

Original Research Article

## Cognitive and Neuropsychiatric Symptom Differences in Early Stages of Alzheimer's Disease: Kuopio ALSOVA Study

Ilona Hallikainen<sup>a</sup> Anne M. Koivisto<sup>a, d</sup> Teemu Paajanen<sup>a</sup>  
Asta Hiltunen<sup>f</sup> Pertti Karppi<sup>g</sup> Matti Vanhanen<sup>e</sup> Tarja Välimäki<sup>b, c</sup>  
Sanna-Kaisa Herukka<sup>a, d</sup> Hilikka Soinen<sup>a, d</sup> Tuomo Hänninen<sup>d</sup>

<sup>a</sup>Institute of Clinical Medicine, Neurology, <sup>b</sup>Department of Nursing Science and <sup>c</sup>Finnish Doctoral Program in Nursing Science, University of Eastern Finland, <sup>d</sup>Department of Neurology, Kuopio University Hospital, and <sup>e</sup>Niuvanniemi Hospital, Kuopio, <sup>f</sup>Department of Neurology, North Karelia Central Hospital, Joensuu, and <sup>g</sup>Mikkeli Central Hospital, Mikkeli, Finland

### Key Words

Alzheimer's disease · Dementia · Memory · Neuropsychiatric symptoms · Neuropsychological tests

### Abstract

**Background/Aim:** Alzheimer's disease (AD) causes impairment in memory and other cognitive functions as well as neuropsychiatric symptoms and limitations in the activities of daily living (ADL). The aim of this study was to examine whether demographic variables, dementia severity, ADL and neuropsychiatric symptoms are associated with cognition in very mild or mild AD. **Methods:** We analyzed the baseline data of 236 patients with very mild or mild AD participating in a prospective AD follow-up study (ALSOVA). The Consortium to Establish a Registry for Alzheimer's Disease neuropsychological battery total score was used in the evaluation of the global cognitive performance. **Results:** Cognition was associated with dementia severity and ADL but not with neuropsychiatric symptoms. ADL functions were associated with both cognitive performance and neuropsychiatric symptoms. **Conclusion:** Even patients with very mild or mild AD may exhibit neuropsychiatric symptoms not related to cognitive impairment. The results of this study emphasize the importance of taking a multidimensional approach to the diagnostic and prognostic evaluation of AD patients already in the early stages of the disease.

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## Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disease which is characterized by impairment in cognitive and functional abilities as well as by neuropsychiatric symptoms. Cognitive impairment can include impairment in memory, visuospatial functions, language and executive functions. In addition, neuropsychiatric symptoms, such as depression, apathy and agitation, seem to be common already in early stages of AD and can have an impact on both patients' and care-givers' well-being [1–3]. Cognitive performance has been consistently associated with functional ability [4–8]; however, the association of neuropsychiatric symptoms with cognition and daily functioning is unclear [7, 9–13], in spite of the fact that the amount of neuropsychiatric symptoms seems to increase in patients with more advanced dementia [14, 15]. Thus, more information is needed to elucidate how these features of AD are interrelated.

The Consortium to Establish a Registry for Alzheimer's Disease neuropsychological battery (CERAD-NB) [16] is a widely used, short and reliable measure of cognitive impairment in AD patients [17, 18]. The method for calculating a total score for the CERAD-NB was published in 2005 [19], and recent studies have supported both the validity and usefulness of the CERAD total score for the detection of mild cognitive impairment and dementia [20–22] as well as for monitoring progression of AD dementia [21]. That is, it seems to be more valuable to use the total score than relying on single subtests. Though the Mini-Mental State Examination (MMSE) [23] has been commonly used, it has been claimed to be of limited value as a screening instrument [24, 25] and in measuring progression of AD [26].

The present study was designed to examine whether global cognitive performance assessed by the CERAD total score is associated with dementia severity, activities of daily living (ADL) and neuropsychiatric symptoms in patients with very mild or mild AD.

## Methods

### *Subjects*

A total of 241 patients with recently diagnosed very mild or mild AD participated in a prospective AD follow-up study (ALSOVA). The total follow-up period will be up to 5 years [1, 2]. The aim of the ALSOVA study is to elucidate the effects and cost-efficiency of psychosocial rehabilitation. The study subjects were recruited from April 2002 to September 2006 from the neurology departments of the University Hospital of Kuopio and North-Karelia Central Hospital and from the geriatric memory clinic of the Central Hospital of Central-Finland.

The patients were diagnosed at neurology departments or geriatric memory clinics according to clinical practice, and the diagnosis of AD according to NINCDS-ADRDA guidelines [27] was verified by the research doctor. The baseline data were not used as part of the diagnostic procedure, but it is possible that same methods (e.g. CERAD) have been used. All subjects had very mild or mild dementia at baseline. Finnish speaking, community-dwelling individuals who were free of comorbid conditions that could have affected cognition and who had a loved one as their caregiver were included.

Three subjects from the original study population of 241 subjects were excluded since they were found to have moderate AD, one subject had a diagnosis of Parkinson's disease and another one suffered from blindness. Ultimately, 236 patients fulfilled the inclusion criteria for this part of the study.

### *Measures*

The extensive data collected included age, gender, education, physical health, medication, household composition, living arrangements, general well-being, caregiver burden, depression, quality of life and society resource utilization [1, 2].

The cognitive evaluation was performed with the CERAD-NB [16] and MMSE [23]. The Finnish version of the CERAD-NB [28] consists of nine subtests; the Delayed Recall of Constructional Praxis and the Clock Drawing Test are additions to the original test battery. The total score for the CERAD-NB was calculated for each participant according to the subtest addition method [19]. The total score was obtained by summing the raw scores from the six subtests (Verbal Fluency Test, modified Boston Naming Test, Word List Memory, Word List Recall, Word List Recognition Discriminability and Constructional Praxis) into a total score (maximum 100 points) according to the original method.

The Clinical Dementia Rating (CDR) scale is a rating scale for evaluating the severity of the memory disorder [29, 30]. The structured interview protocol includes six areas, and the scores in each of these sections are combined to obtain a composite score and a sum of boxes (SOB) score. The Alzheimer's Disease Cooperative Study – Activities of Daily Living Inventory (ADCS-ADL) is a set of informant-based items describing performance of ADL for patients with AD [4]. The Neuropsychiatric Inventory (NPI) is an informant-based interview that assesses twelve behavioral disturbances occurring in dementia patients [31]. The total NPI score is the sum of the subscale scores (frequency × severity). Higher scores indicate more behavioral disturbance.

Data were missing for one subject for Constructional Praxis, Delayed Constructional Praxis and Clock Drawing Test because of problems in vision and for another subject for the Word List Recognition because of difficulties understanding the test instructions. Thus, the data for the CERAD total score were missing for two subjects.

### *Ethical Considerations*

The Ethics Committee of Kuopio University Hospital approved the ALSOVA study protocol. The study participants were recruited from three memory clinics serving three hospital districts. Potential participants received written and oral information of the study, and an initial visit was arranged soon after the diagnosis for those who consented to participate. The voluntary nature of participation and the confidentiality of data collected were emphasized. The informed consent form was signed by both the patients with AD and their caregivers. The caregivers also provided proxy consent on behalf of the individuals with AD.

### *Data Analysis*

Descriptive statistics were used to summarize the variables studied and the characteristics of the participants. The data were analyzed with SPSS for Windows 14.0 software package. The t test was used to compare cognition and severity of dementia and the Mann-Whitney U test to compare ADL and neuropsychiatric symptoms between men and women and between CDR 0.5 and 1 groups. Pearson's correlation was used to analyze relations between the CERAD-NB, MMSE, CDR-SOB, age and education. Spearman's correlation was used to analyze the ADCS-ADL or NPI scores. A p value <0.05 was considered statistically significant.

## **Results**

Almost half of the study participants (n = 115, 48.7%) were men. Most of the patients (66.1%) had mild dementia (CDR = 1) and 33.9% had very mild dementia (CDR = 0.5). In 70.3% of cases, the caregiver was a spouse, whereas in 23.7% of cases, the caregiver was a

**Table 1.** Demographic and clinical characteristics of the AD patients participating in the study

	CDR 0.5 (n = 80)	CDR 1 (n = 156)	All (n = 236)	p value*
Female, %	53.8	50	51.3	
Age, years	73.85 ± 6.95 (56–87)	75.75 ± 6.26 (53–90)	75.11 ± 6.55 (53–90)	0.245
Education, years	8.14 ± 3.32 (1–18)	7.25 ± 3.25 (1–20)	7.55 ± 3.29 (1–20)	0.350
CERAD total score <sup>1</sup> (scale 0–100)	56.09 ± 12.63 (25–96)	49.28 ± 10.77 (22–82)	51.58 ± 11.85 (22–96)	<0.001
MMSE score (scale 0–30)	23.22 ± 2.95 (16–30)	20.62 ± 3.34 (12–30)	21.5 ± 3.44 (12–30)	<0.001
CDR-SOB score (scale 0–18)	2.60 ± 0.70 (1–3.5)	4.91 ± 1.13 (3–8)	4.13 ± 1.49 (1–8)	<0.001
ADCS-ADL score (scale 0–78)	69.63 ± 5.99 (50–78)	61.91 ± 8.78 (34–76)	64.53 ± 8.73 (34–78)	<0.001
NPI score (0–144)	6.31 ± 7.25 (0–32)	10.16 ± 10.63 (0–49)	8.86 ± 9.78 (0–49)	0.028

Values are mean ± SD with ranges in parentheses, unless indicated otherwise.

\* Pairwise comparisons of the difference between very mild (CDR = 0.5) and mild (CDR = 1) AD dementia, significance of difference in two-tailed t test or Mann-Whitney U test, calculated by Bonferroni correction. <sup>1</sup> n = 234.

child. The remaining 6% of caregivers were siblings or children's spouses. On average, the participants were recruited 5 months after diagnosis. Almost all patients (96.2%) were on AD medication, with 93.8% of them using acetylcholine esterase inhibitors and 6.2% using memantine. Table 1 shows the mean age, education in years, CDR-SOB score, CERAD total score, MMSE score, ADCS-ADL score and NPI total score. Only 18.2% of the participants had no neuropsychiatric symptoms, 21.6% had one symptom, 13.1% two and 47.0% displayed symptoms in at least three different NPI domains. The most common neuropsychiatric symptoms were apathy (48.3%), depression (36.4%) and irritability (33.9%).

There was no significant difference in the CERAD total score, MMSE score, CDR-SOB score or NPI score between men and women. Women performed better on the ADCS-ADL than men ( $z = -4.287$ ,  $p < 0.001$ ). Not surprisingly, participants with very mild dementia (CDR = 0.5) outperformed those with mild dementia (CDR = 1) on the CERAD total score ( $t(2,232) = 4.308$ ,  $p < 0.001$ ) and MMSE score ( $t(2,234) = 5.886$ ,  $p < 0.001$ ), received a lower NPI total score ( $z = -2.892$ ,  $p = 0.028$ ) and a greater ADCS-ADL score ( $z = -7.032$ ,  $p < 0.001$ ; table 1). Table 2 shows the results of the correlation analyses between age and education and CERAD total, MMSE, CDR-SOB and ADCS-ADL scores. The length of education was positively correlated with the CERAD total score and the MMSE score, but there was no significant correlation between age and the CERAD total score or age and the MMSE score. Age correlated negatively with ADCS-ADL scores, and education correlated negatively with CDR-SOB scores and positively with ADCS-ADL scores. NPI scores did not correlate with education or age.

Table 2 shows the results of the correlation analyses between the CERAD total, MMSE, CDR-SOB, ADCS-ADL and NPI total scores. The CDR-SOB score was negatively correlated with the CERAD total and MMSE scores, whereas the ADCS-ADL score was positively correlated with the CERAD total and MMSE scores. We also analyzed the correlation between

**Table 2.** Correlations between demographic and clinical characteristics of the AD patients participating in the study

	CERAD total score <sup>†</sup>	MMSE score <sup>†</sup>	CDR-SOB score <sup>†</sup>	ADCS-ADL score <sup>‡</sup>	NPI score <sup>‡</sup>
Education (years)	0.334***	0.278***	-0.204*	0.357***	-0.092
Age (years)	0.062	0.035	0.159	-0.201*	-0.073
CERAD total score		0.618***	-0.319***	0.250***	-0.087
MMSE score			-0.443***	0.314***	0.049
CDR-SOB score				-0.580***	0.231***
ADCS-ADL score					-0.339***

\*\*\*  $p < 0.001$ , \*  $p < 0.05$ , calculated by Bonferroni correction. <sup>†</sup> Pearson's product-moment correlation coefficient; <sup>‡</sup> Spearman's rank correlation coefficient.

the CERAD total and ADCS-ADL scores separately for subjects with low education ( $\leq 8$  years) and subjects with high education ( $\geq 9$  years). The correlation was stronger in the more educated group ( $r = 0.351$ ,  $p = 0.009$ ) but was significant also in the low-educated group ( $r = 0.186$ ,  $p = 0.013$ ). The ADCS-ADL score was negatively correlated with the CDR-SOB score. The NPI total score was not correlated with the CERAD total score or the MMSE score. We also analyzed the correlation between the CERAD total and NPI scores separately in low- and high-educated groups and got similar results. None of the NPI subscales was correlated with the CERAD total score and none of the CERAD subtests was correlated with the NPI total score. The NPI total score was positively correlated with CDR-SOB score and negatively with ADCS-ADL scores.

## Discussion

In this study, we investigated correlations between the CERAD total score, ADL and neuropsychiatric measures in a large group of systematically documented AD patients with very mild or mild dementia. Almost all of them used medication for AD. They all participated in a longitudinal study focusing on the effects and cost-efficiency of early psychosocial rehabilitation. There have been very few studies using the CERAD total score to measure cognitive performance in AD patients. In our study, CERAD total score correlated with the MMSE. As expected, participants with clinical staging of very mild dementia ( $CDR = 0.5$ ) outperformed those with mild dementia ( $CDR = 1$ ). These findings are consistent with results from previous studies [19, 21, 22].

The influence of education on the results of the CERAD-NB subtests has been noted in many studies, but the influence of age and gender has varied across studies [17, 19, 32–35]. Consistent with data on the CERAD subtests for a sample of elderly Finns [33], our results in the AD sample revealed a correlation between the CERAD total score and education but not between the CERAD total score and age. There was no difference in the CERAD total score between genders. Our results are in agreement with those of previous studies about the importance of taking into account the educational level of AD patients in any evaluation of cognitive performance conducted with the CERAD-NB.

Although the mean NPI total score is relatively low, it can represent for example several occasional mild symptoms or two weekly moderate symptoms or one severe symptom. The

mean NPI score in our AD sample is consistent with previous studies with comparable groups of patients [36]. We have previously reported that these symptoms have an impact on both patients' and care-givers' well-being already in early stages of AD [1, 2]. Studies in patients with mild cognitive impairment show that neuropsychiatric symptoms may be a predictor of conversion to AD [37], which emphasizes the role of evaluation of these symptoms already in the early phase of the disease.

There are very few studies where the CERAD total score was used as a measure of cognitive function in the evaluation of associations between cognitive performance, functional ability and neuropsychiatric symptoms. In our study, cognition was significantly associated with ADL. These results are consistent with those from previous studies conducted with the CERAD total score [22] or other cognitive measures [4, 5, 7–9]. Women received better scores in the ADCS-ADL, which probably reflects the traditional way to share housework in marriages in this generation, and this needs to be taken into account when using ADL measures. An association was also detected between ADL and neuropsychiatric symptoms. There are many previous findings indicating that neuropsychiatric symptoms are associated with functional limitations [6, 7, 11, 13], although some studies have found contrasting results [5, 9].

Most reports in the literature indicate that behavioral symptoms and cognition are not related [10, 11] or that the relationship is weak [7, 12]. There is also evidence that any change in behavioral symptoms is independent from changes occurring in cognitive measures [9]. Instead, Harwood et al. [6] described a relationship between psychological and behavioral disturbances and MMSE scores. Our study, using the CERAD total score and MMSE score, indicates that neuropsychiatric symptoms were not correlated with cognitive performance. Our results are consistent with most of the previous evidence, showing that cognitive and behavioral disturbances are rather distinct entities in AD, at least in the mild stage of the disease. Although the correlations between other clinical characteristics (CERAD total, ADCS-ADL, NPI and CDR-SOB scores) were fairly modest (0.23–0.58), they were clearly significant and, on the contrary, the correlations between cognition and neuropsychiatric symptoms did not imply even a tendency of association.

There are some limitations to this study. All patients and their caregivers voluntarily participated in this 5-year follow-up study and met regularly with the study nurse and psychologist. Some of the subjects were randomly selected to participate in early psychosocial intervention. Therefore, this voluntary participation procedure may have produced a selection bias. Thus, this study population may not completely represent the general population of patients with very mild or mild AD. Andersen et al. [38] have reported that recruitment from clinical practice and population-based screening represent study samples with different demographic characteristics.

Our study population at baseline was homogenous in terms of recently diagnosed very mild or mild AD. Therefore, results cannot be generalized to patients with more advanced dementia. The educational level of older persons in Finland is often lower than in other Western countries, and this needs to be considered when interpreting results. Despite these limitations, our results strongly support previous studies.

The strength of our study was the use of several different measures and a more extensive cognitive evaluation than the MMSE in a fairly large study population. Subsequently, it would be valuable to monitor how cognition, neuropsychiatric symptoms and ADL change with time, and to obtain more information about the usability of the CERAD total score in follow-up studies. This kind of follow-up data could also help to find factors that would predict the progression rate of AD.

In conclusion, we detected that cognitive performance was not associated with neuropsychiatric symptoms, but that ADL were associated with both of these factors. It is evident

that both the cognitive level and neuropsychiatric symptoms affect the patients' ability to cope with the demands in everyday life. Our results help to provide information to patients and their caregivers about symptoms during the first years of the disease. Our findings emphasize the need for a multifaceted evaluation of AD symptoms in both the clinical and research setting.

### Appendix: ALSOVA Study Group

Hilkka Soininen, MD, Professor, project director: Department of Neurology, Kuopio University Hospital and School of Medicine, Institute of Clinical Medicine, Neurology, University of Eastern Finland, Kuopio Campus, Finland.

Anne Koivisto, PhD, MD, specialist in neurology, study coordinator and principal investigator: Department of Neurology, Kuopio University Hospital and School of Medicine, Institute of Clinical Medicine, Neurology, University of Eastern Finland, Kuopio Campus, Finland.

Ilona Hallikainen, MPsych, psychologist: Brain Research Unit, Clinical Research Centre, University of Eastern Finland, Kuopio Campus, Finland.

Sanna-Kaisa Herukka, PhD, researcher: Department of Neurology, Kuopio University Hospital and School of Medicine, Institute of Clinical Medicine, Neurology, University of Eastern Finland, Kuopio Campus, Finland.

Asta Hiltunen, MD, specialist in neurology: Department of Neurology, North Karelia Central Hospital, Finland.

Janne Martikainen, PhD, research director: School of Pharmacy, University of Eastern Finland, Kuopio Campus, Finland.

Helena Mäkelä, study nurse: Brain Research Unit, Clinical Research Centre, University of Eastern Finland, Kuopio Campus, Finland.

Pertti Karppi, MD, geriatrician: Mikkeli Central Hospital, Finland.

Kristiina Hongisto, MD, geriatrician: Institute of Public Health and Clinical Nutrition, Department of Geriatrics, University of Eastern Finland, Kuopio Campus, Finland and School of Medicine, Institute of Clinical Medicine, Neurology, University of Eastern Finland, Kuopio Campus, Finland.

Teemu Paajanen, MPsych, psychologist: Brain Research Unit, Clinical Research Centre, University of Eastern Finland, Kuopio Campus, Finland.

Anna-Maija Pietilä, PhD, Professor: Department of Nursing Science, University of Eastern Finland, Kuopio Campus, Finland.

Juhani Sivenius, MD, Professor: Brain Research and Rehabilitation Center Neuron, Department of Neurology, Kuopio University Hospital and School of Medicine, Institute of Clinical Medicine, Neurology, University of Eastern Finland, Kuopio Campus, Finland.

Hannu Valtonen, PhD, Professor: Department of Health and Social Management, University of Eastern Finland, Kuopio Campus, Finland.

Matti Vanhanen, PhD, neuropsychologist: Niuvanniemi Hospital, Kuopio, Finland.

Katri Vehviläinen-Julkunen, Professor: Department of Nursing Science, University of Eastern Finland, Kuopio Campus, Finland.

Tarja Välimäki, MNSc: Department of Nursing Science, University of Eastern Finland, Kuopio Campus, Finland.

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## Disclosure Statement

The authors have no conflicts to disclose. The sponsors had neither a role in the analysis or interpretation of these data, nor in the content of the article.

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