APÊNDICE

NEUROPSYCHOLOGICAL REHABILITATION OF MEMORY DEFICITS IN PATIENTS WITH ALZHEIMER'S DISEASE

Running title: NEUROPSYCHOLOGICAL REHABILITATION IN ALZHEIMER'S PATIENTS

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Abstract

Patients with Alzheimer's disease gradually lose their cognitive competence, particularly memory, and the ability to perform daily life tasks. Neuropsychological rehabilitation is used to improve cognitive functions by facilitating memory performance through the use of external aids and internal strategies. The present study reports on a 14-week neuropsychological rehabilitation program applied to six elderly patients (mean age: 77.4 $\pm$ 2.88 years), 4 females and 1 male, with mild Alzheimer´s disease (Mini-Mental State Examination score: 22.20 $\pm$ 2.17) and their caregivers. All patients had been taking Rivastigmine (6-12 mg/day) for at least 3 months. Before being assigned to training groups all patients were assessed using the Mini-mental state examination, Montgomery-Asberg Depression Rating Scale, Hamilton Anxiety Scale, Interview to Determine Deterioration in Functioning in Dementia, Functional Scale, Memory Questionnaire of Daily Living for patient and caregiver, Quality of Life Questionnaire for patient and caregiver, and a neuropsychological battery. A final evaluation using the same instruments was administered after the 14-week program. The results showed a statistically significant improvement in functional scale ($P = 0.04$) but only a nonsignificant tendency toward improvement in memory and psychiatric symptoms.

Introduction

Alzheimer's disease (AD) is a progressive dementia in which memory deficit is one of its earliest and most pronounced symptoms (1). As the disease progresses, other cognitive functions such as language and general intellectual performance also become impaired. This decline in cognitive function has additional effects. For example, cognitive status is highly correlated with caregiver burden and functional impairment. Both of these factors influence a patient's daily living activities, their ability to live alone and, of course, their quality of life. Patients become insecure about performing simple daily living tasks such as using the telephone, paying bills, going out and returning home alone, and properly dressing themselves.

At the neuropathological level, AD is associated with the development of plaques and neurofibrillary tangles within the brain. Due to an increase in life expectancy for our population and its cost to society in terms of nursing and medical care and human suffering, the impact of senile dementia is substantial. Beyond these social issues, there is a considerable current interest in the possibility of alleviating dementia symptoms and reducing the progression of the cognitive decline, which is one of the most dramatic symptoms of the illness.

Neuropsychological rehabilitation (NR) is a new field of research and as such requires further development in specific areas including more efficient measures for assessment and outcome evaluation. In addition, there should be more accurate documentation regarding the effectiveness of NR methods for AD patients, a better understanding of the factors that influence the outcome of intervention, clearer evidence of both effectiveness and longer-term impact and gains, and a commitment

to ensure that effective intervention is disseminated and implemented in standard clinical setting (2).

Current research in this area is recognizing the relevance of NR for people with dementia (3). Although papers have been published on this issue, with new developments and recent findings, researchers have usually been testing more a single technique to rehabilitate demented patients (4-6), whereas in the present NR study a combination of cognitive techniques was used. The present study was based on the NR definition as “a process of active change aimed at enabling people, who are disabled by injury or disease, to achieve an optimal level of physical, psychological, and social function” (7). NR can maximize functioning across a whole range of areas including physical health, psychological well being, daily living skills, and social relationships (8). Moreover, NR applied to AD patients aims at optimizing functions, minimizing excessive disability risk and preventing the development of negative social psychology (9).

The early identification of the disease is crucial for better treatment results since there are more preserved cognitive functions to work with in the early stages. The work with neurodegenerative diseases like AD involves a psychosocial approach directed at the needs of patients and caregivers. Therefore, an effective interview and assessment should address the patient’s life style, socioeconomic background, as well as functional, psychological and cognitive features. In this context, NR provides a framework for a multidisciplinary treatment of AD.

NR is not a static work and all treatment strategies will depend on the severity of the specific characteristics and environment of AD patients. The advent of drug treatment for AD patients emphasizes the need for NR. Combined cognitive and

pharmacological approaches have been explored, showing promising results as a helpful strategy for AD patients and their caregivers. (10). The goal of this study is to report on the tests and scales used to evaluate and re-evaluate cognitive status, the efficiency of implicit memory techniques and Activities of Daily Living (ADL) training with AD patients in NR programming.

Method

Subjects

After the protocol was approved by the Ethics Committee and informed consent was been signed by each patient, six mildly impaired probable AD patients, diagnosed according to ICD-10 and NINCDS-ADRDA criteria and having used Rivastigmine, 6 to 12 mg/day, for more than 3 months, started an NR training program. All subjects were classified as mildly ill on the basis of Clinical Global Impression (CGI).

Just before and after the 4-month period of cognitive training, all patients were evaluated using the Mini-mental State Examination (MMSE) (11), Montgomery-Asberg Depression Rating Scale (MADRS) (12), Hamilton Anxiety Scale (HAM-A) (13), Interview to Determine Deterioration in Functioning in Dementia (ADL) (14), Functional Scale (Ávila R, unpublished data) (see appendix), Memory Questionnaire of Daily Living (MDLQ) (15) for patient and caregiver, Quality of Life questionnaire (QOL) (16) for patient and caregiver, and Neuropsychological Battery (NB). NB consisted of the Wechsler Memory Revised Scale, Wechsler Intelligence Revised Scale, Fuld Object Memory Evaluation

(FOME), Recognition Memory Face (RMF), Boston Naming Test (BNT) and Verbal Fluency Semantic (animals) and Phonemic (FAS).

The medical condition and socio-economic and demographic characteristics of the patients are presented in Table 1.

TABLE 1 HERE

Memory training program

The modality-specific memory difficulty rehabilitation works better using the intact modality to support the impaired one (17). Since AD patients have their implicit memory almost intact at the onset of the disease, it seems to be the best modality to compensate for explicit memory deficits. This work can be done using emotional and perceptual learning, priming, motor skills, habits, conditioning and categorization (18).

In the present study, motor movements, emotional learning and categorization were applied to increase both learning and memory:

Motor movements: In order to learn a colleague's name, all patients introduced themselves by name and mentioned their hobbies or interests. Patients were instructed to choose a particular motor movement that matched each hobby, like moving fingers to play the piano. This movement should be associated with the person's name and face. At the beginning of each group session a motor movement mimic representing someone's hobby was associated with the person's name. Before recalling his/her name, patients were encouraged to recall his/her hobby. If they could not remember the hobby, movement or name, cues were presented.

Emotional learning: In order to improve learning and memory for words, patients were asked to create a sentence or a short story with the words intended to

be learned or remembered. Each sentence should be constructed in such a way as to evoke a great deal of emotion. Patients were encouraged to remember the sentence and the words. If they could not remember alone, cues were presented like in a recognition test.

Categorization: To improve learning and memory for words the following exercise was given to each patient. First, a list of words was presented to the patients. They were then asked to divide the list into categories (clothing, food, verbs, etc.). In order to recall the list, they were asked to remember the categories.

ADL training

For this procedure, functional tasks were used in which patients were trained on the following four activities: telephone use, giving and receiving messages, diary use and steps to prepare a sandwich. As AD patients have difficulty in transferring spontaneously a learned technique to an actual day-to-day problem, daily living situations were simulated. For example, in order to work on phone skills or receiving messages and taking notes, the training was done using a telephone, paper and pen, simulating a phone call. Similarly, when learning to write appointments in a dairy, a diary was used with real appointments.

Support intervention

Group support intervention was provided for caregivers as well, because of the high incidence of psychiatric disorders present among caregivers compared to the general population. The caregivers attended a monthly group session focusing on orientation about AD course and prognosis, counseling and support. All participants were encouraged to share their experiences and any coping strategies. The caregivers were always instructed to do some activities with the patients as homework.

Group and individual sessions

NR consisted of 60-min weekly group sessions and 30-min weekly individual sessions focusing on implicit and explicit memory training, temporal and spatial orientation, language abilities, developing compensatory strategies (for daily living deficits) and training for ADL, associated with social interaction. The same program was used in both group and individual sessions, but in the individual sessions more attention was given to specific patient difficulties. For example, one patient was able to utilize the aid of a diary very well, but she had great difficulty in using the telephone. Intensive phone training was done in her individual sessions, while the use of the diary was just reinforced.

The Errorless Learning technique described by Baddeley and Wilson (19) was applied throughout the program to enhance each patient's correct procedure and to avoid memorization of the wrong pattern. Throughout the training many facilitating clues were given to the patients, and as the activities became easier for them, fewer clues were given and so on until no clues were necessary. This is because patients with episodic memory deficit are not capable of remembering their mistakes and therefore cannot correct them. Thus they do not learn from their mistakes as those people without such a deficit do. Therefore, it becomes fundamental that the learning be in a facilitating manner, always driving for the correct procedure.

Statistical analysis

Data were analyzed statistically using the SPSS 9.0 software for Windows. Non-parametric tests were used and the effect size (ES) was calculated according to the following formula:

$$ES = \frac{\text{mean post-treatment} - \text{mean pre-treatment}}{\text{pre-treatment standard deviation}}$$

Rockwood et al. (20) stated that ES takes into account the within-group variance in performance at baseline and that a higher number represents a larger therapeutic effect.

Results

Table 2 shows the results of scales applied to patients and caregivers Pre and Post NR. Although there was no statistically significant difference between pre- and post- treatment on the scales, the group revealed a modest improvement after treatment in all scales, with the exception of MDLQ-patient. We speculated that with the cognitive and ADL training, the patients become more aware that they have memory problems and limitations.

TABLE 2 HERE

Although Table 3 does not show significant differences in neuropsychological evaluation between pre- and post-treatment, most tests revealed a modest improvement in performance for patients, except for Verbal fluency and Backward digit span. This improvement was particularly noted in memory tests and functional scales. Table 4 shows the effect size of some tests and scales.

These results are consistent with the NR program, which emphasize memory and ADL training, like use of the phone and of a diary.

TABLE 3 HERE

TABLE 4 HERE

Discussion

AD patients present memory problems in both the storage and retrieval stages causing ADL impairments. It may be possible to reduce these deficits through strategies that use patient implicit memory to learn or re-learn information, and training ADL with external aid.

The results of the present study showed a significant improvement after training only on the functional scale, and modest improvement in some cognitive tests and psychiatric symptoms. This could be partially explained by the small sample size, the low frequency of NR training sessions and by the reduced power to detect pre- and post-NR differences. Nevertheless, the effect size analyses showed positive results of NR training.

Methodological aspects such as no comparison to a control group (AD patients who were under medication but not under NR training) should be mentioned and are justified by the fact that this was a pilot study with the specific objective (test and scale selection) of evaluating pre- and post-treatment results of implicit memory techniques and ADL training.

It is well known that Rivastigmine treatment can improve cognitive function and ADL performance in the first three months of treatment, with stabilization or a slight decrease after this period (21,22). Considering that all patients studied had

been taking the medication for at least three months before the beginning of NR training, the positive effects observed after training can probably be the effect of both treatments, including caregiver orientation.

The present results agree with others published more recently, which showed the absence of statistical significance (10,23,24). However, there are only few controlled studies with specific techniques and training to minimize memory and ADL deficits in AD.

For example, Zanetti et al. (25) conducted a study with mild-moderate AD patients using a procedural memory stimulation program. The authors selected 20 basic and instrumental ADL and included 10 patients in the study. Five patients were trained in half of the 20 daily activities 1 h/day every day for 3 weeks, and five patients were trained in the other half. There was a significant reduction in time spent to perform the trained procedures compared to the untrained ones. This study indicates that the rehabilitation of ADL through the development of procedural strategies may be effective in mild and moderate AD patients. Improvement was also present in “not trained” activities, suggesting that functional achievements may be independent of the learning context .

Camp and McKitrick (26), after preliminary findings, also suggested that “ implicit memory-based intervention is more likely to yield positive results in AD patients than interventions based on explicit memory”.

Studies with NR of memory in AD patients have emphasized the importance of rehabilitation associated with drug treatment. De Vreese et al. (6) divided 24 patients with AD into 4 groups and compared them: 1) placebo, 2) treatment with AChE-I, 3) neuropsychological rehabilitation, and 4) AchE-I + NR. After 3 months

of drug treatment, groups 3 and 4 started NR for a period of 3 months. Patients participated in individual sessions of NR coupled with caregiver training. The results suggested better efficacy of combined treatment (AchE-I + NR), with marked therapeutic effects on cognition, behavior alteration and ADL.

Bottino el al. (27) presented the preliminary results of combined treatment of a group of 6 mild-moderate AD patients for 6 months. They showed stabilization or a small improvement of patient cognitive deficits and ADL by the end of the NR program. The authors suggested that the combined treatment could help stabilization and even result in a reduction of cognitive and functional deficits in AD patients.

Another interesting study compared both treatments, stimulation of procedural memory with ADL training, and partially spared cognitive function training such as memory, attention and language. Each program consisted of 5-week individual training, 3 days a week, with 45-min sessions per day for mild-moderate AD patients. The study concluded that both AD groups showed substantial improvement after training in a direct performance measure of everyday functioning. However, neuropsychological test results suggested that ADL training may be more effective than stimulating “residual” cognitive functions (28).

One of the major general problems and criticisms about teaching complex mnemonic strategies to AD patients is that very few people are actually able to apply these strategies to day-to-day problems. Therefore, it is important to use such mnemonic techniques as specific tools to be employed only when the patients need to learn something important and not as a general principle for daily difficulties (29). For this matter, the best solution seems to be the specific training for specific difficulties.

The current study suggests that the assessment of psychiatric symptoms and ADL activities by scales such as the HAM-A and MADRAS, and by neuropsychological measures including WMS-R, WAIS-R, FOME, RMF, BNT and Verbal Fluency may be able to identify improvements after NR treatment. The Functional Scale used here is also an effective and relevant instrument since it evaluates changes in a more ecological fashion.

This study also indicates that patients can apply implicit memory techniques and perform simple activities routinely. In addition, improving simple activities promotes important gains in behavior, improves patient independence and minimizes caregiver overload.

Our results support the view that an NR program associated with pharmacological treatment (AChE-I) and caregiver support groups applied to mild AD patients represents a realistic goal to slow down AD cognitive deficits and to reduce the psychiatric symptoms. Weekly stimulation of memory, language and training of ADL is believed to be of great value in AD treatment, not only delaying the progress of the disease, but also improving some cognitive functions and ADL.

In conclusion, non-pharmacological strategies applied to AD patients and caregiver support groups are important and may indicate that patients are able to maintain their preserved cognitive functioning for a longer period of time even though AD is a progressive disease.

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Table 1. Clinical and sociodemographic characteristics before cognitive rehabilitation .
Data are ported as means ± SD, with the range in parenthesis.

Variable	Patients (N=5)
Gender	F= 4 (83.3 %) M = 1 (16.7 %)
Age (years)	77.4 ± 2.88 (73-80)
Schooling (years)	6.60 ± 2.32 (2-15)
Marital status	Married: 2 (40%) Widowed: 3 (60%)
MMSE	22.20 ± 2.17 (20-25)
ADL	42.80 ± 4.55 (38- 47)

MMSE = Mini-Mental State Examination; ADL = Interview to Determine Deterioration in Functioning in Dementia.

Table 2. Results of the scales applied to patients and caregivers Pre- and Post-NR

Scale	Pre	Post	Statistical test and P value
MMSE	22.20 ± 2.17 (20-25)	23.80 ± 5.22 (16-29)	Z = -0.31 P = 0.75
*HAM-A	7.60 ± 5.41 (4-16)	2.80 ± 4.09 (0-9)	Z = -1.48 P = 0.13
*MADRAS	5.60 ± 8.41 (0-20)	4.80 ± 6.42 (0-16)	Z = -0.10 P = 0.91
QOL-Patient	37.60 ± 6.91 (29-48)	42.00 ± 7.38 (33-51)	Z = -0.41 P = 0.67
QOL-Caregivers	31.60 ± 5.64 (23-37)	37.00 ± 8.51 (29-38)	Z = -0.21 P = 0.83
*MDLQ-Patients	84.40 ± 44.52 (49-156)	105.60 ± 55.04 (48-187)	Z = -0.52 P = 0.60
*MDLQ- Caregivers	172.00 ± 22.47 (149-197)	143.25 ± 59.20 (111-232)	Z = -0.94 P = 0.34
ADL	42.80 ± 4.55 (38-47)	41.20 ± 4.09 (37-46)	Z = -0.84 P = 0.40
Functional scale	5 ± 2.00 (2-7)	7 ± 0.71 (6-8)	Z = -1.96 P = 0.04

MMSE = Mini-Mental State Examination; MADRAS = Montgomery-Asberg Depression Rating Scale; HAM-A = Hamilton Anxiety Scale; ADL = Interview to Determine Deterioration in Functioning in Dementia ; QOL = Quality of Life questionnaire; MDLQ = Memory of Daily Living questionnaire; ADL = Interview to Determine Deterioration in Functioning in Dementia.

Table 3. Results obtained before and after neuropsychological evaluation.

Tests	Pre	Post	Statistical test and P value
FOME	22.80 ± 15.72 (7-48)	29.60 ± 21.10 (1-60)	Z = -0.94 P = 0.34
Logical memory I	7.80 ± 8.50 (0-22)	11.60 ± 8.05 (2-24)	Z = -1.05 P = 0.29
Logical memory II	3.40 ± 5.64 (0-13)	4.80 ± 9.15 (0-21)	Z = 0.00 P = 1.00
Visual reproduction I	15.80 ± 10.64 (0-21)	16.80 ± 6.98 (8-26)	Z = -0.10 P = 0.91
Visual reproduction II	5.20 ± 7.26 (0-60)	5.60 ± 6.54 (0-16)	Z = -0.33 P = 0.73
Recognition memory face	31.40 ± 4.98 (27-38)	31.80 ± 7.40 (25-41)	Z = -0.21 P = 0.83
Boston	40.60 ± 12.56 (26-52)	46.40 ± 7.80 (38-55)	Z = -0.83 P = 0.40
Forward digit span	5.00 ± 1.41 (3-7)	5.20 ± 1.64 (4-7)	Z = -0.10 P = 0.91
Backward digit span	3.80 ± 1.79 (2-6)	3.60 ± 1.14 (2-5)	Z = -0.21 P = 0.83
Verbal fluency animals	10.80 ± 3.56 (7-14)	10.60 ± 9.29 (1-26)	Z = -0.53 P = 0.59
Verbal fluency F.A.S.	29.80 ± 11.82 (14-45)	27.00 ± 7.65 (14-33)	Z = -0.52 P = 0.59
IQ verbal	87.20 ± 19.38 (70-107)	97.00 ± 21.12 (80-128)	Z = -1.25 P = 0.20
IQ performance	87.20 ± 15.58 (70-114)	89.20 ± 15.50 (71-107)	Z = -0.31 P = 0.75

Boston = Boston Naming Test; FOME = Fuld Object Memory Evaluation; IQ = intelligence quotient .

Table 4. Effect size of treatment in some scales and tests.

Scales and test	**Effect size**
MMSE	0.11
ADL	0.35
Functional scale	1.00
Logical memory I	0.44
Logical memory II	0.24
Visual reproduction I	0.09
Visual reproduction II	0.05
Recognition memory face	0.08
FOME	0.3

MMSE = Mini-Mental State Examination; ADL = Interview to Determine Deterioration in Functioning in Dementia; FOME = Fuld Object Memory Evaluation.

APPENDIX

FUNCTIONAL TEST

Patient´s name: Date of evaluation:

Chores:

1. Receive and take note of a message by phone. Tell the patient: “when the phone rings you should answer it” – “Mr.(s) has a doctor appointment at the hospital next Monday at three o’clock”

a. answers the phone spontaneously

b. says that she will take the message spontaneously

c. takes the message before hanging up the phone

d. checks that she wrote the message down correctly before hanging up the phone

observations:

2. Take note of an appointment in the diary. Tell the patient: “I will tell you an appointment and you will take note of this appointment in your diary: “Mr.(s) has a dentist appointment next Wednesday at two o’clock”

a. manages to locate today’s date in the diary without any help

b. takes note of the appointment on the right day, that is, the day of the appointment.

C. Takes note of the complete details of the appointment.

observation:

3. Write a note giving someone a message. Tell the patient: “I will give you a message for you to tell the other person: “Son, the cleaning lady called informing that she will not be coming to work tomorrow”

a. takes note of the message alone

b. takes note of the message completely.

observation: