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Impairment of Episodic and Working Memory as a Predictor of Dementia Development in Mild Cognitive Impairment Results From Four Years of Prospective Follow up

ABSTRACT: Mild cognitive impairment (MCI) is a risk factor of dementia. Early impairment in episodic memory is considered to be a predictor of progression to dementia. The goal of the study was to evaluate the utility of baseline cognitive testing of episodic and working memory in the risk assessment of the dementia development in MCI. We studied 55 MCI patients and 44 controls, assessed annually by a set of neuropsychological tests for four years. The Petersen criteria were used to diagnose MCI, and DSM-IV criteria were applied to diagnose dementia. Variant analysis revealed significant differences in the results of individual cognitive tests between MCI converters who developed Alzheimer's disease (AD) at follow up, MCI non-converters, and controls ($p < 0,05$). At baseline, MCI converters had significant impairment in all tests comparing to MCI non-converters. APOE4 status had a significant influence on AD development in our MCI group ($p = 0,0022$). The study showed that significant impairment in baseline results of tests evaluating episodic (delayed recall) and working memory in MCI is a good predictor of dementia development in the future.

KEY WORDS: memory, mild cognitive impairment, dementia

Background

Cognitive impairment is one of the most common neurological syndromes in the elderly. The identification of people with increased risk of developing dementia is nowadays the most important strategy for delaying or preventing dementia onset. Mild cognitive impairment, a clinical concept proposed in 1999 by Mayo

Clinic Group¹, only slightly changed during following years², supported by MCI workgroup at the Alzheimer's Association International Conference on Alzheimer's Disease (ICAD) in July 2010, is known to be a good precursor of dementia³. Mild cognitive impairment (MCI) has been described as a transitional state between normal aging and dementia. MCI patients progress to dementia at a greatly accelerated rate compared to general population⁴. However not all MCI patients progress to Alzheimer's disease (AD) or decline in identical rates and a significant proportions of patients remain stable for several years or even improve. So far, known risk factors of the dementia development include: elderly age, low level of education, gait disorders, hippocampal atrophy and ApoE4 status⁵. Significant impairment of episodic memory in the MCI is also considered as a predictor of progression to Alzheimer's disease. The amnesic presentation is the most common presentation of MCI progressing to AD⁶. There are also nonamnesic presentations including executive dysfunction and visual-spatial or language problems⁷. There has been growing interest in how other cognitive processes are affected in the MCI and if their impairment could help to predict progression to the early stage of the AD.

¹ R.C. PETERSEN et al.: *Mild cognitive impairment: clinical characterization and outcome*. "Archives of Neurology" 1999, No. 56, p. 303–308.

² B. WINBLAD et al.: *Mild cognitive impairment: beyond controversies, towards a consensus*. "Journal of Internal Medicine" 2004, No. 256, p. 240–246; B. DUBOIS et al.: *Research criteria for the diagnosis of Alzheimer's disease revising the NINDCS-ADRDA criteria*. "Lancet Neurology" 2007, No. 6 (8), p. 734–746.

³ *Redefining Alzheimer's Disease: NIA and Alzheimer's Association Float New Draft Diagnostic Criteria*. (Alzheimer's Association International Conference on Alzheimer's Disease – ICAD, 2010). Honolulu 2010.

⁴ R.C. PETERSEN et al.: *Mild cognitive impairment...*; B. WINBLAD et al.: *Mild cognitive impairment...*; M.H. TABERT et al.: *Functional deficit in patients with mild cognitive impairment: prediction of AD*. "Neurology" 2002, No. 58, p. 758–764.

⁵ H. AMIEVA et al.: *Annual rate and predictors of conversion to dementia in subjects presenting mild cognitive impairment criteria defined according to a population-based study*. "Dementia and Geriatric Cognitive Disorders" 2004, No. 18, p. 87–93; P.B. ROSENBERG, D. JOHNSTON, C.G. LYKETSOS: *A clinical approach to mild cognitive impairment*. "American Journal of Psychiatry" 2006, No. 163 (11), p. 1884–1890; R.C. PETERSEN et al.: *Prevalence of mild cognitive impairment is higher in men*. "Neurology" 2010, No. 10, p. 889–897.

⁶ R.C. PETERSEN et al.: *Prevalence of mild cognitive impairment...*

⁷ R.C. PETERSEN et al.: *Apolipoprotein E status as a predictor of the development of Alzheimer's disease in memory-impaired individuals*. "JAMA" 1995, No. 273 (16), p. 1274–1278; H. WOLF et al.: *The prognosis of mild cognitive impairment in the elderly*. "Journal of Neural Transmission" 1998, No. 54, p. 31–50; S. TERVO et al.: *Incidence and risk factors for mild cognitive impairment: A population-based three-year follow-up study of cognitive healthy elderly subjects*. "Dementia and Geriatric Cognitive Disorders" 2004, No. 17, p. 196–203; G. TOGNONI et al.: *From mild cognitive impairment to dementia: a prevalence study in a district of Tuskany, Italy*. "Acta Neurologica Scandinavica" 2005, No. 112, p. 65–71; G.G. YENER et al.: *Diagnosis profile and comparison of risk factors in major types of dementia: an hospital based study*. "Journal of the Neurological Sciences" 2004, No. 21 (4), p. 301–310.

At the beginning of the disease, cognitive problems in AD do not have global nature, but they involve specific aspects of memory process – episodic memory. Episodic memory deficit is the earliest and the most severe cognitive deficit in AD but is also a feature of normal aging. Episodic memory refers to encoding (remember), storage and retrieval (recall) the events embedded in context, that the events occurred, in spatio-temporal relations. It requires access to the context and personal participation in an event. Episodic memory (together with semantic memory) is a category of long-term, declarative, explicit memory systems. The key function of episodic memory is to allow an individual to remember personal and extrapersonal past experiences and happenings⁸. Memory for past events is based on encoding and retrieval (recall) accompanied by specific contextual details (recollection or contextual memory) or on the feeling that an item is old or new in the absence of contextual details. The ability to recognize a previously experienced stimulus is supported by two processes: recollection of the stimulus in the context of other information associated with the experience, and a sense of familiarity with the features of the stimulus⁹.

Results from functional neuroimaging studies of episodic memory show the dissociable role of the medial temporal lobes regions supporting qualitatively different aspects of memory encoding and retrieval processing. Activity in the hippocampus and posterior parahippocampal gyrus is associated with recollection, whereas activity in the anterior parahippocampal gyrus is associated with familiarity. The hippocampus is critical for recollection but not familiarity. It is involved in encoding and retrieval the relation between memory items. It supports recollection by associating item and context information. The parahippocampal cortex (posterior parahippocampal gyrus) also contributes to recollection, it is selectively activated during the processing of contextual information of episodic memory. It supports recollection by encoding and retrieving contextual (especially spatial) information. By contrast, the entorhinal and perirhinal cortices (located in the anterior parahippocampal gyrus) contribute to the encoding and retrieval of a single item. It supports familiarity by encoding and retrieving specific item information and is necessary for familiarity-based recognition¹⁰. A more recent work suggests that other

⁸ R. PERRI et al.: *Amnesic mild cognitive impairment: difference of memory profile in subjects who converted or did not convert to Alzheimer's disease*. "Neuropsychology" 2007, No. 21 (5), p. 549–558; S. BELLEVILLE et al.: *Characterizing the memory changes in persons with mild cognitive impairment*. "Progress in Brain Research" 2008, No. 169, p. 365–375.

⁹ S. BAUDIC et al.: *Executive function deficits in early Alzheimer's disease and their relations with episodic memory*. "Archives of Clinical Neuropsychology" 2006, No. 21, p. 15–21; S.M. DASELAAR, M.S. FLECK, R. CABEZA: *Triple dissociation in the medial temporal lobes: recollection, familiarity, and novelty*. "Journal of Neurophysiology" 2006, No. 96 (4), p. 1902–1911.

¹⁰ R.A. DIANA, A.P. YONELINAS, C. RANGANATH: *Imaging recollection and familiarity in the medial temporal lobe: a three-component model*. "Trends in Cognitive Sciences" 2007, No. 11 (9), p. 379–386.

brain structures make up a large-scale network that appears to support successful encoding and retrieval of episodic information¹¹.

Retrieval processing are modulated by how items are encoded. Encoding processing refers to the memory as well as to the executive function. Episodic memory encoding process requires strategy and plan of operation with contribution of executive functions as well as insight to own cognitive processes (frontal functions). Prefrontal area plays a precedent role in memory and learning process. Executive functions are required to initiate, plan, control and manage the organization of complex cognitive functions. The efficiency of executive functions is reflected by capacity of working memory. Working memory is used to refer to a limited capacity system that is capable of storing and manipulating temporary information involved in the performance of complex cognitive tasks. It means an ability to keep information for a short-time and to manipulate them. Working memory encompasses aspects of attention and executive control. Working memory assumes a central role of executive controller (central executive system), of limited attentional capacity, aided by visual (visuo-spatial sketchpad) and verbal (phonological loop) temporary storage systems¹². Two functional components make up the phonological loop: a phonological short-term store, from which verbal information traces spontaneously fade after a few seconds and the articulatory rehearsal mechanism. Visuo-spatial sketchpad is comprised of distinct visual and spatial components: visual and spatial temporary stores where visual and spatial information are represented and separate rehearsal mechanisms for visual and spatial information which rehears the contents of the both stores and can be used to plan movement. The main functions of the central executive system is to be co-ordination of the subsidiary systems, attention set-shifting, focusing, switching and dividing attention, inhibition and updating and manipulation of information. Working memory is strongly involved in context through episodic buffer, where from executive system take necessary information. An episodic buffer places working memory at the interface of episodic memory and executive function. In episodic buffer, information from separate conscious memory systems (visuo-spatial and verbal temporary storage system and long-term memory) are integrated into single

¹¹ D.A. WOLK, B.C. DICKERSON: *Fractionating verbal episodic memory in Alzheimer's disease*. "NeuroImage" 2011, No. 54 (2), p. 1530–1539.

¹² J.D. HUNTLEY, R.J. HOWARD: *Working memory in early Alzheimer's disease: a neuropsychological review*. "International Journal of Geriatric Psychiatry" 2010, No. 25 (2), p. 121–132; S.E. PRICE et al.: *Learning and memory in amnesic mild cognitive impairment: contribution of working memory*. "Journal of the International Neuropsychological Society" 2010, No. 16 (2), p. 342–351; N. UNSWORTH: *Variation in working memory capacity, fluid intelligence, and episodic recall: a latent variable examination of differences in the dynamics of free recall*. "Memory & Cognition" 2009, No. 37 (6), p. 837–849; N.S. FOLDI: *Getting the hang of it: preferential gist over verbatim story recall and the roles of attentional capacity and the episodic buffer in Alzheimer disease*. "Journal of the International Neuropsychological Society" 2011, No. 17 (1), p. 69–79.

memory chunks. Episodic buffer functions-strategic retrieval and manipulation of information. Neurological correlates of working memory: left supramarginal gyrus and left hemisphere speech areas, such as Broca's area and premotor cortex, (verbal working memory), frontal, posterior parietal and occipital cortex (visuo-spatial working memory): premotor and right superior parietal cortex for spatial storage and rehearsal, inferior parietal areas for object storage, dorsolateral prefrontal cortex (central executive system function) with left parietal cortex during the manipulation of information and dorsolateral prefrontal cortex and anterior cingulate gyrus during dual task paradigms needed attention.

The neuropsychological test battery is essential to diagnose MCI and cognitive testing may also help to predict the possibility of dementia development. Since new NINCDS-ADRDA research criteria for the diagnosis of Alzheimer disease were proposed by Dubois in 2007¹³, the utility of baseline results of cognitive testing has attracted great interest from researchers seeking to identify individual at high risk of developing dementia before the occurrence of structural deficit. The MCI workgroup presenting new clinical and cognitive criteria for MCI due to AD at the Alzheimer's Association International Conference on Alzheimer's Disease 2010 in July 2010 emphasize that "episodic memory impairment is clearly the most common impairment seen in the prodromal phase to AD", but other domains may be impaired¹⁴. They have not at this point incorporated the terms amnesic or nonamnesic MCI. According to new assumptions, meeting the clinical and cognitive criteria for the disorder without structural and molecular biomarkers should be sufficient for the diagnosis MCI of a neurodegenerative etiology. For diagnosis MCI of the Alzheimer type, the patient should meet clinical and cognitive criteria for the disorder, plus should have positive findings from 1 of the structural or functional biomarkers, such as MRI evidence of hippocampal atrophy, or decreased FDG PET in temporoparietal cortex¹⁵.

Aim, material and methods

The main goal of the present study was to estimate the utility of the baseline cognitive testing, without using disease specific biomarkers and neuroimaging techniques, in predicting dementia development in future. We have also tried to find the most accurate neuropsychological set of tests being a good predictor of dementia

¹³ B. DUBOIS et al.: *Research criteria...*

¹⁴ *Redefining Alzheimer's Disease...*

¹⁵ Ibidem; J. HORT et al.: *EFNS guidelines for the diagnosis and management of Alzheimer's disease*. "European Journal of Neurology" 2010, No. 17, p. 1236-1248.

development in the future and finally we wanted to establish the rate of progression to dementia among our population of MCI patients.

Patients were recruited prospectively from out-patient clinic of Neurology Department in Katowice. Control group was mainly recruited from patients relatives. The final sample included: 55 amnesic-MCI patients (30 male and 25 female) and 44 (25 male and 19 female) cognitively unimpaired controls matched for age, gender and education. After formal approval of the Local Ethics Committee informed written consent was obtained from all participants. All participants underwent medical, neurological and neuropsychological examination.

Mini-Mental State Examination (MMSE) and Clock Drawing Test (CDT) were used to evaluate general cognitive functioning. Extensive neuropsychological testing assessing memory was performed in each subject: episodic memory was assessed with Rey Auditory Verbal Learning Test (RAVLT Total Learning, long delayed recall [20 minutes] and recognition), for verbal-auditory modality and Rey-Osterreith Complex Figure (ROCF Copy and short delayed [3 minutes] recall) for nonverbal visuo-spatial modality evaluation; Serial Seven Test (SST) was used to assess verbal working memory and Trail Making Test B (TMT B) was used for visuo-spatial and verbal working memory estimation reflecting executive functions. Trail Making Test A (TMT A) was assessed for cognitive speed and attention estimation¹⁶.

Beck Depression Inventory (BDI) and Montgomery-Asberg Depression Rating Scale (MADRS) were used to assess depressive symptoms. Patients with depression were excluded from the study¹⁷.

A Mayo Clinic Group criteria by Petersen were used to diagnose MCI¹⁸. Patients with other medical, psychiatric or neurological diagnosis that could interfere cognitive status were excluded from the study.

The cognitive status in the control group was assessed with MMSE and CDT¹⁹. Subject was classified as cognitively normal when has had no subjective complaints on memory impairment and there were no objective cognitive impairment confirmed by MMSE (27–30 pts) and CDT (done without errors). Patients were examined at baseline and then were followed up annually for four years. Dementia was diagnosed

¹⁶ E. STRAUSS, E.M.S. SHERMAN, O. SPREEN: *A Compendium of Neuropsychological Tests: Administration, Norms and Commentary*. [Oxford], Oxford University Press 2006; M.D. LEZAK, D.B. HOWIESON, D.W. LORING: *Neuropsychological Assessment*. New York – Oxford, Oxford University Press 2004.

¹⁷ A.T. BECK et al.: *An inventory for measuring depression*. "Archives of General Psychiatry" 1961, No. 4, p. 53–63; S.A. MONTGOMERY, M. ASBERG: *A new depression scale designed to be sensitive to change*. "British Journal of Psychiatry" 1979, No. 134, p. 382–389.

¹⁸ R.C. PETERSEN et al.: *Mild cognitive impairment...*

¹⁹ M.F. FOLSTEIN, S.E. FOLSTEIN, P.R. MCHUGH: *Mini-mental state. A practical method for grading the cognitive state of patients for the clinician*. "Journal of Psychiatric Research" 1975, No. 12, p. 189–198; K.L. SCHULMAN, R. SHEDLETSKY, I.L. SILVER: *The challenge of time: Clock drawing and cognitive function in the elderly*. "International Journal of Geriatric Psychiatry" 1986, No. 1, p. 135–140.

according to the DSM-IV criteria²⁰ and Alzheimer's disease was diagnosed according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINDS-ADRDA)²¹ and for vascular dementia the criteria of the National Institute of Neurological Disorders and Stroke with Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-ARIEN) were used²². No other type of dementia was developed by our MCI patients. Genetic testing of apolipoprotein E gene (APOE) polymorphism was performed. DNA was first isolated with QIAamp DNA Blood Mini Kit by QIAGEN following standard procedures. DNA was then amplified using polymerase chain reaction (PCR) with Taq Polymerase by Innogenetics. For detection of APOE allele in 112 and 158 codons INNO-LiPA ApoE test based on phenomenon of reverse hybridization described by Saiki et al. was used²³. The final product was a purple precipitate corresponding to APOE allele. CT or MRI scanning of the brain was performed to exclude subjects with symptomatic cognitive impairment caused by brain pathologies such as stroke, tumor, subdural hematoma etc.

Statistical analyses were performed by experienced statistician with Statistica PL (release 6.9). Demographic data were analyzed with variant analysis or t-test for qualitative variables. Spearman correlation test or Mann-Whitney U test were used to analyze the results of our study. $p < 0,05$ was accepted as statistically significant.

Results

After four years of follow up 10 (6 male and 4 female) of the original MCI patients demonstrated significant cognitive decline sufficient to diagnose dementia and constituted the Progressive MCI group (PMCI). 9 patients were diagnosed as having dementia of Alzheimer type and 1 patient with vascular dementia. The remaining 45 (24 male and 21 female) MCI patients showed no change in cognitive status and were included in the Stable MCI group (SMCI) (table 1). An overall rate of conversion to dementia was 18,1% for four years, making 4,52% annual rate of progression.

²⁰ *Diagnostic and Statistical Manual of Mental Disorders: DSM-IV*. Washington, American Psychiatric Association 1994.

²¹ G.C. ROMAN et al.: *Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-ARIEN International Workshop*. "Neurology" 1993, No. 43, p. 250–260.

²² R.K. SAIKI, C.H. LEVENSON, H.A. EHRlich: *Genetic analysis of amplified DANN with immobilized sequence specific oligonucleotide probes*. "Proceedings of the National Academy of Sciences" 1989, No. 86, p. 6230–6234.

²³ *Ibidem*.

TABLE 1. Demographic data of studied groups

| Demographic parameter | Total MCI | Progressive MCI* | Stable MCI* | Controls | p-value |
|----------------------------|------------------|------------------|------------------|------------------|---------|
| Number | 55 | 10 | 45 | 44 | |
| Female (n/%) | 25 (45,45%) | 4 (40%) | 21 (46,67%) | 19 (43,18%) | NS** |
| Male (n/%) | 30 (54,55%) | 6 (60%) | 24 (53,33%) | 25 (56,82%) | NS** |
| Age (years \pm SD) | 70,75 \pm 5,73 | 73,20 \pm 3,82 | 70,20 \pm 5,96 | 68,68 \pm 7,76 | NS*** |
| Education (years \pm SD) | 13,45 \pm 3,26 | 14,10 \pm 3,28 | 13,31 \pm 3,28 | 14,45 \pm 2,83 | NS*** |

* MCI group divided according to cognitive impairment progression after four years of follow up.

** Pearson's Chi-square test.

*** Mann-Whitney U test, NS – statistically non significant.

Variant analysis revealed significant differences between MCI group as a whole and cognitively normal group results in all kind of the neuropsychological tests assessing memory used in the study (table 2). MCI patients were impaired in their overall level of cognitive functioning and showed memory deficits under immediate and delayed recall conditions, recognizing description and working memory.

TABLE 2. Comparison of MCI and control group according to the neuropsychological tests results from the baseline

| Neuropsychological test name | Total MCI | Controls | p-value* |
|------------------------------|--------------------|-------------------|----------|
| MMSE | 26,78 \pm 1,74 | 29,0 \pm 41,00 | 0,00027 |
| Episodic memory evaluation | | | |
| RAVLT Total learning | 29,38 \pm 7,84 | 39,29 \pm 6,92 | < 0,0001 |
| RAVLT Long Delayed recall | 4,29 \pm 2,73 | 6,38 \pm 2,55 | 0,00076 |
| RAVLT Recognition | 11,67 \pm 2,77 | 13,58 \pm 1,32 | 0,00214 |
| ROCF Copy | 33,16 \pm 4,65 | 35,38 \pm 1,35 | 0,01936 |
| ROCF Short Delayed recall | 11,4 \pm 7,99 | 16,84 \pm 6,51 | 0,0002 |
| Working memory evaluation | | | |
| TMT part A | 67,17 \pm 24,12 | 42,71 \pm 11,23 | < 0,0001 |
| TMT part B | 172,13 \pm 84,59 | 79,96 \pm 17,10 | < 0,0001 |
| SST | 77,31 \pm 29,91 | 50,41 \pm 3,99 | < 0,0001 |

MMSE – Mini Mental State Examination (pts.), RAVLT – Rey Auditory Verbal Learning Test (number of words), TMT – Trail Making Test (sec.), ROCF – Rey-Osterrieth Complex Figure (pts.), SST – Serial Seven Test (sec.).

* Mann-Whitney U test.

At baseline, MCI converters (PMCI) had significant impairment in MMSE ($p = 0,027$), RAVLT long delayed recall ($p = 0,029$), ROCF short delayed recall ($p = 0,040$) and TMT A&B ($p = 0,031$) scores comparing to MCI non-converters (SMCI) (table 3).

TABLE 3. Comparison of the baseline neuropsychological tests results and the risk of developing dementia of Alzheimer's type

| Neuropsychological test name | Total MCI | Progressive MCI | Stable MCI | p-value* |
|------------------------------|----------------|-----------------|----------------|----------|
| MMSE | 26,78 ± 1,74 | 25,6 ± 1,71 | 27,04 ± 1,65 | 0, 0275 |
| Episodic memory evaluation | | | | |
| RAVLT Total learning | 29,38 ± 7,84 | 26,1 ± 4,86 | 30,11 ± 8,22 | NS |
| RAVLT Long Delayed recall | 4,29 ± 2,73 | 2,8 ± 1,40 | 4,62 ± 2,85 | 0,0299 |
| RAVLT Recognition | 11,67 ± 2,77 | 11,2 ± 3,19 | 11,78 ± 2,7 | NS |
| ROCF Copy | 33,16 ± 4,65 | 31,7 ± 6,36 | 33,49 ± 84,02 | NS |
| ROCF Short Delayed recall | 11,4 ± 7,99 | 7,1 ± 5,53 | 12,36 ± 8,18 | 0,0402 |
| Working memory evaluation | | | | |
| TMT part A | 67,17 ± 24,12 | 83,67 ± 17,26 | 63,87 ± 24,08 | 0,0230 |
| TMT part B | 172,13 ± 84,59 | 208,89 ± 53,57 | 164,78 ± 88,12 | 0,0318 |
| SST | 77,31 ± 29,91 | 89,73 ± 9,34 | 74,56 ± 27,18 | NS |

MMSE – Mini Mental State Examination (pts.), RAVLT – Rey Auditory Verbal Learning Test (number of words), TMT – Trail Making Test (sec.), ROCF – Rey-Osterrieth Complex Figure (pts.), SST – Serial Seven Test (sec.).

* Mann-Whitney U test (comparing Progressive MCI to Stable MCI), NS – statistically non significant.

The frequency of APOE4 allele carriers was higher in the MCI group than in controls ($n = 25, 45,45\%$, Pearson's Chi-square test; $p = 0,0187$). After dividing total MCI group into PMCI and SMCI statistically significant difference was also found in APOE4 status ($n = 7, 70\%$, Pearson's Chi-square test, $p = 0,0022$) (table 4).

TABLE 4. APOE status in the examined groups

| APOE status | Total MCI | Progressive MCI | Stable MCI | Controls |
|---------------------|--------------|-----------------|------------|-------------|
| N | 55 | 10 | 45 | 44 |
| APOEε4 carriers | 25 (45,45%)* | 7 (70%)** | 18 (40%) | 10 (22,73%) |
| APOEε4 non carriers | 30 (54,55%) | 3 (30%) | 27 (60%) | 34 (77,27%) |

* $p = 0,0187$, Pearson's Chi-square test, comparing MCI to controls.

** $p = 0,0022$, Pearson's Chi-square test, comparing Progressive MCI to Stable MCI.

Discussion

During four years of follow up 18,1% (n = 10) of MCI patients developed dementia, while 81,9% (n = 45) remained stable. Our annual rate of conversion was 4,52%, what is a concordance with data from the literature²⁴. Our MCI group was not representative for general population because only patients referred to our department on the basis of memory complaints were included into the study. Most of them were well educated (academic education). In this case even minor deficits may interfere high intellectual functioning than in people with only primary education. Probably highly educated people are also more aware of the need of early diagnosis of cognitive impairment. That is why in our group we could not verify the influence of education level on dementia development, but data from the literature suggest that there is such relation, and that low education could be a risk factor for dementia development²⁵.

There are many studies indicating that the frequency of depression in the MCI is over 30%²⁶ and that depression has an influence on development of cognitive impairment²⁷. That is why, to collect as homogenic group as possible, we excluded people with any depressive symptoms, even if the depression criteria was not fulfilled. On this basis we avoided including people whose cognitive problems were a consequence of depression.

APOE ϵ 4 allele is a well known genetic risk factor for dementia of Alzheimer's type. It was estimated that in the MCI there are also more APOE ϵ 4 carriers than in general population²⁸. In our MCI group there were 45,45% (n = 25) APOE ϵ 4 allele carriers and in the control group 22,73% (n = 10) and it was statistically significant (Pearson's Chi-square test, p = 0,01875). This data are consistent with the literature, also in Polish population²⁹. In our MCI group, subjects who developed dementia after follow up were more likely to be the APOE ϵ 4 carriers than those who were stable at that time (Pearson's Chi-square test, p = 0,0022).

²⁴ R.C. PETERSEN et al.: *Prevalence of mild cognitive impairment...*

²⁵ H. AMIEVA et al.: *Annual rate and predictors of conversion to dementia...*; G. TOGNONI et al.: *From mild cognitive impairment to dementia: a prevalence study in a district of Tuskany, Italy*. "Acta Neurologica Scandinavica" 2005, No. 112, p. 65–71.

²⁶ J.L. GATZ et al.: *Do depressive symptoms predict Alzheimer's disease and dementia?* "Journal of Gerontology" 2005, No. 60 (6), p. 744–747.

²⁷ Ibidem; T. GABRYELEWICZ et al.: *The rate of conversion of mild cognitive impairment to dementia: predictive role of depression*. "International Journal of Geriatric Psychiatry" 2007, No. 22, p. 563–567.

²⁸ M.R. FARLOW et al.: *Impact of APOE in mild cognitive impairment*. "Neurology" 2004, No. 63, p. 1898–1901.

²⁹ Ibidem; R.C. PETERSEN et al.: *Apolipoprotein E status as a predictor...*; R.J. CASELLI et al.: *Cognitive domain decline in healthy apolipoprotein E ϵ 4 homozygotes before the diagnosis of mild cognitive impairment*. "Archives of Neurology" 2007, No. 64 (9), p. 1306–1311.

It confirms that APOE ϵ 4 allele may predispose to early dementia development in the MCI group.

Episodic memory is selectively impaired in early, preclinical phases of amnesic manifestation of Alzheimer's disease. It is suggested that in early phase of Alzheimer's type dementia other cognitive dysfunctions are also present³⁰. Neuropsychological evaluation is a key element of mild cognitive impairment diagnosis and important component of diagnostic criteria of Alzheimer's disease. Most neuropsychological tests are not selectively assessing many aspects of memory and other cognitive functions and many factors may interfere the neuropsychological tests results³¹. Methods assessing episodic memory are based on encoding and learning processes. At the beginning of learning process episodic memory is started first followed by semantic memory processes. Evaluation of memory process is concentrated on immediate and delayed retrieval, free recall and recognition. Learning and encoding influence memory reproduction abilities. Memorizing process needs mnemonic strategy with engagement of executive functions. Plateau in consecutive immediate recall trial means lack of strategy indicating frontal but not temporal lobe dysfunction.

In this study encoding strategies during learning are not presented in final results, but recent researches suggest that subjects with amnesic MCI demonstrate diminished use of strategic encoding strategies during learning, related to the strategic function of the episodic buffer, confirming the presence of executive functions impairment³². Delayed recall worse than delayed recognition discrimination may be the result of not only selectively impaired hippocampal contextual memory, but also the defect of strategy. That is why evaluation of executive function is also important in neuropsychological diagnosis of memory disorders. Performing specific task assessing different aspects of memory is also depended from visuo-spatial and language abilities, that is why we have found different modality in memory systems in our study. Final effect of evaluating memory processes depends on many aspects not always clearly indicating episodic memory deficit, which is most reliably assessed by delayed recall trials.

Until now there are not widely accepted cut-off points for neuropsychological tests in MCI diagnosis criteria, but the impairment is typically 1.0 to 1.5 standard deviations below the mean of the individual, adjusted for age and education. In Poland the major problem is very low number of neuropsychological tests stand-

³⁰ R.C. PETERSEN et al.: *Prevalence of mild cognitive impairment...*; R. PERRI et al.: *Amnesic mild cognitive impairment...*; S. BELLEVILLE et al.: *Characterizing the memory changes...*; S. BAUDIC et al.: *Executive function deficits...*; S.M. DASELAAR, M.S. FLECK, R. CABEZA: *Triple dissociation in the medial temporal lobes...*

³¹ E. STRAUSS, E.M.S. SHERMAN, O. SPREEN: *A Compendium of Neuropsychological Tests...*; M.D. LEZAK, D.B. HOWIESON, D.W. LORING: *Neuropsychological Assessment...*

³² R. PERRI et al.: *Amnesic mild cognitive impairment...*; S. BELLEVILLE et al.: *Characterizing the memory changes...*

ardized and validated for Polish population requiring individual attitude to particular patient. Making diagnosis in individual patient seen for the first time becomes a challenge and always needs taking into consideration someone's intra-individual cognitive functioning.

In our study we have found that the baseline evaluation of cognitive functions in further converters to Alzheimer's disease in comparison to stable MCI group, neuropsychological tests results were significantly lower in delayed recall tests than in encoding and recognition processes evaluation. Besides significantly lower results in cognition speed and attention in converters, encoding and recall process was comparable in both group (stable and progressive MCI). Comparing total MCI group to controls we found significantly worse encoding, retrieval and executive functions representing working memory. Our results confirm the previously published data, that mild cognitively impaired patients with memory plus other cognitive domain deficits, rather than those with pure amnesic MCI, constituted the higher-risk group for development of dementia.

Conclusions

Significant impairment in baseline results of tests evaluating episodic memory (especially in delayed recall subtests) and working memory in MCI may be a good predictor of Alzheimer's type of dementia development in the future. Cognitive tests battery still must be expanded to allow as accurate diagnosis as possible. MCI must be identified by using a more detailed procedure for the assessment of cognitive decline than the evaluation of memory alone. There is no appropriate set of neuropsychological tests for MCI diagnosis, so far.

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