for three different age groups of 50-59, 60-69, and 70 and above, the digit span and semantic fluency scores decreased as age increased. However, letter fluency increased correspondently with age. Comparing for education of three levels, 1-4 years, 5-8 years, and 9 years and above, the Digit Span and CVFT scores increased in parallel with the increase of education.

After being adjusted for age and educational level, every test remained significantly different between MCI and normal subjects as shown in Table 2.

Receiver operating characteristic (ROC) curves were constructed for a range of cut-off points to explore the sensitivity and specificity of each cognitive test. The areas under the curve demonstrate fair accuracy of the cognitive tests. The optimal cut-off points for each cognitive test with sensitivity and specificity were summarized in Table 3.

Logistic regression analysis showed that the test, which predicted the likelihood of diagnosis of MCI, was the Digits Backward test. Each increment in one digit would decrease the likelihood of diagnosis of MCI (OR 0.643 for each increment of 1 digit, p = 0.009, 95% confidence interval 0.462-0.896). The Digits Forward test and CVFT tests were not predictive of the diagnosis. Table 4 summarizes the logistic regression analysis of the tests.

Discussion

Physicians frequently used 6 ± 1 as a normal range of Digits Forward span and 5 ± 1 for Digits Backwards span in the assessment of patient's attention[15]. In our study, this normal range is applicable

Table 3. Suggested optimal cut-off points of each cognitive test from a receiver operating characteristic (ROC) curves

Test	Area under the curve	Cut-off points	Sensitivity	Specificity
Digit forward score	0.713	12	63%	69%
Digit backward score	0.730	4	77%	57%
Semantic fluency				
Fluency for animals	0.627	14	83%	42%
Fluency for fruits	0.691	15	67%	62%
Letter fluency				
Letter Koh (Thai alphabet)	0.663	9	50%	73%
Letter Soh (Thai alphabet)	0.709	7	80%	57%

Table 4. Regression estimates and predictive values for the digit span test and CVFT

Tests	OR	95% confidence interval	p-value
Digits Forward	0.785	0.570-1.082	0.140
Digits Backward	0.643	0.462-0.896	0.009
Semantic fluency for animals	1.027	0.906-1.164	0.678
Semantic fluency for fruits	0.881	0.753-1.032	0.116
Letter Koh verbal fluency	1.012	0.861-1.189	0.885
Letter Soh verbal fluency	0.878	0.746-1.033	0.116

for the Thai population only in Digits Forwards span where only 13.7 per cent of normal subjects could not repeat at least 5 Digits Forward. However, this is not applicable in the Digits Backward span as there was only 26.5 per cent of the normal subjects who could repeat at least 4 Digits Backward.

CVFT is the way to assess semantic knowledge, language and executive functions[16]. In the letter fluency test, subjects had to seek a strategy for guiding the search of words such as using the same initial consonant, variation on a word, or variations on a theme. In semantic fluency test, subjects may outline subcategories to facilitate their recall.

Age, gender and educational level have been shown to affect the performance for the cognitive tests[1,2]. The authors compared these factors between normal and MCI groups, which did not show any statistical difference. However, females had a poorer performance on both digital span and CVFT except semantic fluency for fruits, which may result from the familiarity for kitchen and market shopping of the female. Several studies have confirmed the influence of age and education on the cognitive tests but did not find the gender influence on the tasks[17,18]. A systematic review showed that women outperformed men on verbal fluency, perceptual speed tasks, fine motor skills, verbal memory and verbal learning. Men outperformed women on visuospatial ability, mathematical problem solving and visual memory[19]. No gender differences on attention and working memory were found. However, some studies did find that gender had a significant effect on the verbal fluency only females being better in semantic fluency for fruits and men being better in semantic fluency for tools[20].

In the present study, both Digit Span and CVFT scores decreased with the increment of age and reduction of education. We found that the letter fluency increased with the increment of age. The present study result supports the findings of previous studies that semantic but not letter fluency is typically poorer in the elderly and against the finding of some studies that reported no difference in letter fluency test with the increased age[21]. Educational level is associated with the performance of the tests in that the higher education correlated with the better performance. The dramatic increase in the letter fluency score was observed in patients with 9 years of education or above compared to patients with less than 9 years education.

In the present study, normal subjects aged 50 and above generated about 10 words for letter

fluency compared to 12-16 words of the Western elderly. Semantic fluency averages for the presented normal subjects ranged from 15-18 words, which is less than 19-21 words of the Western elderly[22]. The authors found that semantic fluency decreased dramatically in patients aged 70 years and over. Semantic fluency is less difficult than letter fluency for adults[16]. The pattern of worse performance for the letter fluency also exists in the MCI patients, which is not correspondent to patients with AD[7]. Alzheimer patients have more difficulty with semantic fluency than letter fluency, which may result from the breakdown in semantic knowledge about categories.

The MCI patients had lower digit span than normal especially Digits Backward. Disorders of attention (for example, delirium) cause severe impairment in digit span, especially in Digits Backward[15]. In Alzheimer patients, the digit span is preserved in the early stage of the course. On the contrary, patients with subcortical dementias have lower digit span. In the present study, the authors included amnestic MCI, either single domain or multiple domains. If they progress to dementia, these groups of patients are more likely to progress to Alzheimer's disease more than other dementias[23]. The digit span in these subjects of preclinical stage of Alzheimer's disease should be well preserved. However, the present study showed that even patients with amnestic MCI still have poorer performance on digit span compared to normal subjects regardless of age, gender and educational level. The logistic regression shows the less likelihood of the diagnosis of MCI if the patient can repeat more numbers of digits backward. This implies the attention deficit and the memory impairment the MCI patients have.

The present study has a limitation. The number of normal subjects is too small to be categorized into separate groups based on age and education. This makes the normal value of the tests be applicable only in general, not individually. A larger study should be investigated into the effect of age, gender, and educational level on the scores of these tests in a normal Thai population.

Conclusion

MCI patients have lower Digit Span and CVFT scores than normal subjects. The increment in Digits Backwards score showed the less likelihood of the MCI diagnosis. This might reflect the semantic knowledge impairment, executive dysfunction, and attention deficit in the MCI patients. Age, gender, and education have an impact on the performance of the tests.

Acknowledgements

The authors wish to thank the contributions of all staff in The Bangkok Longitudinal Study by Siriraj Hospital for the Older Men and Women (BLOSSOM) who helped collect the data. We also wish to thank the participants and their caregivers, without whom this research would not have been possible.

Financial disclosures

This research was supported by Novartis (Thailand) Limited for transportation and neuropsychiatric tests.

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การจำตัวเลข และความคล่องของภาษาพูดในคนปกติ และผู้ป่วยที่มีการรู้คิดบกพร่องเล็กน้อยในชุมชนไทย

วีรศักดิ์ เมืองไพศาล, สมบูรณ์ อินทลาภาพร, ประเสริฐ อัสสันตชัย

ภูมิหลัง: *ในปัจจุบันนี้การศึกษาทางถึงความแตกต่างของการทดสอบการจำตัวเลข และความคล่องของภาษาพูดในคนปกติ และผู้ป่วยที่มีการรู้คิดบกพร่องเล็กน้อย (เอ็มซีไอ) ยังมีไม่มาก*

วัตถุประสงค์: *เพื่อศึกษาถึงความถึงความแตกต่างของการทดสอบการจำตัวเลขและความคล่องของภาษาพูดในคนปกติและผู้ป่วยที่มีการรู้คิดบกพร่องเล็กน้อย และผลกระทบของอายุ เพศ และระดับการศึกษาต่อความสามารถในการทำการทดสอบดังกล่าว*

วัสดุและวิธีการ: *ผู้นิพนธ์รวบรวมข้อมูลจากคนปกติ 30 คน และผู้ป่วยที่มีการรู้คิดบกพร่องเล็กน้อย 77 คน (จากผู้ที่เข้าร่วม การศึกษา 517 คน) ที่มีอายุตั้งแต่ 50ปี ขึ้นไปจากชุมชนในกรุงเทพมหานคร และทดสอบการจำตัวเลขและความคล่องของภาษาพูด*

ผลการศึกษา: *ผู้ป่วยที่มีการรู้คิดบกพร่องเล็กน้อยสามารถจำตัวเลขทั้งไปหน้าและย้อนกลับได้น้อยกว่า บอกชื่อสัตว์และผลไม้ได้น้อยกว่า และบอกชื่อคำที่ขึ้นต้นด้วยตัวอักษรที่กำหนดได้น้อยกว่าคนปกติ การวิเคราะห์ logistic regression ในการทำนายการวินิจฉัยภาวะการรู้คิดบกพร่องเล็กน้อยแสดงให้เห็นว่าความสามารถในการจำตัวเลขย้อนกลับ สามารถทำนายการวินิจฉัยภาวะการรู้คิดบกพร่องเล็กน้อยโดยเพิ่มความแม่นยำ 0.643 ในแต่ละหลัก ของตัวเลขที่ผู้ป่วยจำได้ (ค่าความเชื่อมั่นร้อยละ 95 เท่ากับ 0.462-0.896 และมีนัยสำคัญ 0.009) คะแนนการจำตัวเลขย้อนกลับเท่ากับ 4 มีความไวในการแยกผู้สูงอายุปกติจากผู้ป่วยที่มีการรู้คิดบกพร่องเล็กน้อยได้ร้อยละ 77 และความจำเพาะร้อยละ 57 ผู้หญิงมีความสามารถในการทำการทดสอบการจำตัวเลขและความคล่องของภาษาพูดน้อยกว่าผู้ชาย ยกเว้น ความสามารถในการบอกชื่อผลไม้ ความสามารถในการทำการทดสอบการจำตัวเลขและความคล่องของภาษาลดลงเมื่ออายุมากขึ้น ยกเว้นความสามารถในการบอกคำที่นำหน้าด้วยตัวอักษรที่กำหนดซึ่งผู้ที่อายุมากกว่าสามารถทำได้ดีกว่า ผู้ป่วยที่มีการศึกษาสูงจะมีความสามารถในการทำการทดสอบสูงกว่า*

สรุป: *ผู้ป่วยที่มีการรู้คิดบกพร่องเล็กน้อยมีความสามารถในการจำตัวเลข และความคล่องของภาษาพูดน้อยกว่าคนปกติที่มีระดับของอายุ และการศึกษาเดียวกัน ความสามารถในการจำตัวเลขย้อนกลับสามารถทำนายการวินิจฉัยการรู้คิดบกพร่องเล็กน้อยได้ อายุ เพศ และระดับการศึกษาส่งผลต่อระดับความสามารถในการ ทำการทดสอบ*