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Neurobehavioral manifestation in early period of Alzheimer Disease and Vascular Dementia

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Summary

Introduction. AD and VD are preceded by a preclinical stage. Small but tangible cognitive impairments sometimes occur many years before the onset and diagnosis of dementia. The ongoing degenerative process can be conductive to behavioural and psychological symptoms.

Aim. The aim of the study was to investigate the rates of neurobehavioral symptoms in the preclinical stages of AD and VD.

Methods: Two hundred and ninety one residents of nursery homes were included in the study. Participants of the study did not display symptoms of dementia in accordance with DSM IV criteria and obtained at least 24 points on the MMSE scale and were on the first or second level of the Global Deterioration Scale. Participants were screened for behavioural and psychological symptoms with the NPI – NH scale, while their cognitive functioning was evaluated by means of the ADAS-cog. Participants of the study were evaluated with the MMSE scale annually. Participants who obtained less than 24 points on the MMSE scale were evaluated by a senior psychiatrist. Diagnosis of dementia was done on the basis of DSM criteria. Alzheimer's Disease was diagnosed on the basis of NINCDSADRDA criteria and vascular dementia on the NINDS-AIREN criteria. The study was carried out over a period of seven consecutive years.

Results. A hundred and fifty people were included in the final analysis – in 111 of them were found not to be afflicted with dementia, 25 were found to have AD and in 14 VD was diagnosed. The control group differed from the AD and VD group with respect to the initial level of cognitive impairment (ADAS-cog) and the intensity of behavioural and psychological symptoms (NPI –NH scale). Particular items of the NPI –NH scale differentiated the two groups to a different degree. In people with AD the greatest differences were observed with respect to agitation/aggression, mood swings, irritability/emotional liability and the rates of anxiety. People with VD, similarly to people with AD, significantly differed from the control group with respect to mood disorders and irritability/emotional liability, as well as disinhibition and anxiety. People with VD were found not have high rates of agitation/aggression. In the AD group,

the shorter the period between the evaluation with the NPI-NH scale and the diagnosis of AD was the greater the rates of agitation/aggression, anxiety, and elevated mood/euphoria were.

Conclusion. In preclinical stages of both AD and VD behavioural and psychological symptoms occur very frequently. The closer the diagnosis of dementia is the greater the possibility of behavioural and psychological symptoms occurring, especially in AD.

Key words: cognitive symptoms, aggression, depression

Introduction

Diagnosis of dementia is usually made only when damage to the brain leads to marked difficulties in functioning. In light of contemporary therapeutic possibilities this is usually much too late. Meanwhile neuropathological changes greatly precede the onset of symptoms of dementia [1, 2]. The brain is able to compensate for the severe changes for a fairly long time which allows the individual to function normally [3, 4]. The majority of dementative processes are preceded by a preclinical stage characterized by a number of disorders which are not necessarily related to the cognitive sphere of functioning [5]. Although up to now most studies have been done on preclinical stages which precede full-blown forms of AD, it is very probable that different forms of VDs are also preceded by a preclinical stage [6-9].

Besides disorders related to the cognitive sphere, behavioral and psychological symptoms are typical symptoms noted in the course of dementia [10]. Their intensity differs, depending on the progression of dementative changes [11, 12].

The fact that during the preclinical stage of AD especially a number of significant brain regions are damaged – namely the middle part of the medial temporal lobes and parts of the hippocampal formation as well as those of the nucleus basalis of Meynert and that of the locus coeruleus) [13, 14] allows us to surmise that a number of psychopathological changes may occur during this period. A closer look at the behavioral and psychological symptoms during the preclinical stages of dementia disorders may be of diagnostic value.

The aim of the study was to evaluate the rates of BPRS in the preclinical stages of AD and VD.

Method

The initial population were residents (n = 345) of two nursery homes located in the city of Gdynia. Prospective study participants had to meet the following criteria: consent to participate in the the study, be above 55 years of age, obtain the first level (without impairments of cognitive functioning) or second level (mild impairment of cognitive functioning) on the Global Deterioration Scale (GDS) according to Reisberg et al. [15], obtain 24 or more points in the Mini Mental State Examination (MMSE, version without adjusting MMSE scores for age and quality of education) [16].

The study exclusion criteria were: a DSM diagnosis of a dementia disorder regardless of etiology, obtaining a third or higher level on the GDS scale (Global Deterioration Scale), current or past history of one of the following disorders: affective

disorder, schizophrenia, alcoholism, addiction to prescription medication or any other psychoactive drug,, epilepsy, Parkinson's disease, mental retardation; any impairments of consciousness or awareness at the time of the clinical evaluation, locomotor impairments, impairments of sight or hearing which might impair participants ability to follow the instructions of clinical test, severe somatic diseases. An additional exclusion criterion was taking any psychotropic medication for at least 7 days during the 30 day period leading up to the study or taking a psychotropic drug for any amount of time during the 14 day period leading up to the study.

Two hundred and ninety one people were included in the baseline study: (224 women and 67 men; the mean age was 75,54).

Alzheimer's Disease Assessment Scale (ADAS) was used to evaluate cognitive functions [17]. In our study we made use of the 11-item subscale which evaluates cognitive functions (ADAS – cog) (word-finding difficulty in spontaneous utterances, world recall task, following commands, naming objects and fingers, constructional praxis, ideational praxis, orientation, word-recognition task, recall of test instructions, spoken language ability, comprehension of spoken language). Score on the cognitive part ranges from 0 to 70, where 0 is interpreted as lack of impairment and 70 points to severe dementia.

Behavioral and psychological symptoms were evaluated by means of the Neuropsychiatric Inventory – nursery homes version (Neuropsychiatric Inventory – Nursing Home Version) (NPI) created by Cummings et. al. [18, 19]. The version of the inventory used in the study is comprised of 12 categories of items (listed in tab. 1). Each of the diagnosed disturbances is then evaluated in terms of frequency of occurrence on a 4-point scale (1-sporadically, 4 – very often) and severity (intensity) on a 3-point scale (1- mild, 3 – severe). Some versions of the inventory additionally include an evaluation of how badly a given disturbance affects people in the patients' surrounding (nuisance), but this aspect was analyzed in the current study. In tests of validity and test-retest reliability the NPI scale obtained high values [19].

Next, with the use of the MMSE scale study participants were evaluated annually (in the period between May and August). People who obtained less than 24 points on the MMSE scale were then evaluated by a senior psychiatrist, who diagnosed or ruled out dementia. Diagnosis of dementia was done on the basis of DSM criteria. [20]. When a diagnosis of dementia was made further evaluation of the participant was carried out, including laboratory tests aimed at determining the etiology of the process. Alzheimer's Disease was diagnosed on the basis of NINCDS-ADRDA criteria [21] and vascular dementia was diagnosed on the basis of NINDS-AIREN criteria [22]. Additionally, during the diagnostic procedure we used the Hachinski Ischemia Scale (1974) [23]. An obtained result of 4 or more points ruled out a diagnosis of AD. Participants who obtained 4 or more points on the Hachinski scale and did not meet the NINDS-AIREN criteria were categorized as afflicted with „dementia of an unknown etiology" and were excluded from further analyses. Of all the additional clinical tests, the following were considered essential in the diagnostic process: a computer tomography of the head or a core MRI, a basic biochemical profile (which checked the blood levels of creatinine, glucose, aminotranspherases, ferases, electrolites), blood morphology (with smear), USR test and a general urine profile. Additionally, if clinical symptoms were present

or clinical tests showed abnormalities which could indicate a vitamin B12 deficiency or a dysfunction of the thyroid gland, additional tests were done to check the level of vitamin B12 or the level of thyroxine or triiodothyronine.

Observation was carried out over the course of seven consecutive years. In the 7th year of the observation all the participants who were still being observed were once again evaluated by a senior psychiatrist regardless of their last score obtained on the MMSE scale.

Evaluation by means of the NPI -NH scale and the GDS scale was always done by a senior psychiatrist, whereas social workers and nursing staff employed in the nursery homes where the participants resided carried out the MMSE and were invaluable source of information necessary to carry out the NPI -NH. Evaluation with the ADAS-cog scale was carried out by a clinical psychologist.

Before the study begun, a training workshop was held for personnel who were to take part in the study. During the training workshop personnel were instructed how to use all the clinical scales in people with dementia and those without dementia. Next a pilot study was carried out on a group of 20 people both with dementia and without dementia. After carrying out the pilot study we went over the difficulties the study personnel encountered when implementing the methodological procedures..

In the process of statistically verifying the obtained results we used the t-test for two independent samples and calculated the Spearman's Rank Correlation Coefficients.

For all the used statistical tests the adopted significance level (p) was 0,05. Those test results for which the significance level was equal to or lower \than 0,05 ($p < 0.05$ or $= 0.05$) were considered significant, whereas others ($p > 0.05$) were not considered significant. Additionally, when verifying the assumption that a given trait is characterized by a normal distribution in the general population (when carrying out the t-test for two independent samples) we used the Chi-square test, while the null hypothesis (variances are equal) was verified by means of the two-sample test for variances.

Results

From the 291 people who were initially included in the study population 150 people (115 women and 35 men) were included in the final analyses after the seven year observation period, the mean age was: 73.30; SD = 8.97., ADAS – cog: 6.22; SD = 3.03; NPI –NH: 20.41; SD = 12.73. People who were included in the final analyses met the following criteria:

- CONTROL group: ruling out a dementia diagnosis during evaluation done in the 7th Lear of the observation period n = 111 (women: 88 men: 23), mean age: 72.69, SD = 8.92, score on ADAS-cog scale: 5.25, SD= 2.73, score on the NPI –NH scale: 18.08, SD = 12.43
- AD & VD group: a diagnosis of AD related dementia or VD at any stage of the study n = 39 (women: 27 men: 12), mean age: 75.03; SD = 9.02, score on ADAS-cog scale: 8.97; SD = 1.98, score on NPI –NH scale: 27.05; SD = 11.31; AD: (women: 18 men: 7), mean age: 76.12; SD = 8.50, score on ADAS-cog scale: 9.16; SD = 2.10, score on NPI –NH scale: 26.84; SD = 11.80 VD n = 14 (women: 9 men: 5),

mean age: 73.07; SD = 9.90, score on ADAS-cog scale: 8.64; SD = 1.78, score on NPI –NH scale: 27.43; SD = 10.78

All the above mean values were noted during the baseline evaluation.

Table 1 is a comparison of the analyzed variables in the control group and people in whom AD and VD was diagnosed during the observation period. Age did not prove to be a discriminating factor (p=0,08 for AD and p = 0,32 for VD), whereas the control group differed from the AD and VD group with respect to the initial level of cognitive impairment (ADAS-cog scale) and the rates of behavioral and psychological symptoms. It has to be said though that particular items of the NPI –NH scale differentiated the two groups to a different degree. In people with AD the greatest differences were observed with respect to agitation/aggression, mood disorders, irritability/emotional lability and the rates of anxiety. People with VD, similarly as in the case of AD, significantly differed from the control group with respect to mood disorders and irritability/emotional lability, and additionally with respect to disinhibition and anxiety both in terms of frequency and intensity. In turn, in contrast to the AD group, in people with VD greater intensity of agitation/aggression was not observed. The AD and VD groups differ only in terms of the intensity of disinhibition. A couple of other variables seem to differentiate different forms of dementia: the severity of depression/dysphoria (p=0,09), intensity of anxiety (p=0,08).

Tab. 1 Mean values of age, ADAS – cog scale, and NPI –NH scale obtained during the baseline evaluation in the control group and in the AD and VD groups (t-test for two independent means)

	CONTR mean N = 111	AD mean N = 25	VD mean N = 14
AGE (baseline)	72.69	76.12	73.07
ADAS	5.25	9.16*	8.64*
NPI-NH:			
A. DELUSIONS			
Frequency:	0.43	0.40	0.29
Intensity:	0.41	0.36	0.21
Frequency x Intensity	0.41	0.36	0.21
B. HALLUCINATIONS			
Frequency:	0.13	0.12	0.14
Intensity:	0.13	0.12	0.21
Frequency x Intensity	0.13	0.12	0.21
C. AGITATION/AGGRESSION			
Frequency:	0.32	0.64*	0.36
Intensity:	0.29	0.68*	0.36
Frequency x Intensity	0.32	1.04*	0.50

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D. DEPRESSION/DYSPHORIA			
Frequency:	0.60	1.08*	1.29*
Intensity:	0.53	0.92*	1.50*
Frequency x Intensity	0.71	1.68*	2.71*
E. ANXIETY			
Frequency:	0.61	1.00*	1.00*
Intensity:	0.52	0.80	1.29*
Frequency x Intensity	0.67	1.16*	1.79*
F. ELEVATED MOOD/EUPHORIA			
Frequency:	0.33	0.36	0.21
Intensity:	0.33	0.36	0.14
Frequency x Intensity	0.37	0.40	0.14
G. APATHY			
Frequency:	0.98	1.12	1.07
Intensity:	0.80	0.80	0.79
Frequency x Intensity	1.36	1.48	1.50
H. DISINHIBITION			
Frequency:	0.28	0.28	0.64*
Intensity:	0.23	0.28#	0.93*#
Frequency x Intensity p = 0,052)	0.39	0.40	1.29*
I. IRRITABILITY/LABILITY			
Frequency:	0.67	1.12*	1.07*
Intensity:	0.89	1.32*	1.43*
Frequency x Intensity	1.07	2.24*	2.43*
J. ABBERANT MOTOR BEHAVIOR			
Frequency:	0.14	0.16	0.14
Intensity:	0.22	0.24	0.21
Frequency x Intensity	0.22	0.24	0.21
K. SLEEP DISTURBANCES AND ABBERANT NIGHTITME BEHAVIOR			
Frequency:	0.76	1.16	0.64
Intensity:	0.89	1.40	0.79
Frequency x Intensity	1.70	2.76	1.29
L. APPETITE CHANGES			
Frequency:	0.07	0.08	0.14
Intensity:	0.07	0.08	0.14

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Frequency x Intensity	0.07	0.08	0.14
NPI-NH total	18.08	26.84*	27.43*

* statistically significant differences with respect to the control group
# statistically significant differences between AD and VD

Annual evaluation with the MMSE scale allowed us to diagnose new cases of dementia. Of all the new cases of AD (n = 25), in the first year we diagnosed 3 cases, in the second year we diagnosed 2, in the third year 5, in the fourth 4, in the fifth 5, in the sixth 4, and 2 during the final follow-up evaluation 2. In the VD group we diagnosed 2 cases in the first year, 1 in the second year, 3 in the third year, 2 in the fourth year, 3 in the fifth year, 2 in the sixth year, and 1 in the seventh year.

Due to the postulated link between behavioral and psychological symptoms and the progression of the degenerative process which directly precedes the onset of the clinical stage of the disease we looked for a link between the psychopathology as diagnosed by means of the NPI – NH scale in the baseline evaluation and the year the participants' were diagnosed with dementia after they had been included in the study population and put under observation.

In table 2 we list the Spearman's rank correlation coefficients between the NPI-NH scale and the period of time (in years) between the baseline evaluation and the diagnosis of dementia. We only list those categories for which the frequency or intensity were statistically significant. In people with AD the links were found between the general score on the NPI-NH scale and the following three categories: agitation/aggression, anxiety, and elation/euphoria. All the correlations were negative which means that the disturbances intensify as the person afflicted approaches the onset of the clinical stage of the dementia and subsequent diagnosis. In the VD group no statistically significant correlations were noted.

Tab. 2 Chosen Spearman's Rank Correlation Coefficients for the score obtained on the NPI-NH scale with the period of time (in years) between the baseline evaluation and the diagnosis of dementia.

	R	p level
	Year of disease onset	
C. AGITATION/AGGRESSION		
Frequency:	-0.43	0.03
Intensity:	-0.40	0.05
E. ANXIETY		
Frequency:	-0.42	0.04
Intensity:	-0.36	0.08
F. ELATION/EUPHORIA		
Frequency:	-0.47	0.02
Intensity:	-0.42	0.03
NPI-Sum total	-0.55	0.00

Discussion

Both AD related dementias and most forms of VD are preceded by a preclinical stage which sometimes lasts many years [1-9]. Ongoing degenerative mechanisms are conductive to the occurrence of a number of symptoms. So fat, cognitive impairments have garnered greatest attention in research articles. In longitudinal observations disturbances of many cognitive functions were noted including episodic memory, executive functioning, perceptual speed, attention, verbal ability, and visuospatial skill. More studies have been done on AD however there is evidence that disturbances of cognitive functions also precede the diagnosis of VD [6]. Similarities between AD and VD with respect to disturbances of cognitive functions have been noted. [8]. Nevertheless, the fact that the processes which underlie AD and VD are different allows to suspect that the profile of disturbances is also probably slightly different for both forms of dementia. Some data indicate that Alzheimer patients were more impaired than those with vascular dementia on episodic memory, while the patients with vascular dementia were more impaired on semantic memory, executive/attention functioning, and visuospatial and perceptual skills. [24]. Patients with VAD performed worse on tests that are influenced by frontal and subcortical mechanisms. Patients with AD performed worse on memory and some language subtests. [25].

In the study population the cognitive impairments, as evaluated by means of the ADAS-cog scale, were more severe in the preclinical stages of AD and VD and no differences were noted in this respect between the two forms of dementia.

Damage which occurs during the preclinical stages of dementia to many brain structures which are important for the functioning of the neurotransmissive systems of the brain can be conductive to the onset of behavioral and psychological symptoms, [26-28]. At the same time, similarly as with cognitive functioning, we can expect some differences between VD and AD with respect to the nature of the behavioral and psychological symptoms.

In our study, we noted significantly greater intensity of behavioral and psychological symptoms in the preclinical stages of AD and VD. There have been much fewer studies devoted to behavioral and psychological symptoms which occur in the preclinical stage than there have been about cognitive functions, but the ones that have been done also point to greater psychopathology in the preclinical stages of VD and AD. It has been particularly pointed out that mood disturbances are very prevalent in the preclinical stage of dementia [28].

It has also been noted that subtle personality changes tend to occur early; these include apathy, irritability and inability to pay attention [29]. Participants who were in the preclinical stage of dementia were characterized by greater rates of mood disturbances, anxiety and irritibilaty/lability. Additionally, in the AD group aggressive behaviors were more prevalent. Some authors link the presence of the above disturbances with further progression of dementia. Agitation can precede faster progression of cognitive disturbances. [30]. It seems that the presence of most behavioral and psychological symptoms may be a sign of poorer clinical outcome with respect to cognitive functioning [31, 32]. Depressive symptoms have sparked more controversy

– some studies have linked them with greater progression of dementia [31], whereas in other studies they did not affect clinical outcome [33]. It seems that the impact of depressive symptoms is different in AD than it is in VD. [34].

It has to be said that the all the cited studies investigated the preclinical stage of AD. In our study, however, observation started before the onset of major disturbances in functioning and thus before clinical diagnosis of dementia.

However, the mere fact of making a clinical diagnosis of dementia is not important in terms of the pathological mechanisms which underlie it since very often these have been long present and have already began to gradually destroy neurons. By leading to neuropathological changes which are already present in the preclinical stage, these mechanisms are conductive to behavioral and psychological symptoms. Damage to the cholinergic system of the temporal and frontal lobes plays a significant role here [35, 36]. Gorman et al. [37] noted that after administering acetylcholinerase inhibitor – physostygmine – to patients suffering from dementia there is a marked reduction of aggressive behaviors, whereas administering scopolamine exacerbates hostile, uncooperative behaviors in people afflicted with AD [38, 39]. Sunderland et al. [38] showed that adminestering scolapamine exacerbates disturbances of thought content in AD. Studies on the use of acetylcholinerase inhibitors in the treatment of AD have noted that they positively affect some of the psychopathological symptoms of the disease [40].

The differences between AD and VD with respect to the frequency and intensity of behavioral and psychological symptoms mainly pertained to disinhibition which was markedly increased in the preclinical phase of VD. This can be linked to greater pathology of the frontal lobes in vascular processes. Although this result was not statistically significant it does seem that aggressive behaviors occur less often in the early stages of VD, whereas symptoms of depression/dysphoria are more pronounced. This would be concurrent with the results of earlier studies [34, 41, 42].

The occurrence of behavioral and psychological symptoms is not only related to the localization of dementative changes but also to their severity. We may indirectly conclude that the closer a patient is to the diagnosis of dementia the more progressed the dementia process is and so some of the behavioral and psychological symptoms should also me more pronounced [43]. A search for a link between the year of dementia onset and the scores obtained on the NPI-NH scale confirmed the above suppositions with respect to some of the symptoms (agitation, anxiety, euphoria) in case of AD. No such correlation for the VD group may suggest the existence of different mechanisms but is more probable that this result was caused by the fact that there were too few participants in the VD group.

During periods which lead directly to the onset of clinical forms of dementia the progression of the dementative process can rapidly speed up [44]. It is assumed that in case of AD 3 to 4 years prior to diagnosis there is a marked increase in the build up of cognitive dysfunctions [45]. Quite possibly, behavioral and psychological symptoms may not be caused that much by the advanced progression of the dementative process but rather by the change in the dynamic of dysfunction accumulation.

Unfortunately, at the present stage of analysis we did not evaluate the dynamic of the accumulation of cognitive disturbances, therefore we cannot fully discuss the observed phenomena.

The link between progressive destruction of the brain behavioral and psychological symptoms is probably not simple. The influence of environmental factors should not be underestimated – they can be particularly significant in the early stages of dementia development. Most often these are such complex phenomena that there is no way to quantify them. The present study was based on residents of nursery homes which allowed us to eliminate probably a large number of uncontrolled environmental variables.

Due to the fact that we did not monitor the degenerative changes with neuroimaging, interpretation of the obtained results is fraught with significant limitations. Radiological evaluation along with neuropsychological evaluation would be the best measure of the progression of the disease. The reliability of the obtained results is also affected by the size of the VD and the AD groups. The size of the study population is particularly important in this respect since differences in the occurrence of behavioral and psychological symptoms during the preclinical stage of dementia are of quantative character. The existence of pathognomic symptoms in early forms of AD and VD is very unlikely.

Conclusions

Despite unquestionable limitations the carried out study indicates that behavioral and psychological symptoms occur more often in the preclinical stages of both AD and VD. The closer the diagnosis of dementia is the greater the possibility of the occurrence of behavioral and psychological symptoms, especially in AD.

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