研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書 籍 名	出版社名	出版地	出版年	ページ
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Ⅲ研究成果の刊行物・別刷

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ORIGINAL ARTICLE

Computerized visuo-spatial memory test as a supplementary screening test for dementia

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Abstract

Background: To prepare for a super-aging society, effective dementia screening tests are required. The most salient deficit appearing from the early stages of dementia/Alzheimer's disease (AD) is a deterioration in memory. The Hasegawa Dementia Scale-revised (HDS-R) and the Mini-Mental State Examination (MMSE) are widely used in Japan to screen for dementia. Both place an emphasis on memory function, but neither examines visuo-spatial memory (VSM) function, even though VSM deficits are a sensitive marker for the detection of conversion to dementia. Furthermore, brief tests of VSM that are appropriate for screening have not been standardized. Thus, in the present study, we devised a brief, computer-aided short-term VSM test.

Methods: Sixty-six aged people were evaluated. Using the Clinical Dementia Rating (CDR), it was found that 29 could be considered normal controls (NC; CDR 0), 10 had mild cognitive impairment (MCI; CDR 0.5), 15 had mild dementia (CDR 1), and 12 had moderate to severe dementia (CDR 2–3). The VSM test estimated how many locations each subject could memorize. Several numbered circles were shown on a monitor and subjects were required to memorize the location of these circles sequentially. After the numbers on the circles on the screen had disappeared, the subjects were required to indicate the circles in ascending order. A touch panel screen was used for this test to make it easier. The HDS-R was applied to subjects with MCI and dementia.

Results: The mean (±SD) VSM score in subjects with MCI (5.70 ± 0.96) was significantly lower than that in NC subjects (6.69 ± 0.82), but significantly higher than that in subjects classified as CDR 1 (4.67 ± 0.87). There was no significant difference in VSM scores between subjects classified as CDR 1 and CDR 2–3 (3.80 ± 0.80). There was a moderate significant correlation between VSM and HDS-R scores.

Conclusion: In the present study, the VSM test detected differences in VSM function among NC subjects and subjects with MCI and mild dementia. The software program for the VSM test is distributed for free so that it can be widely used.

Key words: *Alzheimer's disease, Clinical Dementia Rating, dementia, mild cognitive impairment, screening test, visuo-spatial memory.*

INTRODUCTION

With the impending retirement of the baby-boomer generation, effective methods for the prevention and early detection of dementia are urgently required to prepare for the aging of society in Japan. For earlier treatment, a better understanding of the preclinical phase of dementia is important, as well as knowledge of the course of the disease after the onset of clinical symptoms. The most salient early feature of dementia/Alzheimer's disease (AD) is memory deficit,

with dementia/AD reflecting a chronic amnestic process before the actual clinical expression of dementia.

Memory skills can be subdivided according to the type of information stored, with three types most commonly studied, namely verbal, spatial, and object information. Verbal information includes words, letters, or other materials that are primarily coded linguistically. Spatial information corresponds to information regarding the spatial positions of stimuli. Object information involves the storage of non-spatial visual features or object identity.[1] In the present study, we focused on spatial short-term memory for the various reasons. First, meta-analyses of neuroimaging data have revealed a dissociation among the brain regions related to spatial, object storage, and verbal memory; spatial memory recruits the bilateral parietal lobes more intensely than do the other two categories.[1] The bilateral parietal lobes are affected by an AD-related pathology before the onset of clinical symptoms[2] and are key structures in the conversion from amnesic mild cognitive impairment (MCI) to dementia/AD.[3] Second, longitudinal population-based studies have revealed that visuo-spatial memory (VSM) deficits are a sensitive marker of conversion to dementia.[4,5] Practically speaking, VSM deficits have a severe impact on daily life. The major complaints made by patients are of misplacing things, having to rummage around to find them, and becoming lost because they have forgotten landmarks, etc.

In the present study, we developed a short, computer-aided, short-term VSM test operated using a touch panel that is easy to operate, even for patients with dementia. We think that the VSM test may be an effective supplemental test to the standardized screening tests used in Japan to identify dementia, including the Mini-Mental State Examination (MMSE) and the Hasegawa Dementia Scale-revised (HDS-R), which is similar to and well-correlated with the MMSE.[6] The MMSE and HDS-R place an emphasis on memory function, but neither examines the VSM function. The Benton Visual Retention Test (BVRT) is commonly used as a VSM test. However, the BVRT involves factors other than visual retention, such as visual form discrimination and visual construction.[7] Furthermore, it is a time-consuming test. Most primary care doctors believe that cognitive screening for dementia is needed in medical practice, but few routinely perform such screening. The largest barrier for both doctors and patients is that the tests are time consuming,[8] so a brief test that could be used to screen for dementia would be of considerable value. Herein, we describe the brief VSM test and compare the results of this test between patients with dementia, those with MCI, and the healthy elderly.

METHODS

Sixty-six aged people (18 men and 48 women) were tested in the outpatient clinic. The only inclusion criterion was age ≥55 years. The exclusion criteria were: psychiatric diseases, delirium, verbal incomprehension (including aphasia), and motor deficits, such as paralysis, because the test uses a touch panel. The Ethics Board of Gunma University School of Health Sciences approved all procedures (no. 21–26) and informed consent was obtained from all participants or their proxies. Patients were diagnosed as having AD, dementia with Lewy bodies (DLB) or MCI on the basis of published criteria, namely the National Institute of Neurological and Communicative Disorder and Stroke, Alzheimer's disease and Related Disorders Association (NINCDS-ADRDA)[9] for AD, the third report of the DLB Consortium[10] for DLB, and a report from the International Working Group on Mild Cognitive Impairment[11] for MCI. Normal controls (NC) were identified on the basis of an interview and a questionnaire regarding the frequency of dementia-like symptoms and instrumental activities of daily living completed by their family and/or carers. Patients and some of those in the NC group underwent magnetic resonance imaging (MRI) and a set of cognitive tests (e.g. HDS-R, cube-copying test, clock-drawing test, trail-making test (TMT), and the stroop test). Of the patients with dementia, 18 had AD, six had DLB, and three had some other form of dementia. In the preset study, subjects were classified according to the Clinical Dementia Rating (CDR). In the present study, those with CDR 0.5 were regarded as MCI, even though different classifications have been proposed whereby CDR 0.5 encompasses both mild and earlier dementia[12] or it can correspond to very mild dementia.[13] We tested 29 NC subjects who corresponded to CDR 0, 10 patients with MCI (CDR 0.5), 15 patients with mild dementia (CDR 1), and 12 patients with moderate to severe dementia (CDR 2–3). Demographic data are presented in Table 1.

Visuo-spatial memory test

Participants were seated approximately 70 cm away from the screen of a 15″ touch panel connected to a PC running C++ software based on Windows XP. The VSM test measures memory capacity with regard to spatial memory configuration. We adopted the modified task of Kawai *et al.*[14] Numbered circles were displayed on the monitor for 8 s and subjects were required to memorize the location of these circles sequentially (Fig. 1a). In the first trial, three numbers (1, 2, and 3) were shown on the computer screen. After 8 s, the numbers disappeared, and three blank circles remained (Fig. 1b). Subjects were required to touch the patches sequentially in ascending order based on their memory (1, 2, 3—; Fig. 1c). There was a training session just prior to the actual test; subjects were allowed to practice twice with three numbers. Those who did not understand the task after two trials in the training session were excluded from the study. Memory capacity was measured using the staircase method. If the first response was correct, the number of stimuli increased in the second trial and so on. Alternatively, if the participant made an error, the number of stimuli decreased in the subsequent trial. When the sequence was switched from ascending to descending or vice versa, the number of stimuli was recorded as a reversal point score. The experiment was continued until four reversal points were obtained; the number of trials in one session was not fixed. The average of the four reversal point scores was used as the VSM score for that session. In the VSM test, the location of the stimuli was randomized to minimize the learning effects of repetition, and reproducibility was checked by preliminary experiments performed on 11 patients with dementia who were not included in the study itself; the tests were conducted twice at 1-week intervals and the results were correlated ($r = 0.76$).

The cut-off value was determined using the receiver operating characteristic (ROC) curve.[15] The cube-copying test and the clock-drawing test were scored as an accurate or inaccurate description. The TMT was scored as time, whereas the stroop test was scored as error rate. Results for patients with MCI and dementia were analyzed using the Japanese version of SPSS, 17th edition (SPSS, Chicago, IL, USA).

Table 1 Demographic data for the four groups

	n	Age (years)	VSM score	HDS-R score
NC (CDR 0)	29	78.3 ± 5.3	6.7 ± 0.8	ND
MCI (CDR 0.5)	10	73.7 ± 10.3	5.7 ± 1.0	27.0 ± 1.6
CDR 1	15	77.6 ± 9.3	4.7 ± 0.9	22.6 ± 3.1
CDR 2-3	12	81.9 ± 4.5	3.8 ± 0.8	12.1 ± 3.8

Unless indicated otherwise, data are given as the mean ± SD.
Normal control (NC) subjects were identified on the basis of an interview with a doctor and a questionnaire completed by their family and/or carers.
ND, not done (scores for the Hasegawa Dementia Scale-revised (HDS-R) were not obtained for NC subjects); MCI, mild cognitive impairment; CDR, Clinical Dementia Rating; CDR 1, mild dementia; CDR 2–3, moderate to severe dementia; VSM, visuo-spatial memory.

RESULTS

There were no significant differences in age or gender among the four groups (age: $P = 0.07$, one-way ANOVA; gender: $P = 0.50$, Chi-squared test).

The mean (±SD) VSM memory scores for subjects in the CDR 0 (NC), CDR 0.5 (MCI), CDR 1 and CDR 2–3 groups were 6.69 ± 0.82, 5.70 ± 0.96, 4.67 ± 0.87, and 3.80 ± 0.80, respectively (Table 1, Fig. 2). One-way ANOVA indicated the presence of significant

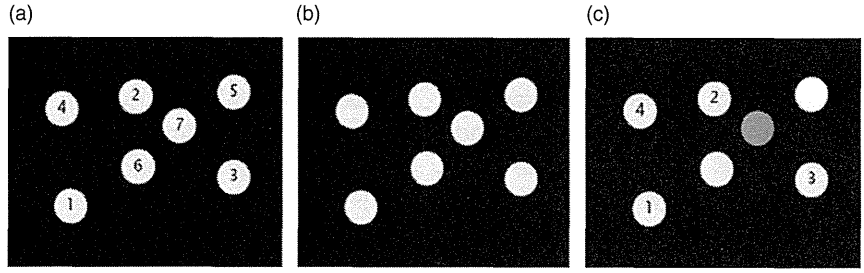

Figure 1 Example of the display seen on the touch screen for seven stimuli. (a) Seven numbered circles were shown on the touch panel screen. (b) After 8 s, the numbers disappeared. (c) Subjects were asked to touch the circles in ascending order. When subjects answer correctly, the number was displayed, but when they answer incorrectly, the circle turned red for a while and subjects could try again and continue with the test. In this case, the number was displayed in response to a correct answer. However, once the subject answer incorrectly, the trial was judged a failure and one less numbered circle (in this example, six circles) was displayed in the next trial.

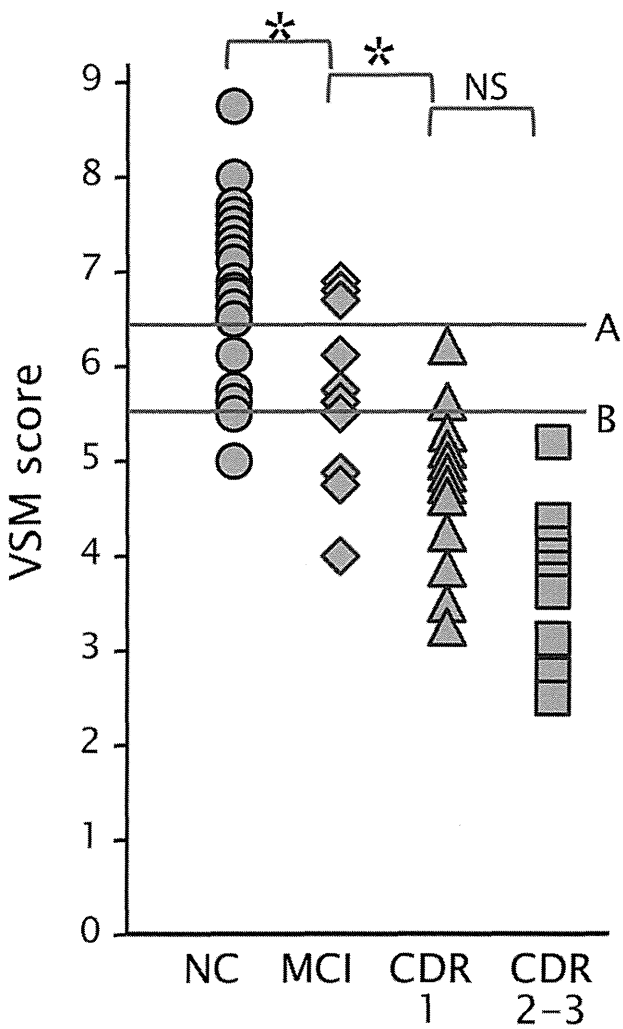

Figure 2 Cut-off points of 6.375 (A) or 5.5 (B) were evaluated for normal control (NC) subjects or patients with mild cognitive impairment (MCI). There were significant differences between the NC and MCI groups, as well as between the MCI and Clinical Dementia Rating (CDR) 1 (mild dementia) groups, whereas the difference between the CDR 1 and CDR 2–3 (moderate to severe dementia) groups did not reach statistical significance ($P = 0.06$).

differences between the four groups ($P < 0.001$). The results of post hoc analysis with Bonferroni correction indicated significant differences between the NC and MCI groups ($P = 0.01$), as well as between the MCI and CDR 1 groups ($P = 0.02$); however, the difference between the CDR 1 and CDR 2–3 groups was marginal ($P = 0.06$; Fig. 2). When the cut-off point for NC or MCI was set to 6.375, the sensitivity of the VSM test for MCI was 70% and the specificity was 76%. When the cut-off point for MCI or dementia was set to 5.5, the sensitivity of the VSM test for dementia was

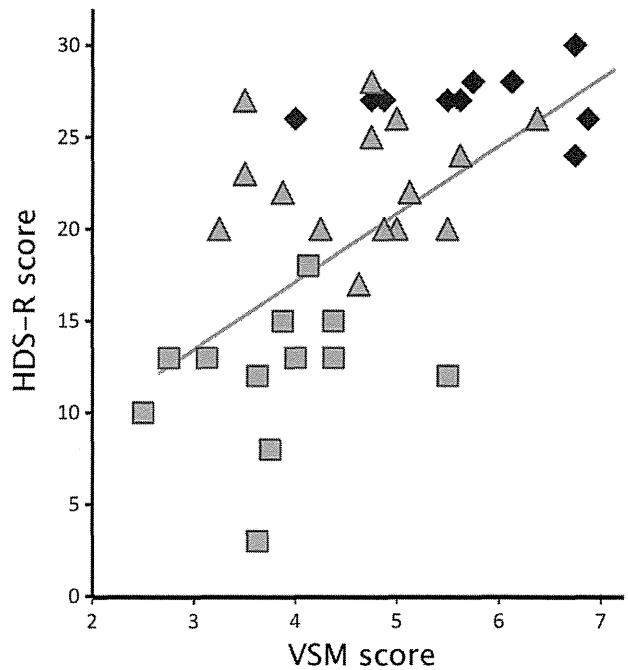

Figure 3 Correlation between scores on the visuo-spatial memory (VSM) test and Hasegawa Dementia Scale-revised (HDS-R) in subjects with mild cognitive impairment (◆), Clinical Dementia Rating (CDR) 1 (mild dementia; △), and CDR 2–3 (moderate to severe dementia; □). There was a significant correlation between total scores on the VSM test and HDS-R ($r = 0.61$, $P < 0.001$). The equation for the regression line was: $y = 3.7x + 3.1$ ($r^2 = 0.37$).

93% and the specificity was 85%. Scores were not correlated with the age ($r = -0.12$).

Group averages of HDS-R scores for the CDR 0.5 (MCI), CDR 1 and CDR 2–3 groups are given in Table 1. One-way ANOVA indicated the presence of significant differences between these three groups ($P < 0.001$). The results of post hoc analysis with Bonferroni correction also indicated significant differences between MCI and CDR 1 ($P = 0.003$), as well as between CDR 1 and CDR 2–3 ($P < 0.001$). The VSM scores and HDS-R total scores were moderately correlated ($r = 0.61$; $P < 0.001$), which indicates that spatial memory deficits are correlated with the general decline of cognitive function (Fig. 3).

The sensitivity of the cube-copying test was 25% for MCI and 67% for dementia. The sensitivity of the clock-drawing test was 31% for MCI and 63% for dementia. The average VSM score of those who succeeded in the cube-copying test was 4.94, compared with an average VSM score of 3.71 for those who failed the test. The average VSM score of those

who succeeded in the clock-drawing test was 4.94, compared with an average VSM score of 3.94 for those who failed the test. There were no correlation between VSM scores and TMT scores ($r = -0.37$) or between VSM scores and stroop scores ($r = -0.33$).

The average number of trials was 10.5 in the NC group, 9.3 in the MCI group, 8.1 in the CDR 1 group, and 8.0 in the CDR 2–3 group. Almost all subjects were unfamiliar with the use of a computer, but no one refused to undergo the examination.

DISCUSSION

The brief VSM test used in the present study detected deterioration of the VSM function at the MCI level, before the onset of dementia. It was effective in evaluating individual memory function in patients with MCI and mild dementia (CDR 1), but was ineffective for subjects in the advanced stages of dementia (CDR 2 or more). There was no significant difference in VSM scores between patients classified as CDR 1 and those classified as CDR 2–3, which may have resulted from the floor effects for CDR 2–3. The trial using three numbers was easy, even for moderately demented subjects.

We paid particular attention to reducing the psychological burden of subjects. The level of difficulty can be varied according to each individual: the number of stimuli is increased only when subjects give correct answers, thus subjects are not forced to perform a task that is beyond their capacity. Because the subjects can continue the trial even if they answer incorrectly in the middle of the test (Fig. 1), they can feel a sense of accomplishment.

As for the feasibility of the VSM test in clinical practice, its brevity is an advantage. The examination time varies according to the number of trials but, generally, one session was completed within 3 min. Another advantage of the VSM test is that the results can be quantified without arbitrariness. Using the BVRT in a multiple-choice format has been proposed to facilitate quantitative evaluation of VSM and to shorten the examination time.[16] Besides, the VSM showed a higher sensitivity than the clock-drawing and cube-copying tests, which are often used in clinical practice.

There was a correlation between the results of the test and general cognitive function, as determined using the HDS-R. As a whole, the VSM function is impaired in line with the deterioration of other functions. We recommend using the VSM test as a compliment to routine screening tests, such as the HDS-R or MMSE, which lack a VSM task, to provide further information when analyzing individual profiles of cognitive function. The MMSE and HDS-R are themselves mosaics of subordinate cognitive examinations and analyzing subordinate tests should be more important than the total score.[17] In practice, it is often that other tests are also performed, such as the clock-drawing[18] and/or cube-copying tests,[19] to supplement the cognitive factors examined in the MMSE and/or HDS-R. In the present study, there was no correlation between VSM scores and TMT or stroop test scores, which are standardized tests of frontal lobe function. This emphasizes the point that the VSM test evaluates a different function from those tests and combined application of these tests should provide information regarding various aspects of each patient's cognitive function.

A limitation of the present study was that educational levels of the subjects were not considered. Performance can be influenced by the education level, as reported for the BVRT.[20]

Over all, the VSM test is effective and practical in a clinical setting. The computer program, which can be run in Windows, is available as a free download so that it can be used widely (see Acknowledgements).

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TUBE FEEDING CAN BE DISCONTINUED BY TAKING DOPAMINE AGONISTS AND ANGIOTENSIN-CONVERTING ENZYME INHIBITORS IN THE ADVANCED STAGES OF DEMENTIA

To the Editor: Dysphagia, loss of the capacity for voluntary movement, speech, and continence, is one of the most serious symptoms in the advanced stage of dementia. Difficulty swallowing food is generally treated by changing the consistency of food from a hard mass to a soft paste and oral care. Recently, dopamine agonists and angiotensin-converting enzyme inhibitors (ACEIs) were reported to be effective at preventing aspiration pneumonia through increasing substance P levels, which enhances swallowing and cough reflexes.[1] We administered these drugs to some patients in the advanced stages of dementia and herein report three representative patients in whom oral food intake has been prolonged and tube feeding has been delayed for 7 months to 2 years.

CASE 1

A 67-year-old man with early-onset Alzheimer's disease (AD) in stage 7e according to functional assessment staging of AD (FAST) experienced swallowing difficulty 9 years after onset, and tube feeding was considered. He was medicated with the dopamine antagonist tiapride (25 mg) because of hyperactivity and violent behavior 2 years before; despite the disappearance of symptoms, medication had been continued. We first stopped tiapride and administered the dopamine agonist amantadine chloride (50 mg) and levodopa (100 mg). After 2 weeks, he smiled and spoke to caregivers, which surprised them. As a result of improved swallowing because of larger doses of amantadine chloride (150 mg) and levodopa (200 mg), he has maintained oral intake for 2 years; during this period, he experienced fever once, caused by aspiration pneumonia. His body weight increased from 51.4 kg (body mass index (BMI) = 20.6 kg/m^2) at the beginning of therapy to 56.3 kg (BMI = 22.5 kg/m^2) after 8 months and is now maintained at 54.5 kg (BMI = 21.8 kg/m^2) 2 years after the start of therapy.

CASE 2

An 81-year-old woman with AD in FAST stage 7e experienced swallowing difficulty 10 years after onset. She was mute, kept food in her mouth without swallowing for minutes, and started to sleep during eating. She was first medicated with the ACEI captopril (25 mg), but her body weight continued to decrease, from 46.8 kg (BMI = 22.3 kg/m^2) to 39.8 kg (BMI = 18.9 kg/m^2) over a period of 9 months. She received combined medication of captopril, amantadine chloride (150 mg), and levodopa (300 mg), and the herbal medicine Rikkunshito (5.0 g) for appetite improvement. She regained her appetite, became awake during meals, and showed increased facial expressions (smiling and laughing). Her weight has been at 39.9 kg (BMI = 19.0 kg/m^2) for 7 months, and she has experienced fever once in the last 7 months.

CASE 3

A 75-year-old bedridden woman with vascular dementia due to recurrent stroke (double hemiparesis: left > right), diabetes mellitus, and hip bone and lumbar fractures developed swallowing difficulty 16 years after her first stroke. Medication with amantadine chloride (100 mg) was started, together with a change of the antihypertensive drug from olmesartan to the ACEI imidapril (12.5 mg). Her body weight decreased from 37.1 kg (BMI = 16.9 kg/m^2) to 36.3 kg (BMI = 16.6 kg/m^2) for 20 months after the start of medication. She has experienced fever once in the last 20 months, and maintains oral intake.

We have prolonged oral food intake and delayed tube feeding by administering dopamine agonists in case 1; dopamine agonists, an ACEI, and Rikkunshito in case 2; and dopamine agonists and an ACEI in case 3. Substance P is critical for the initiation of swallowing and the cough reflex; pharmacological treatment using dopamine agonists could improve both reflexes by enhancing substance P production, whereas ACEIs lead to the inhibition of substance P breakdown,[1] although the first choice is a dopamine agonist, because as shown in cases 1 and 2, it improves the conscious state (arousal), mood (facial expression), and motivation (activity).

The traditional Japanese herbal medicine Rikkunshito was reported to enhance appetite and gastric emptying by increasing the secretion of the orexigenic hormone ghrelin.[2,3] It might be that ghrelin protects against pneumonia by suppressing gastric regurgitation.

In Japan, it is common to use long-term tube feeding introduced by percutaneous endoscopic gastrostomy (PEG), mainly with the purpose of extending life in the end stage of dementia, but PEG is not useful in preventing pneumonia because it causes the silent aspiration of contaminated saliva and regurgitated gastric secretion.[1] To delay tube feeding with PEG, dopamine agonists should be tried first for patients with dysphagia to prolong oral food intake and so help maintain their dignity. ACEIs and Rikkunshito may also be added.

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EFFECT OF MALNUTRITION ON EXECUTIVE FUNCTION IN OLDER EGYPTIANS IN GERIATRIC HOMES

To the Editor: Nutrition is an important determinant of health in elderly patients. The importance of nutritional status has been increasingly recognized in a variety of morbid conditions including cancer, heart disease, and dementia in persons aged 65 and older.[1]

Malnutrition is prevalent in elderly populations, even in the developed world.[2] The prevalence of malnutrition increases with age and is most common in institutionalized individuals.[3]

Undernutrition is associated with exacerbation of health conditions, frailty, and decline in physical and cognitive function.[4]

The aim of this study was to evaluate the effect of malnutrition on executive function in older Egyptian subjects in geriatric homes. The study was a case–control study. Participants were recruited from geriatric homes in Cairo, Egypt, and subdivided into two groups: Group 1: cases, 50 men and women aged 60 and older found to be malnourished (n = 28) or at risk of malnutrition (n = 22) according to the Mini Nutritional Assessment (MNA);[5] and Group 2: controls (matched for age and sex), 50 men and women aged 60 and older found to be well nourished according to MNA. Subjects with dementia (Mini-Mental State Examination score less than 26)[6] or depression (Geriatric Depression Scale score greater than 5)[7] were excluded from the study. Subjects with history of stroke, delirium, alcoholism, drug abuse, psychiatric disease, or thyroid disease were excluded, as were subjects with auditory or visual impairment or any organ failure.

Cognitive and executive functions were assessed using three neuropsychological tests: letter verbal fluency test,[8] animal verbal fluency test,[9] and Executive Interview 25 test (Exit25).[10] Nutritional assessment was performed using the Mini Nutritional Assessment. The mean EXIT25 score was significantly higher (impaired) in both the malnourished group ($P<.001$) and the group at risk of malnutrition ($P=.002$) than in the well-nourished group. Also letter and animal verbal fluency test scores were significantly lower in the malnourished group than in the control subjects ($P<.001$).

Elderly subjects with malnutrition or at risk of malnutrition had poorer cognitive and executive function than well nourished elderly subjects.

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SEVERE HUMAN RHINOVIRUS OUTBREAK ASSOCIATED WITH FATALITIES IN A LONG-TERM CARE FACILITY IN ONTARIO, CANADA

To the Editor: Rhinovirus (HRV) infections are one of the most common causes of viral illnesses in humans. Infection of healthy adults with HRV can lead to a self-limited upper respiratory tract illness, also known as the common cold, but it can cause more-severe disease in elderly patients, such as exacerbations of chronic lung disease, pneumonia, and death.[1,2] Several reports of HRV outbreaks in elderly patients have been described.[3–6] An outbreak of rhinovirus in a long-term care facility (LTCF) causing severe disease

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REVIEW ARTICLE

Overview of non-pharmacological intervention for dementia and principles of brain-activating rehabilitation

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Abstract

Non-pharmacological interventions for dementia are likely to have an important role in delaying disease progression and functional decline. Research into non-pharmacological interventions has focused on the differentiation of each approach and a comparison of their effects. However, Cochrane Reviews on non-pharmacological interventions have noted the paucity of evidence regarding the effects of these interventions. The essence of non-pharmacological intervention is dependent of the patients, families, and therapists involved, with each situation inevitably being different. To obtain good results with non-pharmacological therapy, the core is not 'what' approach is taken but 'how' the therapists communicate with their patients. Here, we propose a new type of rehabilitation for dementia, namely brain-activating rehabilitation, that consists of five principles: (i) enjoyable and comfortable activities in an accepting atmosphere; (ii) activities associated with empathetic two-way communication between the therapist and patient, as well as between patients; (iii) therapists should praise patients to enhance motivation; (iv) therapists should try to offer each patient some social role that takes advantage of his/her remaining abilities; and (v) the activities should be based on errorless learning to ensure a pleasant atmosphere and to maintain a patient's dignity. The behavioral and cognitive status is not necessarily a reflection of pathological lesions in the brain; there is cognitive reserve for improvement. The aim of brain-activating rehabilitation is to enhance patients' motivation and maximize the use of their remaining function, recruiting a compensatory network, and preventing the disuse of brain function. The primary expected effect is that patients recover a desire for life, as well as their self-respect. Enhanced motivation can lead to improvements in cognitive function. Amelioration of the behavioral and psychological symptoms of dementia and improvements in activities of daily living can also be expected due to the renewed positive attitude towards life. In addition, improvements in the quality of life for both patients and caregivers is an expected outcome. To establish evidence for non-pharmacological interventions, research protocols and outcome measures should be standardized to facilitate comparison among studies, as well as meta-analysis.

Key words: *Alzheimer disease, behavioral and psychological symptoms of dementia (BPSD), dementia, empathy, intersubjectivity, patient-centered rehabilitation.*

OVERVIEW OF NON-PHARMACOLOGICAL TREATMENT

In tandem with the rapid aging of the population, the prevalence of dementia is increasing steeply. Despite considerable progress in the treatment of causative diseases, such as Alzheimer's disease (AD), dementia remains incurable. Thus, it is of considerable importance to delay disease progression and functional decline; it is expected that non-pharmacological interventions for dementia will have a significant role in this

respect. The American Association for Geriatric Psychiatry (AAGP) position statement proposes a care/treatment model that combines pharmacological and non-pharmacological treatment for patients with AD.[1]

In the present review, we describe recent trends in non-pharmacological treatment for dementia and then propose our brain-activating rehabilitation (BAR).

APPROACHES TO COGNITIVE SYMPTOMS

Time–place disorientation and memory deficits are the most prominent features of AD from the early stages, and cognitive rehabilitation, such as reality orientation and memory training, is widely used. However, cognitive rehabilitation inevitably identifies what patients are not capable of. Patients' realization of their disorientation and/or memory deficits can devastate their self-confidence, leading to depression and withdrawal. Until the mid-1980s, reality orientation training was conducted in a confrontational atmosphere, with adverse effects reported, including frustration, anxiety, depression, and a lowering of self-esteem.[2,3] Thus, the consensus statement of the AAGP warned of the potentially harmful effects of reality orientation training.[4] Now, a consensus has been reached that training must be conducted in a person-centered manner.[5]

Errorless learning was proposed in consideration of patients' dignity. Errorless learning is a teaching technique that prevents learners from making mistakes.[6,7] Therapists should be careful to ensure that patients succeed in any attempt; if errors are made, the therapists should not point out these errors. For patients with memory deficits, trial-and-error learning is not effective. One can learn from errors only when prior errors can be compared with the present results. However, recollection of past errors is difficult for patients with memory deficits, and the errors can be reinforced by priming effects.[8]

Another challenge in cognitive rehabilitation is the relevance to daily living. Cognitive training is meaningless unless it serves to enhance cognitive function in daily living. However, memory skills recovered by cognitive rehabilitation are hardly generalized in daily living.[7] Thus, the benefits to patients may be rather small, even after a great deal of time and effort have been invested in memory training.[9] To deal with the issue, tailor-made therapy has been proposed to meet each patient's specific needs (e.g. to put names to faces of business associates).[10] Tailor-made therapy needs to be conducted in a manner that is most consistent with the patient's wishes; thus, the intervention programs should not be fixed, but improved to fit the current functioning of the patient and their particular situation.

APPROACHES TO THE BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA

The AAGP model recommends non-pharmacological treatment as the first-line management strategy for behavioral and psychological symptoms of dementia (BPSD),[1] and positive evidence has been accumulated regarding non-pharmacological approaches.[11,12] Interventions for BPSD have focused on the patients themselves. However, BPSD can result from an interaction between the patients and their caregivers, including families.[13] A discrepancy between a patient's capabilities and the demands of his/her caregivers may trigger BPSD. Changes in caregivers' attitudes towards patients can ameliorate BPSD; thus, there is a strong need for caregiver education.[14–16] The AAGP states that caregivers' behavior is the most effective therapy, the benefits of which could last for months for neuropsychiatric symptoms such as agitation, aggression, delusions, hallucinations, repetitive vocalizations, and wandering.[1] Conversely, BPSD has a significant impact on caregivers' burden and stress.[17,18] Thus, caregivers, especially families, also require counseling in addition to education, and the quality of life (QOL) of families is considered as main the outcome in addition to the QOL of patients.[14–16]

Consideration of patients' emotion, the concept of tailor-made therapy, and family education and care are the important issues common to non-pharmacological approaches regardless of differences in aims and techniques. Thus far, research has focused on categorizing approaches and evaluating the efficacy of each approach. However, Cochrane Reviews on non-pharmacological interventions have highlighted the insufficiency of the available evidence.[19–22] It should be necessary to change the strategy in considering non-pharmacological interventions as follows

BRAIN-ACTIVATING REHABILITATION

The essence of non-pharmacological intervention is intersubjectivity among patients, families, and therapists, with each situation being unique. This is an

Table 1 Principles of brain-activating rehabilitation for dementia

1. Enjoyable and comfortable activities in an accepting atmosphere
2. Activities associated with empathetic two-way communication between therapists and patients, as well as between patients
3. Therapists should praise patients to enhance their motivation
4. Therapists should try to offer each patient some social role that takes advantage of his/her remaining abilities
5. Errorless learning for a pleasant atmosphere and to maintain patients' dignity

intrinsic difference between non-pharmacological and pharmacological interventions, in which study designs are strictly regulated. To obtain good results with non-pharmacological therapy, the core is not 'what' approach is taken but 'how' the therapists communicate with their patients. The therapeutic effects of non-pharmacological intervention can be highly influenced by therapists' attitudes, therefore we propose new therapeutic principles for non-pharmacological intervention (i.e. BAR).

Criteria and principles of BAR

The five principles of BAR are given in Table 1. Any approaches associated with these five principles are considered to be BAR.

Activities should be enjoyable and comfortable, to make the patients–therapist interaction as pleasant as possible

A happy feeling accompanied by a smile motivates patients. A comfortable and pleasant atmosphere is important because their lives are filled with unpleasant things due to their cognitive deficits. Activities with errorless learning are conducive to a pleasant atmosphere and to maintain a patient's dignity. A positive emotion presumably activates brain areas related to reward, which plays a critical role in motivation.[23] The dopamine system is an essential component of the brain reward circuitry.[24–27] The release of dopamine is stimulated by happy feelings and this release enhances motivation; dopamine release is not evoked by a negative mood.[28,29]

Happy feelings could relieve patients' relentless stress. Chronic exposure to stress hormones has an impact on brain structures. Animal studies have revealed that, particularly in old age, the hippocampus is highly vulnerable to the effects of the stress hormone glucocorticoid.[30] Regarding humans, a longitudinal study reported that basal glucocorticoid levels were higher in AD patients than in a control group,[31] with the magnitude of the increase in glucocorticoid levels strongly correlated with hippocampal atrophy and memory deficits.[32] In addition to the hippocampus, the frontal lobe is sensitive to glucocorticoid in aged humans.[33] Pleasant activities relieve patients' relentless stress, even if only during the therapy sessions.

Activities should be associated with two-way communication between the therapist and patient, as well as between patients

Because of memory deficits and disorientation, AD patients suffer from discommunication with others even from the early stages of the disease. Communicating with them while taking into consideration their feelings makes them feel relieved.

For AD patients, the importance of empathetic non-verbal communication increases with the progression of the disease because it becomes more difficult to verbalize what they think and feel due to the amnesic and transcortical sensory aphasia. Patients with AD enjoy talking together, but what they say is not always comprehensible. For them, the purpose of communication is not to get information, but to enjoy exchanges of affection and empathy. Such emotional empathy exchange enhances relationships between therapists and patients because patients feel accepted and understood.

Therapists' smiles could be a pleasant stimulus for patients. The perception of others' smiles results in spontaneous activation of homologous muscles related to smiling in the observer; the mirror neuron system is the physiological basis for this phenomenon.[34] Then, a happy feeling is evoked by afferent feedback from the neural structures involved in the facial movement (facial feedback hypothesis[35]). In this manner, a happy feeling is evoked as an automatic reaction to seeing others smile; thus, therapists' smiles can make patients feel happy.

According to the Functional Assessment Staging of Alzheimer Disease (FAST),[36] the ability to smile at others (e.g. families and caregivers) remains even at Stage 7e (advanced stage), just before consciousness is lost. Patients with AD lose function in reverse order of development after birth.[36] At the developmental stage, a social smile is acquired at around 4 months of age, after the disappearance of the neonatal smile;

infants smile in response to a caregivers' smiles (in most cases, mothers' smiles). This could be the primary intersubjective communication by which positive feelings are shared. Stern defines such affective interactions as 'mirroring' or 'empathetic responsiveness'.[37] Thus, an exchange of smiles is effective, even for patients at advanced stages.

Regarding empathy, the validation method[38] is useful. The therapists/caregivers should pay close attention to recognize and confirm patients' emotions. For example, therapists/caregivers should not point out a patient's disorientation; a patient's self-esteem is restored in the context of the 'reality' in which they perceive themselves to be in.

Therapists should praise patients and recognize their individuality

Being publicly praised and appreciated is a typical social reward. Social rewards also recruit the dopaminergic reward system and stimulate motivation.[39–41] For demented patients, a series of failures may provoke reproach from families or caregivers and so these patients are rarely praised in daily living. Therefore, public praise during rehabilitation sessions may enhance patients' motivation and restore their self esteem. Therapists should help patients regain their self-confidence, despite their failures. Self-efficacy is the belief that one is capable of achieving certain goals, regardless of whether the belief is true or not.[42] One of the components affecting self-efficacy is social persuasion (i.e. praise and encouragement). In the phase of learning or training in some skills, errorless learning[6,7] is efficient.

As mentioned above in 'approaches to cognitive symptoms', a patient's mood may be lowered by 'excess disability'.[43] In constrast, the experience of being praised could be a pump-priming effect to lift the patient from a vicious cycle of failure and 'excess disability' to a virtuous cycle of willingness and the manifestation of potential capacity.

Patients should play a social role

The loss of their own role increases a patient's feeling of alienation, which drives demented patients to withdraw from social life. Social roles could help patients confirm their identity and regain their dignity. Thus, therapists should pay attention to what each patient is good at, and attach meaning and significance to whatever he/she can do (e.g. to sing a song to please other participants; to applaud performers etc.). By acting out social roles, patients may start to care about each other and become aware that they are appreciated by doing what they can for others. As such, social contact has been proven to reduce the risk of dementia.[44–46]

An example of a BAR program: Activity reminiscence therapy

We will explain how the principles of BAR are realized with an example of activity reminiscence therapy. Activity reminiscence therapy is a therapeutic method that combines reminiscence and activity. In ordinary reminiscence therapy,[47] elderly people talk about their memories and experiences, which the therapists listen to attentively with an empathetic attitude. In activity reminiscence therapy based on BAR principles, the patients teach therapists or caregivers how to use old-style tools that are familiar to them because they used such tools in their childhood or as housewives (Fig. 1).

The advantage of this method is the 'role-reversal'; the patients are teaching the therapists or caregivers who help them in daily living (the fourth principle). Patients may feel timid or even inferior to the therapists or caregivers in daily living; thus, this sort of role-reversal helps them regain their self-confidence. Through this process, patients recover their sense of social function to pass on knowledge to younger generations. Because of this role-reversal, the patients may enjoy playing the leading role in the therapy (the first principle) and the therapists can praise the patients naturally (the third principle). Regarding the second principle of two-way communication, therapist–patient and patient–patient communication becomes much smoother with tools. Therapists should accept and share the world of the patients, regardless of whether it is 'true' or not. Conversation is based on memories; activities to use old-style tools recruit procedural memories, which remain after the loss of episodic memory.[48] Thus, it is expected that participants will enjoy conversations.

Effects of BAR

Effects on cognitive ability

Although BAR does not directly focus on cognitive enhancement as such, it is naturally expected that enhanced motivation will lead to improved cognitive

Figure 1 Activity reminiscence therapy. (a) Washing sheets using a washboard. Before electric washing machines became common, housewives did the laundry using washboards and basins. However, the younger generations rarely use washboards. Being appreciated and praised, Alzheimer's disease (AD) patients really enjoy their role of teaching and passing on their knowledge to younger generations. (b) Beanbag juggling: A beanbag is a palm-sized sack with beans inside, played with by tossing and catching (i.e. 'beanbag juggling'). Concerning the physical aspects of this activity, beanbag juggling requires rhythmic visuomotor coordination. Because the procedural memories remain robust, AD patients enjoy beanbag juggling with younger staff. Emotion-based communication over a game is enjoyable even for participants with impaired verbal skills.

ability. One of the key perspectives considering approaches to dementia is that the cognitive status does not necessarily correspond to the degree of pathological lesions in the brain. Regarding the brain's resistance to neuropathological damage, the 'cognitive reserve hypothesis' has been proposed, as described below.

The cognitive reserve refers to the observation that the degree of brain pathology or brain damage does not directly explain the clinical manifestation or cognitive performance of patients. Thus, people with a greater cognitive reserve are able to withstand a greater pathological AD burden without becoming demented by adopting alternative cognitive strategies and/or recruiting compensatory brain networks.[49–54] Increasing evidence indicates the presence of plastic changes in the synaptic efficacy in mature brains, which could be the physiological underpinning of this phenomenon.[55] A good example of 'the cognitive reserve' is the Nun study,[56] which reported non-linear associations between AD pathology in the postmortem brain and cognitive status in participants. Some participants in the study were cognitively intact, although their brains fulfilled the criteria for AD pathology. In a recent community-based study, minimal to moderate AD pathology was found in most brains of older people without dementia who were 80 years or older.[57] Enhanced cognitive ability was reported after activity reminiscence therapy intervention based on BAR principles.[58] The improvement was observed in the overall scores for immediate and delayed recall on the Wechsler Memory Scale-Revised after 1-h interventions once a week for 12 weeks.

Effects on BPSD

Behavioral and psychological symptoms of dementia often result from the relationship between patients

and their families. Patients with AD tend to overestimate their cognitive and functional abilities compared with what their families report.[59] Because of this discrepancy in evaluation of cognitive ability between patients and families, the patients may feel that they are not understood and accepted by their families, which may accelerate BPSD. In such cases, we recommend that families participate in the therapy session. By participating in the therapy, the families come to understand the underlying reasons for the patient's behavior.

Effects on daily living

Improvements in the activities of daily living (ADL) are also seen after BAR. Deficits in instrumental ADL are caused by a decline in cognitive functions such as executive function. Although disuse syndrome can account for a considerable part of the deficits in basic ADL, there remains room for beneficial effects following intervention with BAR. Patients may lose motivation due to numerous failures and reproach from their families', which suppresses brain function and accelerates disuse syndrome. Cooperation with families is indispensable to maintain enhanced motivation induced by BAR in daily living.

Family care and the QOL of both patients and their caregivers

The final effect of BAR is to make patients feel happy in their daily lives. Thus, it is crucial that patients' families understand the difficulties of living with dementia and learn how to help patients feel happy or smile by participating in BAR. At the same time, families also suffer with patients; thus, therapists should also praise and appreciate the efforts of the families. The BPSD service pack of the International Psychogeriatric Association (IPA) recommends that families and/or caregivers reward themselves for achieving certain goals to ameliorate BPSD.[60] It is desirable that therapists' attitudes towards families become their reward.

EVIDENCE FOR THE EFFICACY OF NON-PHARMACOLOGICAL TREATMENT

The efficacy of BAR should be verified on the basis of evidence. The protocol of any study investigating the efficacy of non-pharmacological treatment should reflect the characteristics of these interventions (i.e. intersubjectivity).

With regard to the outcomes, the broadening of outcome measures, including well-being, mood, and QOL, is desirable to consider the impact of non-pharmacological treatments on families and other caregivers.

For comparisons and meta-analyses among studies, it is desirable to use standardized outcome measures and protocols. In 2008, a European consensus on outcome measures for psychosocial intervention research in dementia care was published to enable meaningful comparisons between different studies and interventions.[61] We hope that the Japanese Psychogeriatric Society promotes the establishment of consensus guidelines for non-pharmacological interventions.

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