Visual Association Memory Test in Differentiating Early Stage of Alzheimer's Disease from Vascular Dementia

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Abstract- We studied the results of the Visual Association Memory Test (VAMT) in differentiating Alzheimer's disease (AD) and vascular dementia (VaD). In addition, other basic neuropsychological tests, including the Mini-Mental State Examination (MMSE) and the Clinical Dementia Rating (CDR) were also used. Generally, with the VAMT, AD patients had a worse performance than VaD patients. Particularly among patients with a CDR = 0.5, the AD patients had statistically significantly lower VAMT scores (score less than 3) ($p = 0.026$) compared to those of VaD patients. However, the VAMT could not predict clinical severity or disease progression. The VAMT, as revealed in this study, is a brief, simply administered, and less biased test, and may offer a diagnostic adjunct to differentiate AD from VaD especially in an early dementia state.

Key Words: Visual association memory test, CDR, MMSE, Neuropsychology, Vascular dementia, Alzheimer's disease

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INTRODUCTION

Alzheimer's disease (AD), a common neurodegenerative disease, is characterized by a progressive dementia with initial memory impairment[1]. Although great progress has been made in the clinical diagnosis, confusion still persists in differentiating AD and vascular dementia (VaD), particularly in a very mild state[1-3]. Several neuropsychological studies have been done in an attempt to distinguish between the two diseases[1-4]. However, there have been very few quick and simple tests to detect early AD[5,6].

In dementia clinics, memory impairment is the cardinal symptom in patients with AD, VaD or other dementia disorders. However, the patterns of memory impairment may vary[7]. In the early stage of AD, memory impairments are usually characterized by forgetfulness, a misplacement of objects, a repetition of the same questions or stories, and getting lost in new places due to pronounced amnesia and an inability to absorb new information. These memory impairments are compatible with the early pathological changes in the medial temporal lobe in AD. Recently, some studies have focused on visual memory in dementia disorders and suggested

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that the Visual Association Memory Test (VAMT) might predict early AD[5,6].

The VAMT is a brief learning task based on imagery mnemonics that requires linking information by creating visual images or making up a story; as in forming a mental image of two interacting objects, using an automatic memory process with no conscious effort[8]. Anterograde amnesia is also a reflection of defects or disturbances in the collecting of our daily events, such as time, name or personal relationships, internally and externally, into episodic long-term memory through encoding, consolidation or storage to form, unintentionally, our life impression or experiences[9]. The VAMT may induce incidental learning by using paired objects and asking subjects to trace the "echoic episodic memory" of the other associated interacting image simultaneously appearing in the first picture card, after showing them the second "cue card". When first seeing the paired pictures, patients usually perceive the interactive presentation with limited attention, but may reflect on the second interacting "missing object" with a cue if they have an intact anterograde memory[6,9]. Patients with automatic memory impairment, such as some dementia victims, often develop a poor connection with daily life and their visual surroundings to form a permanent coding[9]. The purposes of this study were to understand the role of the VAMT in differentiating between AD and VaD, particularly in the early stage of dementia.

SUBJECTS

Subjects enrolled included 27 patients with AD, 23 patients with VaD, and 23 age- and education-matched, non-demented normal controls during a three-year period (2002 to 2004) at Chang Gung Memorial Hospital. These dementia patients were recruited from the dementia clinics and the normal controls were selected from the society after an informed consent. Patients were included in the study if they met each of the following criteria: history of cognitive decline that was gradual in onset and progressive over a period of at least 6 months. The diagnosis for probable AD was made according to NINCDS-ADRDA criteria and DSM IV for AD[10,11]. Patients with an amnesic syndrome who did not have an interference with daily activity were categorized into mild cognitive impairment (MCI) groups and were not enrolled in this study. Therefore, we recruited demented patients who got CDR more than 1 or MMSE ≤23 if the score of MMSE is 2 points lower than their cutoff scores according to their education levels. However, we recruited the AD patients if their MMSE scores were 2 points lower than their cutoff levels, although they had a CDR = 0.5. The diagnosis of VaD was made according to the NINDS-AIREN criteria and DSM IV for VaD[12]. Most VaD patients emerged the clinical demented symptoms 6-12 months after strokes. A high-resolution computed tomography or magnetic resonance imaging scan of the brain revealed findings consistent with the diagnosis of AD. In the AD group, patients who presented with early extrapyramidal, psychotic, or sphincter symptoms, cerebrovascular disorders, brain images revealing multiple lacunar infarcts, low densities in the vascular territories, hydrocephalus, endocrine or nutritional abnormalities such as thyroid function, cortisol, folic acid, or vitamin B12 deficiency, clinically significant hepatic, renal, pulmonary or cardiac conditions, or evidence of syphilis or focal neurological deficits, were excluded. In addition, patients with any other neurodegenerative disorder or patients who could not performed the neuropsychological tests completely were also excluded. In the VaD group, patients who presented with dementic symptoms before vascular insults and patients who did not have clear vascular insults in the brain images were excluded. All patients who had a family history of dementia or severe psychiatric problems, including major depression, schizophrenia or bipolar diseases, were also excluded. The medical history, neurological examination, brain images, and blood screening tests for dementia were carefully studied.

METHODS

All patients provided basic data, detailed neurological examinations, blood routine and hemograms, biochemistry, screening tests, and brain images including high resolution computed tomography (CT) or magnetic

resonance images (MRI). After completing this survey, we gave the patients a series of neuropsychological batteries, including the Mini-Mental State Examination (MMSE), Clinical Dementia Rating (CDR), verbal memory test, attention digit span test, and the clock-drawing test. After these basic evaluations, we also arranged a VAMT for these patients, which took another 5-20 minutes.

The VAMT was composed of six paired, associated pictures, each one presenting two interacting objects which are not commonly connected or co-existing in normal life. Our VAMT cards were modified pictures, including a key hanging from a balloon, a bird standing in a cradle, a triangular flag standing in an urn, a pig standing on a chair, an ape holding an umbrella, and a die putting on a scoop, based on Lindeboom et al.[5]. These pictures were also shown as line drawings, without filling in the colors. First, we showed the sample stimulus figure cards one-by-one to the patient, and asked the patient to name the object in each one. After finishing the six sample stimulus figures, we gave the subject the cue cards in the same order and asked the patient to identify the missing object. For example, in the first turn, we showed the patient the picture of a pig standing on a chair, and then asked the patient to point to the two "objects" and name them, using his own words, without asking the patients to memorize. In the second turn, the paired cue card only showed an empty chair. After showing the cue card, we asked the patient to recall, based on the previous figure, what is missing in the second picture. No hint or the specific mention of the object in Chinese was used with the questions. There was no time latency between the first and second turn. We recorded the right answer as a score: the lowest was zero and the best was six.

Statistical analysis

Among the demographic variables, included gender, age, education in years, and simple neuropsychological scores such as CDR, MMSE, we used the Kruskal Wallis H test to compare the difference between the AD, or VaD and normal controls. The comparison between the AD and VaD groups was measured using the Mann-Whitney U test to analyze the MMSE and VAMT in terms of clinical severity, education in years, and performance distribution. The sensitivity and specificity of these tests were analyzed using the receiver's operating characteristics (ROC) curves, with SPSS, to study the sensitivity of each test in the same disease group. We calculated the Eta value in the Crosstabulation to estimate the relationship between CDR and MMSE or VAMT in order to understand the correlation in these two demented groups.

RESULTS

Ninety-seven consecutive subjects were enrolled into this study, including 27 AD patients, 23 VaD patients and 23 normal controls. Both AD and VaD patients had a statistically significant lower score in MMSE and VAMT, and a higher score in CDR as compare with the normal controls. However there was no difference of the three groups in the age onset and education level after a Kruskal Wallis H test. We used the Mann-Whitney U test and SPSS 10.0 software for the analysis between AD and VaD groups. The patients in these two groups had similar onset ages, but a female predominance was noted in the AD group, and males were predominant in the VaD group ($p=0.006$). Although similar MMSE and clinical severity results were noted in these 2 groups, the performance on the VAMT was worse in the AD group and reached to a statistical significance ($p=0.002$) (Table 1).

Since age or education may influence the neuropsychological performance, we analyzed their influence on the MMSE and VAMT in all subjects by setting age and education as covariates. The MMSE was influenced by education ($p<0.05$), and the VAMT was not influenced by age or education ($p>0.05$). We divided the dementia patients into 2 groups by education, and compared their performances on the MMSE and VAMT, using Mann-Whitney U test. We observed that in the medium-to-high educational level group (years of education ≥6), the VAMT was better able to differentiate between AD and VaD ($p=0.006$), while in the lower educational level group, no difference was noted ($p>0.05$) (Table 2).

Table 1. *Demographic data and neuropsychological findings in AD and VaD patients and normal controls*

Diagnosis	AD	VaD	Normal controls	Mann-Whitney U test p
Total number	27	23	23	
Female gender (%)	77.8%	39.13%	43.5%	0.006*
Average onset age (range) (yr)	70.52 (52-80)	71.18 (57-84)	69.30 (53-78)**	0.778
Education (SD, range) (yr)	5.67 (5.46, 0-16)	4.52 (3.73, 0-16)	7.00 (3.44, 0-12)	0.592
CDR (SD)	0.852 (0.33)	0.80 (0.45)	0	0.289
MMSE (SD)	18.59 (4.10)	18.13 (4.53)	27.09 (1.81)	0.632
VAMT (SD)	1.07 (1.30)	2.52 (1.59)	5.13 (0.97)	0.002*
Verbal Memory Test				
Registration (SD)	6.22 (1.64)	7.46 (1.98)		0.137
Delay Recall (SD)	4.20 (2.82)	5.06 (2.51)		0.256
Recognition (SD)	6.40 (3.34)	7.06 (2.41)		0.575
Verbal Fluency (Name) (SD)	7.67 (1.15)	9.25 (3.74)		0.425
Digit Span Forward (SD)	2.75 (1.71)	3.08 (1.31)		0.609
Digit Span Backward (SD)	3.00 (1.15)	2.17 (0.94)		0.206
Construct Ability (SD)	4.17 (1.17)	2.89 (1.05)		0.058
Digit Cancellation Test (SD)	8.25 (3.81)	10.22 (4.45)		0.208

AD: Alzheimer's disease; VaD: vascular dementia; yr: year; CDR: Clinical Dementia Rating; MMSE: Mini-Mental State Examination; VAMT: Visual Association Memory Test; SD: standard deviation; *: statistical significance between AD and VaD by using Mann-Whitney U test; **: Average age of these normal controls when testing.

Table 2. *Comparison of MMSE and VAMT in different education levels and in variable VAMT scores between AD and VaD patients*

Diagnosis		AD	VaD	
		Mean (numbers)	Mean (numbers)	Mann-Whitney U test
Low edu.	MMSE	16.83 (12)	16.67 (9)	P=0.754
	VAMT	1.17 (12)	2.11 (9)	P=0.193
Med-high edu.	MMSE	20.00 (15)	19.07 (14)	P=0.591
	VAMT	1.00 (15)	2.79 (14)	P=0.006*

AD: Alzheimer's disease; VaD: vascular dementia; MMSE: Mini-Mental State Examination; VAMT: Visual Association Memory Test; Low edu.: years of education < 6; Med-high edu.: years of education≥6; numbers in the parentheses represent the number of patients; *: statistical significance.

Table 3. *The correlation of MMSE and VAMT between AD and VaD patients with different clinical dementia rating scores*

		No. of patients	Mean (range)	SD	P value
CDR = 0.5					
MMSE	AD	10	20.60 (15-23)	3.57	0.648
	VaD	13	20.85 (14-23)	2.64	
VAMT	AD	10	1.10 (0-3)	1.29	0.026*
	VaD	13	2.69 (0-5)	1.65	
CDR ≧1					
MMSE	AD	17	17.41 (12-23)	4.02	0.103
	VaD	10	14.60 (8-23)	4.03	
VAMT	AD	17	1.06 (0-4)	1.34	0.052
	VaD	10	2.30 (0-4)	1.57	

CDR: clinical dementia rating; AD: Alzheimer's disease; VaD: vascular dementia; SD: standard deviation; MMSE: Mini-Mental State Examination; VAMT: Visual Association Memory Test; *: statistical significance.

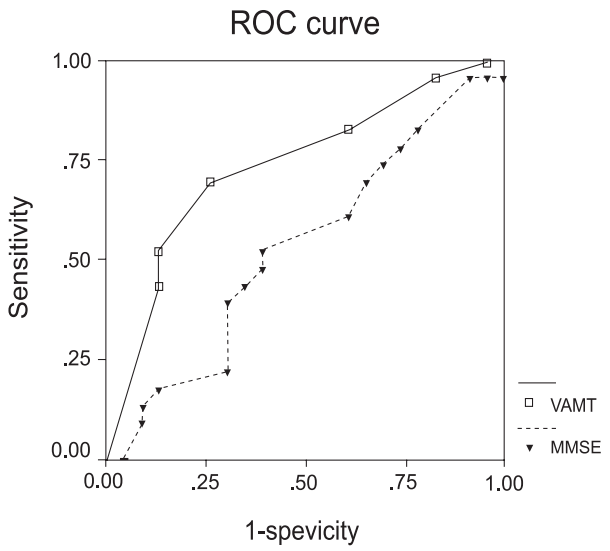

Figure. Receiver operating characteristics (ROC) curves showing discrimination between patients with Alzheimer's disease and normal volunteers by the MMSE and VAMT.

In order to clarify the clinical practice power for early detection, the patients were divided into early dementia (CDR=0.5) and mild-to-moderate dementia (CDR≥1) groups. In the CDR=0.5 group, the VAMT performance was significantly lower in the AD than in the VaD patients (p=0.026). However in the CDR≥1 group, there was no statistical significance between these populations on either test (Table 3).

The sensitivity of VAMT among the two groups was 0.74 with a cutoff 2 though the specificity was around 0.37. The ROC curves showed that the area under the curve was 0.753 on the VAMT and 0.461 on the MMSE in detecting AD from VaD (Figure). Therefore, the VAMT had a better sensitivity than the MMSE.

Using the Crosstabulation analysis and calculating the Eta value, the relationship between CDR and MMSE showed a statistically significance in both AD (p=0.001) and VaD (p<0.001) groups. However, the correlation between VAMT and CDR showed no statistical significance in both AD (p=0.581) and VaD (p=0.313) groups (Table 4).

Table 4. *Correlation between CDR and MMSE or VAMT among the two demented groups by calculating Eta value in the Crosstabulation*

	Type	Eta square	P value
MMSE	AD	0.514	0.001*
	VaD	0.587	<0.001*
VAMT	AD	0.056	0.581
	VaD	0.115	0.313

AD: Alzheimer's disease; VaD: vascular dementia; MMSE: Mini-Mental State Examination; VAMT: Visual Association Memory Test; *: statistical significance, p<0.01

DISCUSSION

The present results demonstrate a difference between VaD and AD patients, including a female predominance in AD and a male preponderance in VaD, similar to those of the previous studies[13]. In addition, there was a significant difference in VAMT performance between the AD and VaD groups, with 75% of AD patients having scores less than 3 in the VAMT, while there was no difference in the MMSE, CDR and other neuropsychological tests. Particularly in patients with a CDR=0.5, the VAMT demonstrated a better ability to differentiate AD from VaD. Furthermore, the MMSE was influenced by education, while the VAMT results were not statistically significant, by age or education. In patients with a higher level of education, the VAMT had a better predictive ability in differentiating AD from VaD particularly in the early stage of dementia. So VAMT could play a role in overcoming the ceiling affect of MMSE, which is masked by good education[24]. In some well-educated AD patients, a drop of 2-5 points per year in MMSE might has been found and they would face a predicament of drug withdrawal. The VAMT did not have a better predictive ability regarding clinical dementia severity than did the CDR or MMSE. Therefore, the VAMT itself only reflected the memory spectrum.

In our study, the VAMT was able to act as an adjunct to differentiate between AD and VaD, especially in the early stage of dementia. AD patients had a worse performance and usually had scores less than 3 in the VAMT, even in a very early stage. In early-stage AD, the memo-

ry deficits are episodic memory impairments, followed by inattention and semantic memory deficits with a relative preservation of the working memory and digit span[14,15]. By Baddeley's three-component model of working memory[16], the memory problems of early AD patients were mainly in new information consolidation, storage and getting into long-term memory. Though memory problems in VaD were diverse according to the sites of vascular injury, but the deficits were relatively common in abstraction and working memory, rather than memory retention[4,17]. To our understanding, loss of mental imagery is relatively rare, even in severely amnesic patients, because they still can generate vivid images, but gain no benefit from this imagery mnemonics due to a poor retention of the imaged materials[18,20]. According to the SPECT image studies, reduced cerebral blood flow in the temporo-parietal area is common in the early stage of AD[21]. In VaD, the cerebral blood flow is decreased, for the most part, in the frontal-predominant area[21]. Functional MRI studies revealed an activation increment in the medial temporal lobe and neocortical regions while performing a imagery memory task[22], reflecting a compensatory response to the accumulated AD pathology[23]. In our study, early dementia patients with medium to high education revealed satisfactory MMSE scores but showed very poor VAMT test results. Therefore, the VAMT had a better ability to distinguish between VaD and AD than the MMSE, particularly in high-educated early dementia patients. We could not figure out that the high-educated persons are really vulnerable to imagery memory or just because the basically demented deficit. But the status might be explained that high-educated persons are usually more sensitive about their own cognitive decline.

Because VAMT contained only six points, most AD patients had a very low score even in a very early stage. Therefore, the VAMT could not predict clinical severity or disease progression in AD and VaD patients. The MMSE evaluated the overall cognitive function, and was correlated with education and attention. The CDR reviewed current daily activities or life independence, including memory, orientation, problem solving, community affairs, hobbies and self-care. Our results also revealed that the MMSE and CDR are better in evaluating disease severity. On the other hand, the VAMT can evaluate memory deficits, instead of the total cognitive domain, as in the MMSE, and management ability in the CDR. Attentional requirement is not the only way to encode or register the sensory information processed into short term memory. Incessantly perceptual priming-like effect occurred in our daily life improving our memory into consolidation. Otherwise, intentional and incidental memory system may be not absolutely separated and medial temporal lobe may play a crucial role in both memory systems[25]. So VAMT may provide a different memory approach, which is available in our life, instead of the simple explicit memory test performed in MMSE. This can explain the poor correlation among the VAMT, CDR and MMSE.

One main bias in this study is on the diagnosis of mixed type dementia. Though we have already excluded possible AD patients with vascular risk factors, some VaD patients may be associated with AD. The pattern of memory deficits also varied among VaD groups because of the different vascular insult regions. So the specificity of the VAMT is not satisfactory for differentiating among different dementia types, but the sensitivity is above 75% in detecting AD from VaD patients and 97.2% in detecting AD from the normal controls.

In conclusion, the VAMT is a good diagnostic adjuvant because it is a brief, simple, and less biased test, and does not require well-trained raters, making it practically applicable, especially in the early diagnosis of demented patients. However, further investigation in a larger series and population is warranted.

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