The Deterioration of Different Cognitive Domains in Relation to Alzheimer's Disease Severity: A Cross-Sectional Study

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SUMMARY

The sequence of deterioration in different cognitive domains, depending on the severity of Alzheimer's disease (AD), is still largely unknown. The aim of this study was to use the Mini–Mental State Examination (MMSE) scale to divide subjects into six groups of disease severity and compare the deterioration in cognitive domains (orientation in time and place, working memory, concentration, recall, language, and visuospatial orientation) between the groups. A total of 624 participants with a median age of 76 years (interquartile range (IQR) 70–80 years) were included in the study. A significant difference in age was observed between participants with severe cognitive impairment compared to other participants. No difference in sex structure was observed between the groups. The highest fluctuation, even in persons without cognitive impairment, was observed in the recall and concentration domains, followed by visuospatial orientation. The first deteriorated domains with progression of the disease were concentration and visuospatial orientation. Deterioration then continued in orientation in time and place, language, and working memory. The results can be used to predict the development of the disease, as well as for the adequate planning and testing of therapeutic approaches for AD.

KEYWORDS

Alzheimer's disease; *Screening*; *Cognitive decline sequence*

Introduction

Neurodegenerative diseases are among the major causes of morbidity and mortality globally[1]. Alzheimer's disease (AD) is the most common neurodegenerative disease[2], estimated to make up 60–80% of all dementia cases in the world[1]. A dramatic increase in the numbers of AD patients in the USA is predicted if adequate preventive measures are not introduced[3]. AD is very heterogeneous, with symptoms depending on the affected parts of the neural network[1]. Progression is usually slow with an increase in memory loss and deterioration of different cognitive domains leading to the loss of functional abilities[1]. Cognitive domains are classified in different ways, usually by applying a hierarchical approach from basic to more complex functions. Domains are often interdependent and various approaches are applied to measure cognitive functioning[4]. The Mini–Mental State Examination (MMSE) scale is commonly used in the evaluation of AD patients' condition[5]. The MMSE scale is the most used instrument for cognitive function evaluation in clinical practice and clinical trials[6,7]. It is easy to conduct and consists of eleven questions evaluating the deterioration of different cognitive domains. The scale covers orientation (in time and in place), registration (working memory), attention and calculation (concentration), recall, language, and visuospatial orientation (motor skills and construction)[4,8]. With increased numbers of impaired cognitive domains measured by MMSE, the risk of all-cause mortality increases as well[6]. Also, cognitive scores are consistent predictors of subsequent functional decline, playing an important role in monitoring AD patients[9].

The sequence of deterioration for different cognitive domains in AD is still poorly investigated. Taking into consideration the heterogeneity of AD and its slow rate of development, the design of any studies in this area is complex. Usually, longitudinal studies are performed. The alternative approach is to analyze patients belonging to different severity groups and compare the deterioration of cognitive domains between them. This approach was applied by Henneges et al., who evaluated the sequence of cognitive decline in AD patients included in the multicenter GERAS study. Their results provided a valuable tool for making predictions of AD progression[2].

The aim of this study was to recognize Alzheimer's disease at the level of primary health care and evaluate the deterioration of different cognitive domains depending on disease severity by using the MMSE scale.

Methods

General practitioners reviewed all records from their team and detected patients with confirmed AD. Additionally, they screened subjects suspected of having dementia by using the MMSE scale. Demographic data were collected for each participant.

Ethical statement

The study was approved by the Agency for medicinal products and medical devices of Bosnia and Herzegovina. The Helsinki Declaration from 1975 and its amendments from 1983 were followed in all procedures. Before any procedure was started, each participant signed an informed consent form.

Statistical analysis

The normality of data distribution was evaluated by visual inspections of histograms, box-plots and Q-Q graphs, and by the Kolmogorov–Smirnov test. To compare age and sex, the subjects were divided into groups without cognitive impairment (MMSE score 24–30), with moderate cognitive impairment (MMSE score 18–23) and with severe cognitive impairment (MMSE score 0–17)[10]. The Kruskal–Wallis H test was used to compare age and MMSE scores among the three groups. Pearson's chi-square test was used to compare sex distribution between the groups.

To obtain the most accurate results of cognitive impairment comparison in the seven examined domains (orientation in time, orientation in place, registration, concentration, recall, language, visuospatial orientation), all participants were divided into six categories, i.e. each group of cognitive impairment severity was divided into two subgroups:

1. N_{high}: no impairment, higher MMSE score (27–30)
2. N_{low}: no impairment, lower MMSE score (24–26)
3. M_{high}: moderate impairment, higher MMSE score (21–23)
4. M_{low}: moderate impairment, lower MMSE score (18–20)
5. S_{high}: severe impairment, higher MMSE score (9–17)
6. S_{low}: severe impairment, lower MMSE score (0–8)

The comparison of cognitive impairment in the seven examined domains between six categories of cognitive impairment was performed by using the Kruskal–Wallis H test, followed by pairwise comparisons performed by using Dunn's (1964) test with the Bonferroni correction for multiple comparisons with adjusted *P*-values presented.

All tests were two-sided with $P < 0.05$ accepted as a statistically significant difference. Statistical analysis was performed using the SPSS (Statistical Package for Social Sciences) program version 23.0 and the R Statistical Software (Foundation for Statistical Computing, Vienna, Austria) version 4.2.2. Visualization was performed by using the ggplot2 package[11].

Results

The total number of general practitioners who participated in the study was 32, with a total of 60,619 patients registered in their teams. Our analysis of registered patients' records showed that 21,581 (35.6%) were over 65 years of age, and 603 (1.0%) were diagnosed with dementia. The median total number of registered patients per medical team was 1,913, while the median number of patients over 65 years of age registered per medical team was 617 (Table 1).

A total of 624 participants with a median age of 76 (interquartile range, (IQR) 70–80) were

Table 1. Data on patients belonging to the teams of general practitioners, median (min–max)

Parameter	Number of general practitioners (n = 32)
Total number of registered patients	1913 (1480–2250)
Number of patients older than 65 years	617 (312–1400)
Percentage of patients older than 65 years in the total number of registered patients (%)	32.3 (17.7–66.7)
Number of patients diagnosed with dementia	10 (3–153)
Percentage of patients with diagnosed dementia in the total number of registered patients (%)	0.3 (0.2–6.8)

included in the study. By comparing three groups of participants with different levels of cognitive impairment (no impairment, moderate, and severe impairment) using the Kruskal–Wallis H test, a significant difference in age between the groups was observed ($P < 0.001$) (Table 2). A post-hoc analysis using Dunn's (1964) test with the Bonferroni correction revealed statistically significant differences in age between participants with severe cognitive impairment and participants without impairment ($P < 0.001$), and with moderate cognitive impairment ($P < 0.001$). No difference in sex structure was observed between the groups. The median MMSE score for all participants was 21 (Table 2).

Each of the three categories of cognitive impairment severity was divided into two subcategories, and the resulting six groups were analyzed in terms of detecting score differences in the seven examined domains (Table 3).

TABLE 2. Characteristics of the included subjects

Parameter	All subjects (n = 624)	No cognitive impairment (n = 190)	Moderate cognitive impairment (n = 249)	Severe cognitive impairment (n = 185)	*P*-value comparing three groups of subjects
Age, years median (IQR)	76 (70–80)	73 (69–79)	75 (70–80)	78 (72–83)	**< 0.001**
Sex, male (n, %)	247 (39.6)	84 (44.2)	97 (39.0)	66 (35.7)	0.215
MMSE score median (IQR)	21 (17–24)	26 (25–28)	21 (19–22)	13 (9–16)	**< 0.001**

IQR = Interquartile range; MMSE = Mini-mental state examination. The Kruskal–Wallis H test was used to compare age and MMSE scores among the three groups of severity of cognitive impairment. Pearson's chi-square test was used to compare sex between groups.

TABLE 3. Mini-mental state examination (MMSE) scores by different tested domains for the six groups of patients

Total MMSE score	Group	Number of patients	Orientation in time	Orientation in place	Working memory	Concentration	Recall	Language	Visuospatial orientation
0–8	S_{low}	39	0 (0–1)	1 (0–1)	0 (0–1)	0 (0–0)	0 (0–0)	2 (0–4)	0 (0–0)
9–17	S_{high}	146	3 (2–3)	3 (2–4)	2 (1–3)	0 (0–1)	0 (0–1)	5 (4–6)	0 (0–0)
18–20	M_{low}	122	4 (3–4)	4 (3–5)	3 (2–3)	1 (0–2)	1 (0–2)	7 (6–7)	0 (0–1)
21–23	M_{high}	129	4 (4–5)	4 (4–5)	3 (2–3)	2 (1–3)	2 (1–2)	7 (6–8)	0 (0–1)
24–26	N_{low}	96	5 (4–5)	5 (4–5)	3 (3–3)	3 (2–4)	2 (2–3)	8 (7–8)	1 (0–1)
27–30	N_{high}	92	5 (5–5)	5 (5–5)	3 (3–3)	5 (4–5)	3 (2–3)	8 (8–8)	1 (1–1)

The results are presented as a median (interquartile range, IQR). Six groups of patients belonging to different cognitive impairment levels were analyzed: N_{high}: no impairment, higher MMSE score (27–30), N_{low}: no impairment, lower MMSE score (24–26), M_{high}: moderate impairment, higher MMSE score (21–23), M_{low}: moderate impairment, lower MMSE score (18–20), S_{high}: severe impairment, higher MMSE score (9–17), S_{low}: severe impairment, lower MMSE score (0–8).

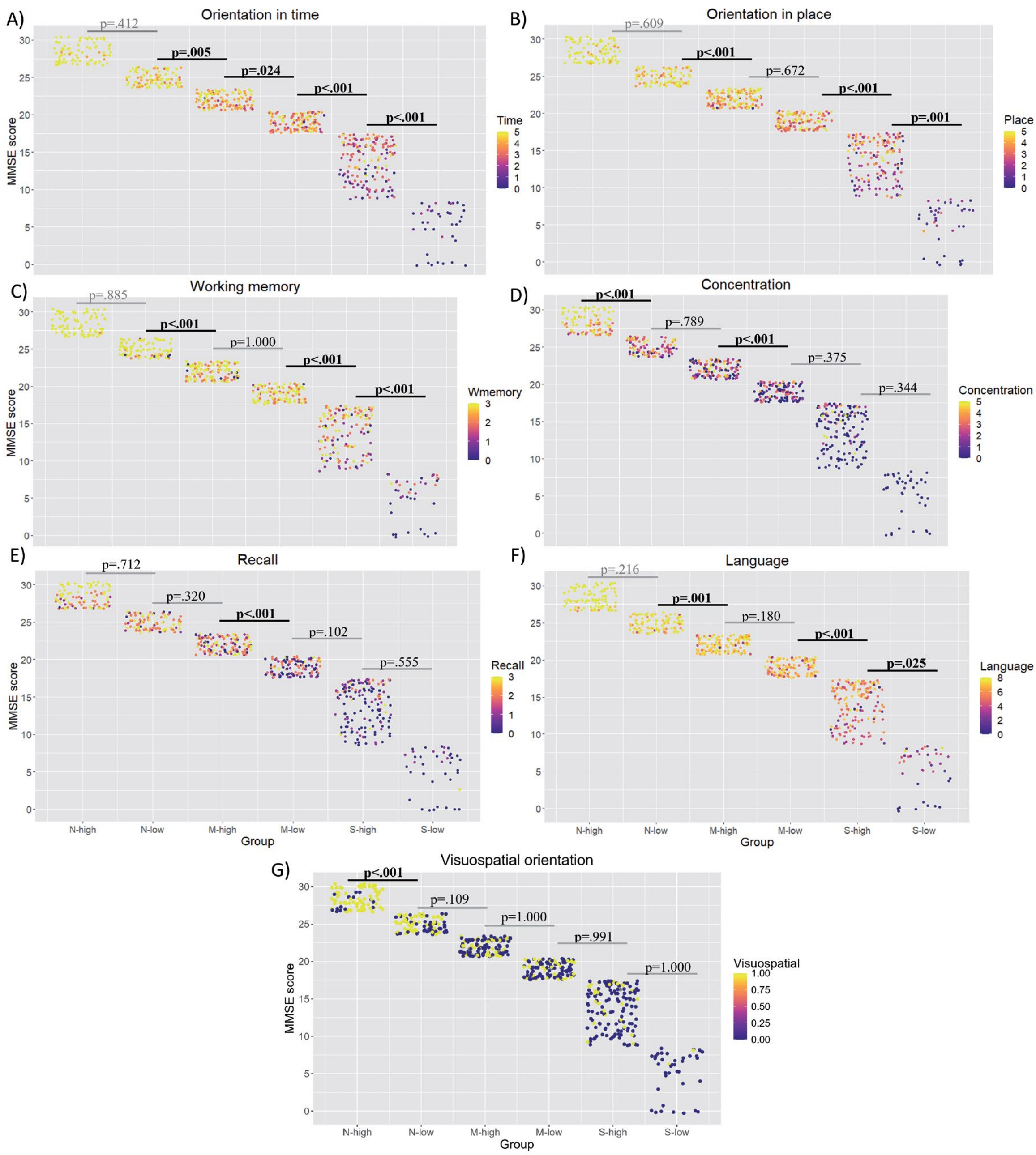

FIG. 1. Score values based on the Mini–mental state examination (MMSE) scale for individual categories of cognitive impairment in the seven analyzed domains: A) orientation in time, B) orientation in place, C) working memory (registration), D) concentration, E) recall, F) language, G) visuospatial orientation. Six individual categories of cognitive impairment were analyzed: N_{high}: no impairment, higher MMSE score (27–30), N_{low}: no impairment, lower MMSE score (24–26), M_{high}: moderate impairment, higher MMSE score (21–23), M_{low}: moderate impairment, lower MMSE score (18–20), S_{high}: severe impairment, higher MMSE score (9–17), S_{low}: severe impairment, lower MMSE score (0–8). The Kruskal–Wallis H test was applied followed by pairwise comparisons using Dunn's (1964) test with the Bonferroni correction for multiple comparisons with adjusted *P*-values presented. Visualization was prepared by using the ggplot2 package[11].

In the N_{high} group, the scores varied only for questions in the domains of concentration (maximum score 5) and recall (maximum score 3), while most subjects achieved the maximum number of points in the other domains (Table 3). The N_{high} group consisted of 92 participants. In the domain of recall, only 53 (58%) of them had the maximum score of 3, while 29 (32%) had a score of 2, 8 (9%) a score of 1, and 2 (2%) a score of 0. In the concentration domain, of the 92 participants in the N_{high} group only 53 (58%) had the maximum score of 5, while 20 (22%) had a score of 4, 17 (18%) a score of 3, and 2 (2%) a score of 2.

In the N_{low} group, a significant deterioration in the concentration and visuospatial orientation was observed in comparison to the N_{high} group. In the M_{high} group, a significant change was observed in orientation in time and place, working memory and language when compared to the N_{low} group. By further increasing the level of cognitive impairment and analyzing the M_{low} group, the first significant decrease in recall scores when compared to the M_{high} group was observed. Orientation in time dropped significantly through all five levels of cognitive impairment severity, while visuospatial orientation dropped significantly only at the first level in the N_{low} group compared to the N_{high} group, and after that there was no statistically significant difference in scores. This result should be interpreted cautiously, considering that orientation in time represents a scale from 0 to 5, while visuospatial orientation represents a scale from 0 to 1 (Table 3, Figure 1).

Discussion

In this study on screening patients for Alzheimer's disease, 32 medical doctors were included with 60,619 patients registered in their teams. Of these, 21,581 (35.6%) patients were over 65 years of age and 603 (1.0%) patients had previously been diagnosed with dementia. It is estimated that 1 in 10 individuals who are 65 or older has this disease[12]. When considering this estimate and the fact that only 1 in 100 persons over the age of 65 had previously been diagnosed with dementia in our study, it is evident that adequate screening and diagnostic procedures are warranted to recognize and treat this disorder.

Using the MMSE scale, the level of cognitive impairment was assessed for a total of 624 subjects with a median age of 76 years (IQR 70–80 years). We compared three groups of subjects with different levels of cognitive impairment — no impairment, moderate impairment and severe impairment. A significant difference in age between participants with severe cognitive impairment compared to the other participants was observed. Older age is the main risk factor for the development of neurodegenerative diseases, including AD. The brain is mainly composed of cells that do not divide and are sensitive to aging processes. The prevalence of AD increases with age, so it is estimated that AD is present in about half of the individuals aged 95 years or more in the United States of America[12].

In our study, no difference in sex structure was observed between the groups with different AD severity, however there were more female patients in the entire cohort (677, i.e. 60.4%). The female sex is considered a risk factor for AD development. In a prospective study evaluating 2,611 participants for up to 20 years, the average remaining lifetime risk for AD in participants aged between 65 and 80 was estimated to be 12.4% for the female sex and 6.6% for the male sex[13]. However, controversial results exist regarding the role of sex in disease progression and severity. In a longitudinal study that followed 294 participants for up to three years, no significant difference was found in the number of female or male participants who developed AD from mild cognitive impairment. Different risk factors for progression to AD from mild cognitive impairment at baseline were found for women (advanced age, clinically significant depressive symptoms at baseline, the presence of one or more apolipoprotein E ε4 alleles) and men (severe periventricular white matter hyperintensities, lower Korean MMSE scores, higher Clinical Dementia Rating sum of boxes scores)[14]. Suh et al. found that sex is not significantly related to faster MMSE score decline in AD patients[15]. On the other hand, there are several epidemiological studies showing faster cognitive decline in women compared to men[16]. In a longitudinal study following 559 participants with mild cognitive impairment due to AD for up to ten years, the worsening of the Alzheimer's Disease Assessment Scale–Cognitive subscale (ADAS-cog) score was significantly faster in women compared to men[17]. Also, there are controversial results regarding sex-specific therapy response in AD patients[18]. This area is still not fully explored, partially because various clinical trials do not include or report sex differences in analyzing treatment responses[19]. Although there are sex-dependent biological differences contributing to different rates of cognitive decline, it is important to point out that sex is unequally associated with other risk factors for the development of AD, such as the level of education, and there could be a bias in studies evaluating sex as a risk factor for AD severity[20].

Different domains of cognitive impairment had different rates of variability within groups of patients with similar MMSE scores, and also different rates of significant deterioration, depending on the participants' total MMSE scores. Each of the three categories of cognitive impairment severity (without cognitive impairment (MMSE score 24–30), moderate cognitive impairment (MMSE score 18–23) and severe cognitive impairment (MMSE score 0–17))[10] was divided into two subcategories, and the resulting six groups were analyzed in terms of detecting score differences in the seven examined domains (orientation in time, orientation in place, working memory, concentration, recall, language, and visuospatial orientation)[2]. The recall and concentration domains had the highest variability in scores, as early as in the group without cognitive impairment, indicating the earliest changes. Domains with the earliest significant deterioration between the examined groups were concentration and visuospatial orientation, followed by orientation in time and place, language, and working memory. Although the deterioration of orientation in time started early, it was also the slowest to progress, so significant differences were seen between all five groups of patients, from N_{low} to S_{low}. AD progression rate and the level of disability depend on various factors, reflecting a very complex process resulting in heterogeneous clinical pictures. The first phase of the disease is usually accompanied by memory loss, followed by language and communication skills deterioration. Cognitive impairment leads to functional disability in more severe forms of AD[21].

The recall domain showed variability in the number of achieved scores even in the N_{high} group, so early differences among individuals older than 65 years were present. Only 58% of the participants in the N_{high} group had a maximum score of 3 in this domain. Also, this was the only domain in which a significant drop in scores was observed only in the M_{low} group. Other studies show that recall is among the first domains to be impaired in AD[5]. Small et al. performed a longitudinal study on very old individuals (75 to 95 years) by evaluating the correlation between MMSE scores and changes in different cognitive domains[22]. Scores were compared between subjects who developed probable or possible AD and those who remained dementia-free in a period of three years. No reliable difference in recall score change was found between the groups. The average MMSE score for recall at baseline was among the lowest ones, with a large standard deviation, indicating similar results to our study, where subjects performed differently in this domain even if no or mild cognitive impairment was present, as measured by MMSE. Similarly, Cloutier et al. found a rapid decline in delayed recall in mildly cognitively impaired persons just prior to diagnosis[23]. Also, Henneges et al. found that recall domain impairment starts very early and was observed even in subjects with an MMSE score of 27–30, while full impairment was found in mild AD with an MMSE score of 22[2]. Memory loss is one of the most recognized and earliest AD symptoms[24]. Earlier recall decline and long-term memory decline could be expected due to changes in the brains of mild AD patients compared to healthy age-matched controls, as an early reduction of the entorhinal cortex and parahippocampal white matter were found in mild AD patients. The entorhinal cortex is the most heavily damaged cortex in AD[25]. It is crucial for memory formation[26,27], together with the hippocampus and the parahippocampal region in general[28]. Pathological changes in the brains of AD patients lead to a disruption of hippocampal formation input and its output to the cortex, leading to changes in memory[29]. Stoub et al. found that parahippocampal white matter volume can be used as a predictor of time to development of AD and episodic memory performance[28]. Memory and frontal/executive domains are deteriorated in the highest percentage of mild AD patients[24].

Concentration and visuospatial orientation were the first domains in which impairment was observed in the N_{low} group compared to the N_{high} group. Concentration deterioration was one of the earliest to appear in our study. Scores for this domain varied in the N_{high} group suggesting a very early decline. Concentration continued to deteriorate with a decrease of MMSE scores until the M_{low} group. Similarly, Henneges et al. found that the start of concentration domain impairment was related to mild AD with an MMSE score of 24. However, they detected full impairment in severe AD with an MMSE score of 13[2]. In a study on 51 patients with mild AD with an MMSE score higher than 19, it was found that the attention (concentration) domain was the first non-memory domain to become deteriorated. A similar percentage of participants also experienced deterioration in the visuospatial domain[24]. Visuomotor dysfunction could be one of the first signs of AD. De Boer et al. suggest that deterioration in visuospatial orientation could be a more important symptom of AD than it is currently assumed[5]. Visuospatial orientation in the MMSE scale is evaluated by drawing interlocking pentagons. To successfully perform this part of the test, the integration of eye and hand movements is achieved by adequate activation of the posterior parietal cortex. By using neuroimaging techniques, it was found that the inferior parietal white matter region is more reduced in very mild to mild AD compared to age-matched healthy controls[25]. Also, AD patients have worse visuomotor control when compared to healthy individuals[30]. However, results regarding the deterioration of this domain are controversial. Henneges et al. found that the visuospatial domain starts to deteriorate in moderate AD with an MMSE score of 18[2]. When analyzing of this domain with the MMSE scale, scientists should note that the maximum score is 1, while other domains have a wider range of scores, so additional measurement instruments should be used to evaluate the decline of this domain in AD.

In our study, orientation in time was the only domain in which a significant difference in score was observed between all compared groups, from N_{low} to S_{low}. Similarly, Small et al. found the greatest changes in orientation in time and orientation in place during a three-year follow-up of very old persons who developed probable or possible AD[22]. In a longitudinal study that followed patients for 12 months, Sevigny et al. found that orientation (with regard to persons, time and place) measured by the ADAS-cog scale was the only domain with significant deterioration in mild AD. The orientation domain was also the most sensitive criterion to differentiate patients belonging to different severity groups[31]. Also, Henneges et al. found that the start of orientation in time impairment was among the earliest related to normal or very mild cognitive decline (MMSE score 27–30), while full impairment was found in severe AD (MMSE score

11)[2]. Ashford et al. found that orientation in time is lost before orientation in place[32].

Orientation in place, language, and working memory were the three domains in which a significant drop in scores was observed for the first time in the M_{high} group. The domain of orientation in place had similar results to orientation in time. However, the change was more uniform and the score was similar for two subgroups of no disease and moderate disease subjects. Similar to our results, Henneges et al. found that the start of orientation in place impairment was related to mild AD with an MMSE score of 22, while full impairment was found in severe AD with an MMSE score of 4[2]. In our study, language deterioration continued until the most severe group with the lowest MMSE scores. Similarly, Henneges et al. found that the start of language domain impairment was related to mild AD with an MMSE score of 22, while full impairment was found in severe AD[2]. Language deterioration starts early in AD[33], but the MMSE scale has a limited ability to detect mild language deterioration, since the questions evaluating this domain are relatively easy[34].

We found that working memory deteriorated until the lowest MMSE score group. Literature results regarding working memory deterioration are controversial. Cloutier et al. found a rapid decline of working memory in mildly cognitively impaired persons just prior to diagnosis in a longitudinal study using different measurement instruments[23]. Contrary to this, Henneges et al. used MMSE for evaluation and found that the start of working memory (or registration) domain impairment was related to severe AD with an MMSE score of 9, while full impairment was found in severe AD with an MMSE score of 1[2]. The results might differ depending on the measurement instruments used.

The strength of our study lies in the large number of included health care professionals and patients. However, it had several limitations. First, using MMSE subscores to evaluate the deterioration of different cognitive domains depending on the total MMSE score is an approach that applies the same scale as a reference for disease severity, and as an instrument to measure and evaluate the deterioration of different cognitive domains. Despite this limitation, a similar approach has been used previously[2]. Different MMSE subscores depend on disease severity, and there are various approaches and modifications of the MMSE test that focus on certain types of cognitive domains[35]. Second, since the study was not longitudinal, the time to deterioration of different cognitive domains could not be evaluated. The third limitation was the MMSE scoring itself. Generally, the MMSE scale has limited sensitivity in the early stages of AD[34] and has a floor effect in severe AD. It cannot be used to create narrow stages of AD progression. Also, the MMSE scale is sensitive to levels of education, cultural background, and age[21]. Additional measuring instruments, besides MMSE, should be applied in future studies with similar aims.

Conclusion

In this study, the earliest cognitive deterioration in AD patients was observed in the recall and concentration domains, followed by visuospatial orientation, orientation in time and place, language, and working memory. The results indicate the importance of certain cognitive domains and the difference in their deterioration with increasing disease severity. They can be used to predict the development of the disease in clinical practice, as well as for adequate planning and analyzing the results of studies testing therapeutic approaches for AD.

CONFLICT OF INTEREST Aziz Šukalo, MD, Jasna Džananović Jaganjac, PhD, Amna Tanović, MD, Meliha Mehić, MD, Almasa Jandrić, MPharm and Una Glamočlija, PhD disclose the following relationships: employees of Bosnalijek d.d., a pharmaceutical company producing memantine-based medicine. Bosnalijek d.d. had a role in the design of the study, in the collection, analysis and interpretation of data, in the writing of the manuscript and in the decision to publish the results.

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SAŽETAK

Pogoršanje različitih kognitivnih domena ovisno o težini Alzheimerove bolesti: presječno istraživanje

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Slijed pogoršanja u različitim kognitivnim domenama, ovisno o težini Alzheimerove bolesti (AD), i dalje je uglavnom nepoznat. Cilj ove studije bio je pomoću Mini–Mental State Examination (MMSE) ljestvice podijeliti ispitanike u šest skupina prema težini bolesti i usporediti pogoršanje u kognitivnim domenama (orijentacija u vremenu i mjestu, radna memorija, koncentracija, prisjećanje, jezik i vizuoprostorna orijentacija) između skupina. U istraživanje su bila uključena ukupno 624 sudionika s medijanom dobi od 76 godina (interkvartilni raspon (IQR) 70 – 80 godina). Uočena je značajna razlika u dobi između sudionika s teškim kognitivnim oštećenjem u usporedbi s ostalim sudionicima. Nije uočena razlika u spolnoj strukturi između skupina. Najveće fluktuacije, čak i kod osoba bez kognitivnog oštećenja, uočene su u domenama prisjećanja i koncentracije, a zatim u vizuospacijalnoj orijentaciji. Prve domene koje su se pogoršale s progresijom bolesti bile su koncentracija i vizuospacijalna orijentacija. Pogoršanje se zatim nastavilo u orijentaciji u vremenu i prostoru, jeziku i radnom pamćenju. Rezultati ovog ispitivanja mogu poslužiti za predviđanje razvoja bolesti kao i za adekvatno planiranje i testiranje terapijskih pristupa za AD.

KLJUČNE RIJEČI

Alzheimerova bolest; *Probir*; *Slijed kognitivnog pogoršanja*