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CORRELATION OF COGNITIVE DECLINE AND BEHAVIORAL CHANGES IN PATIENTS WITH PRESENILE AND SENILE ONSET ALZHEIMER'S DISEASE

D. M. PAVLOVIĆ[1], ALEKSANDRA M. PAVLOVIĆ[2,3] and MAJA LAČKOVIĆ[2,4]

[1] *Faculty for Special Education and Rehabilitation, University of Belgrade,* 11000 Belgrade, Serbia
[2] *Faculty of Medicine, University of Belgrade,* 11000 Belgrade, Serbia
[3] *Neurology Clinic, Clinical Center of Serbia,* 11000 Belgrade, Serbia
[4] *Psychiatry Clinic, Clinical Center of Serbia,* 11000 Belgrade, Serbia

Abstract – Alzheimer's disease (AD), the most prevalent dementia, is characterized not only by cognitive but also behavioral changes that pose the heaviest burden to caregivers. Differences in the clinical picture depending on the time of disease onset have been observed. We correlated cognitive and behavioral deficits in patients with presenile- and senile-onset AD to explore the differences. We tested 60 AD patients, 19 male and 41 female, mean age 65.2 years with the Dementia Behavior Disturbance Scale (DBD) and a standard neuropsychological battery. The patients were divided according to their DBD score into two groups: group I – score 0-2 (n=24; 40%), group II – score 3≥ (n=36; 60%), comparable in disease duration and neurological findings. The cognitive scores were significantly higher in the group with less behavioral changes than in the group with more behavioral changes: Mini Mental State Examination score (p=0.0015), serial subtraction (p=0.0009), block design (p=0.0049), copy of complex figure (p=0.0125), complex visual organization (p=0.0099), divided attention, visual memory and speech comprehension. A significantly higher frequency of behavioral disturbances was registered in patients with senile onset than in the presenile-onset group (p<0.005). There were no sex differences. Our data show a correlation between cognitive decline and behavioral changes in late onset AD patients, indicating that more behavioral disturbances were associated with a more severe degree of cognitive decline, especially in non-verbal functions and attention deficits, compared to early onset patients.

Key words: Alzheimer's disease, senile onset, behavior, cognition

INTRODUCTION

AD is a neurodegenerative disease that causes selective neuronal loss in brain regions involved in memory, language, personality and cognition in general (Feng and Wang, 2012). AD is the most frequent type of dementia and can begin before the age of 65 (presenile or early onset) and after 65 years (senile or late onset) by usual arbitrary cut off (Rabinovici et al., 2010). The earliest symptom of AD is typically a progressive memory loss of insidious onset, while other cognitive areas, usually language, executive function and visuospatial skills, are also present during the course of the disease (von Gunten et al., 2006). The main pathological features in the cerebral cortex are neurofibrillary tangles (NFT), senile plaques (SP) and neuronal and synaptic loss. As these processes spread from medial temporal cortex along the neocortex, the spectrum of cognitive and behavioral symptoms broadens. The clinicohistopathological relationship has been well established and depends mostly on NFT density in specific regions (von Gunten et al., 2006).

Heterogeneity is present in AD with regard to genetic characteristics, neuropathological findings and neuropsychological profile (Kim et al., 2005). However, the most disturbing feature for family members and caregivers are behavioral changes that lead to the early institutionalization of these patients (Pelletier and Landreville, 2007). Behavioral signs pose the heaviest economical burden for both family and society. The sense of discomfort is significantly associated with overall agitation, non-aggressive physical behavior and verbally agitated behavior (Pelletier and Landreville, 2007).

The investigation of the relationship between cognitive and behavioral changes in AD in relation to the time of disease onset is of interest for both pathophysiological considerations and the everyday management of AD patients. However, this topic has not been addressed so far in detail. The aim of this study was to disclose if behavioral disturbances are more frequent in patients with presenile or senile onset of AD and their relationship with various cognitive measures.

PATIENTS AND METHODS

We conducted a retrospective study with 60 patients from an outpatient behavioral neurology service in a university hospital with AD by NINCDS-ADRDA criteria (McKhann et al., 1984), 19 male and 41 female, mean age 65.2 years, mean education level 13.5 years.

Data were collected from the patients' histories. Behavioral changes were assessed with the Dementia Behavior Disturbance Scale (DBD) (Baumgarten et al., 1990). Behavioral symptoms were graded from 0 to 4 (from absence of symptoms = 0, to most disturbing = 4). Patients were divided arbitrarily into two groups: Group 1 with scores 0-2 that consisted of 24 (40%) patients and Group 2 with scores of 3 and 4 that consisted of 36 (60%) patients.

The groups were compatible in terms of disease duration, neurological status and structural neuroimaging data ($p>0.05$). Disease was staged according to the Clinical Dementia rating (CDR; Hughes et al., 1982).

The comprehensive neuropsychological battery included the Mini Mental State Examination (MMSE) (Folstein et al., 1975), the Block design from Serbian version of WAIS (Veksler's "Individual Intelligence Test" ("Individualni Test Inteligencije") = VITI), the Rey Complex Figure (RCF) (Rey, 1964) copy and delayed recall, the Hooper Visual Organization Test (HVOT) (Hooper, 1958), the Trail Making Test (TMT A & B) (Reitan and Wolfson, 1993), the Rey Auditive Verbal Learning Test (RAVLT) (Rey, 1964), speech comprehension from the Boston Diagnostic Aphasia Battery (BDAE) and the Boston Naming Test (BNT) (Kaplan et al., 1978), categorical and phonemic fluency tests for divergent thinking and the Luria 3 Step Test for limb-kinetic praxia (Lezak et al., 2004). Data were analyzed with the T-test, X2-test and Fisher's test.

RESULTS

We found no gender difference in regard to mean age, mean age at disease onset, mean of disease duration, mean CDR score and MMSE score (T-Test: $p>0.05$). Behavioral changes did not show significant sex difference (X2-test: $p>0.05$). There was no significant difference between senile and presenile AD onset according to mean MMSE score (T-test: $p>0.05$), but patients with senile onset had significantly higher CDR scores (T-test: $p<0.05$). Fisher's test showed significantly higher frequency of behavioral disturbances in patients with senile beginning than in the presenile group ($p=0$ $p<0.05$).

The most frequent disturbances were, according to DBD, apathy (loss of interest in everyday activities) 27, purposeless laughter and crying 16, losing things 11, agitation 9, accusations 7, loses of way outside of home 6, repeating the same questions 5, waking up during the night for no reason 5, repetition of the same activity 4, excessive daytime sleeping 3, pacing 3, night wandering at home 3, resisting to eat 3, wandering outside the home 2, physical aggressiveness 2, and cursing, refusing help, stool incontinence.

We identified a negative correlation between MMSE score and behavioral changes in the senile type of AD (T-Test: $p<0.05$) while there was no correlation in the presenile group ($p>0.05$). Dementia duration did not influence behavior in either group (T-Test: presenile: $p>0.05$; senile: $p>0.05$).

Neuropsychological test scores were significantly higher in the group without significant behavioral disturbances (group I) than in the group with significant behavioral disturbances (group II) for the following assessments: MMSE ($p=0.0015$), serial subtraction "100-7" from MMSE ($p=0.0009$), visual attention span ($p=0.08$ – trend), TMT A ($p=0.019$), TMT B ($p=0.03$), block design (VITI) ($p=0.0049$), picture completion (VITI) ($p=0.050$), RCF ($p=0.0125$), HVOT ($p=0.0099$), RCF recall: 3 minutes ($p=0.019$) and 40 minutes ($p=0.035$), verbal divergent thinking: phonemic fluency ($p=0.012$) and categorical fluency ($p=0.031$), speech comprehension: commands ($p=0.0082$) and CIM ($p=0.001$) as well as dynamic praxia of the left hand ($p=0.003$) and the right hand ($p=0.001$). No statistically significant difference was detected for scores on BNT and RAVLT test, or for verbal attention span.

DISCUSSION

Our data showed more advanced cognitive decline and more behavioral disturbances in senile-onset AD patients than in the presenile-onset group. In addition, late onset patients had higher CDR scores and their behavioral and cognitive aspects were significantly associated. There were no significant differences according to sex and disease duration. The measure of general cognitive deterioration, MMSE score, differs between patients with senile and presenile onset. Significantly lower scores in the late onset AD patients were detected on the testing of sustained and divided attention, constructive and limb kinetic praxia, working and visual memory, divergent thinking, visuospatial gnosia, complex ideational material comprehension and visual attention span.

Verbal measures of confrontational naming and verbal attention span were not significantly different and these functions are known as most resistant to deterioration. In addition, verbal learning did not show differences between presenile and senile-onset patients, probably because these are the core neuropsychological deficits, usually present at the very beginning of the disease.

The most frequent behavioral disturbances in our patients were apathy (loss of interest in everyday activities), purposeless laughter and crying, losing things, agitation and accusations. Patients with behavioral disturbances showed more pronounced neuropsychological dysfunctions of prefrontal functions such as divergent verbal thinking (phonemic fluency), working memory and limb-kinetic praxia, or dynamic apraxia in Luria's terminology. Verbal functions are more resistant to disease process influence than non-verbal functions. Our results are partly similar to the findings of Hirono et al. (1998) in which older age, female sex, longer duration of illness and more severe cognitive impairment were independently associated with the occurrence of psychosis. It has also been shown that aggressive behavior and depressive symptoms are associated with progressive cognitive decline in elderly subjects (Margari et al., 2012).

Investigation with voxel based magnetic resonance imaging (MRI) morphometry revealed a correlation between behavioral disturbance and grey matter brain atrophy of certain areas (Bruen et al., 2008). Delusions were associated with decreased grey matter density in the left frontal lobe, in the right frontoparietal cortex and in the left claustrum; apathy was associated with grey matter density loss in the anterior cingulate and frontal cortex bilaterally, the head of the left caudate nucleus and in bilateral putamen; agitation was associated with decreased grey matter values in the left insula, and in the anterior cingulate cortex bilaterally. These AD symptoms seem to be associated with neurodegeneration of the neural networks supporting functions that are of importance for both behavioral planning and control and cognitive functions. This is consistent with our clinical findings. A prospective study of AD with post mortem verification reported similar

clinical patterns dominated by dysmnesia, dysphasia, dyspraxia and spatial disorientation in both groups, while confabulation, restlessness, confusional episodes, fluctuating course and hallucinosis agitation were somewhat more prevalent in the late onset AD (Gustafson, 1990).

There are various possibilities that can influence the differences that we found between patients with early and late onset. It could be due to more frequent comorbidities, inadequate polypharmacy and the involvement of cerebrovascular factors in older patients, the existence of different AD subtypes or the effects of propagation of uniform pathological process specific to AD. These characteristics can reflect the more extensive cortical pathological changes in older patients involving also the frontal besides the "classical" temporoparietal areas.

Behavioral disturbances were more frequent in patients with senile AD onset. Cognitive status was independent from behavioral changes in the presenile patients but significantly influenced behavior in the senile patients in our groups. Psychotic symptoms have been associated with accelerated cognitive deterioration in some studies (Drevets and Rubin, 1989) but others found no significant influence of age at onset, duration of illness or family history of dementia (Ortof and Crystal, 1989). Memory impairment is present in AD regardless of age of onset, while confabulations, delusions and sleep disturbances are more frequent in late-onset patients (Lauter, 1970). Our findings are in accord with these studies, in addition, we examined cognitive decline with a comprehensive battery of neuropsychological tests. Divided attention decline can have a negative influence on the comprehension of social situations with multiple environmental cues as well as impaired comprehension of complex ideational material.

Cortical atrophy differences were found between patients with presenile and senile AD onset using MRI with voxel-based morphometry (Ishii et al., 2005). Typical parietotemporal and posterior cingulate gray matter loss was found in presenile-onset AD but not in senile-onset AD. These changes point to atypical loci of brain atrophy in late-onset AD mediating behavior in the prefrontal cortex (von Gunten et al., 2006). Clinically, some studies showed that patients with presenile-onset AD have more non-memory disturbance initially with a more rapid progression of cognitive deficits compared with late onset patients (Ishii et al., 2005). In our patients, the main difference between the two groups with different time of onset was in predominantly behavioral disturbances in late onset group. These differences may reflect the two distinct pathological processes with predominant involvement in prefrontal/temporal neocortical structures that mediate behavior. For instance, it is well known that up to 60% of the spindle neurons of the anterior cingulate cortex (ACC) are lost in AD (Nimchinsky et al., 1995) and the dysfunction of ACC positively correlates with the behavioral and psychological symptoms of dementia (BPSD) (Shinno et al., 2007).

The positive correlation between cognitive and behavioral symptoms in late onset AD can be caused by the more frequent existence of comorbidities in the older population with more pronounced vascular factors (Yarchoan et al., 2012). The dysfunction of subcortical structures, as in white matter ischemic changes in older age, are neuropsychologically manifested with a prefrontal type of disturbances and this might be an independent factor but could possibly be intermingled with other contributing factors.

Disease duration was comparable in our patients both with and without behavioral changes, although it is known that behavioral disturbances are more characteristic of the later course of AD, mostly depression, anxiety, psychosis and other BPSD symptoms (Kennedy et al., 2001). These studies do not account for the presenile/senile-onset dichotomy so that they might miss the difference in the course of the disease.

In accordance with the gradual spreading of cortical (and subcortical) AD pathology from typical early temporoparietal areas, it had been showed in various studies that frontal symptoms are related to the severity of the disease (Edhag et al., 2008). The

data that we present reveal that the severity of both cognitive and behavioral symptoms increases in late onset patients and are interrelated. These findings suggest a more rapid progression and more diffuse pathological process in AD patients with behavioral disturbances. These patients had typically senile onset. A higher DBD score is an indicator of a more rapid decline and poorer prognosis in AD patients.

Micronutrient deficiencies due to the progressive decline of gastrointestinal functions and other causes have to be taken into account. Some degree of vitamin B12 deficiency is fairly regularly observed in the senile population, and a vitamin D3 deficiency is almost ubiquitous, to name just a few. Levels of vitamin B12 in serum are progressively reduced with aging so that the clinical deficit is present in about 20% of people over the age of 60 (Nilsson-Ehle, 1998) and in around 40% of hospitalized geriatric patients (Shahar et al., 2001). Among all residents of care facilities for the elderly, normal vitamin B12 levels (>250 pmol/L) are present in only 50% (Mirkazemi et al., 2012). A deficiency of vitamin B12 can cause dementia, personality changes, delirium, psychosis, depression, hallucinosis, polyneuropathy, optic neuropathy and myelopathy (Bernard et al., 1998). Vitamin D deficiency (<50 nmol/L) is associated with increased odds in cognitive impairment in older persons (Llewellyn et al., 2011).

Another possible explanation is the greater cognitive reserve in younger patients that need more AD pathology to develop before comparable changes observed by functional neuroimaging are expressed in late onset cases (Kim et al., 2005). It has been reported that early onset AD patients have more prominent focal neuropsychological symptoms such as aphasia, apraxia and agnosia than those with late onset (ibid). Brain functional imaging in AD yields controversial results, from no differences to a predominance of focal dysfunction in early to more diffuse findings in late onset (ibid). Memory impairment remains uniformly the most prominent neuropsychological deficit in AD (Petersen et al., 1994). Longitudinal studies demonstrate that the rate of cognitive decline in AD is quite consistent from study to study and across different populations and is quite slow at the start of the illness, faster during the middle stage, and once again slow in the terminal phase of the illness (Mohs and Haroutunian, 2002). Interestingly, BPSD are episodic events that wax and wane over the course of AD, without progression (ibid). In our group, BPSD were more prominent in senile-onset patients with more pronounced cognitive deficits. This might be caused by the reduced capacity of comprehension of circumstances and relations in persons with more pronounced cognitive deficits leading to delusional explanations of reality. Genetic factors have also to be appreciated as there are more inherited mutations among early onset dementia (Edhag et al., 2008) but specific gene polymorphisms can also be of interest.

Some studies contradict our results. In the study of Rabinovici et al. (2010) patients with early age of AD onset showed a more rapid progression and more generalized cognitive deficits compared to late onset patients. These discrepancies may be due to the different populations targeted and the additional inclusion of behavioral measures in our study. In our group, there were no young onset patients, thus our cases being more representative of a continuum of the disease than distinguishing between the two subtypes. A comparable burden of fibrillar amyloid-beta is associated with greater posterior cortical hypometabolism in early onset Alzheimer's disease according to functional neuroimaging and amyloid-beta imaging, possibly indicating that both early amyloid-beta accumulation and increased vulnerability to amyloid-beta pathology play critical roles in early onset AD (Rabinovici et al., 2010). We did not correlate neuroimaging data between cognitive and behavioral disturbances and specific functional brain areas. Possible aims of investigations would be to examine broader correlations of presenile- and senile-onset AD patients with cognition and behavioral manifestations, also with micronutrient status, medical comorbidities and cerebrovascular factors. Not to be neglected is inadequate polypharmacy that is more often present in older patients (Edhag et al., 2008).

Previous studies did not address the correlation of behavioral and cognitive clinical aspects and age of onset of AD with the comprehensive neuropsychological battery that is available in clinical practice. Our findings reveal the necessity of a high level of alertness for behavioral disturbances in older patients with more pronounced cognitive decline and preventive measures in cases of medical comorbidities, infections, sleep disturbances, vascular risk factors and other relevant areas. In addition, of utmost importance are preventive measures in the early phases of AD.

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