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The influence of vascular factors on the psycho-pathological picture in Alzheimer's Disease

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Summary

Aim. The goal of this study was to evaluate the influence of vascular factors on the psychopathology of Alzheimer's Disease.

Material. The study included 50 people with a DSM-IV diagnosis of Alzheimer's Disease who met the following criteria: they agreed to take part in the study, they had a caregiver who could provide the researchers with all the necessary biographical details about their lives.

Methods. The patients were evaluated with the use of the following scales: Alzheimer Disease Assessment Scale – cognitive part (ADAS – cog) and non-cognitive part (ADAS-ncog), Montgomery-Asberg Depression Scale (MADRS), Instrumental Activity of Daily Living (IADL). Additionally, patients were evaluated by means of the AMDP scale and Hachinski's Ischemic Scale, the score on which was the basis for dividing the study group into those patients who had a minor vascular component (score on Hachinski's scale was 0 – 1 points) and a major vascular component (2 – 4 points).

Results. Statistically significant differences were found between people who had a minor vascular component and those who had a major vascular component. These differences were related to somatic symptoms and orientation, thought disorders, emotional disturbances and "other" symptoms.

Conclusion. In summary, we must mention that the presence of vascular factors did affect the clinical profile in people diagnosed with Alzheimer's Disease. Studies show that vascular factors do not exacerbate the depth of dementia itself but are related to the occurrence of non-cognitive symptoms.

vascular factors / psycho-pathological symptoms / Alzheimer's disease

INTRODUCTION

Until recently, the existence of a vascular pathology was considered an exclusion criterion for the diagnosis of Alzheimer Disease (AD). However, currently there is a tendency to view vascular processes as risk factors in Alzheimer's Disease. Some prospective studies have noted increased blood pressure and stroke incidents as risk factors in Alzheimer's Disease. [1, 2]. AD and dementias are similar in more ways than one and the following are just some examples: more frequent occurrence of ApoE 4, low level of acetylcholine metabolites in the cerebrospinal fluid and amyloid accumulation. Furthermore, the number of damaged microcirculation vessels correlates with amyloid deposits found in the cerebral cortex. [3]. It has also been indicated that cardiac ischemia is a risk factor in AD. [4]. Additionally, elevated serum cholesterol levels are related to more frequent occurrence of dementia of the Alzheimer type. [5].

Vascular changes are found in 1/3rd of patients afflicted with Alzheimer's Disease [6]. Furthermore, some vascular changes (amyloid angiopathy, periventricular leukoencephalopathy) are

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diagnosed in nearly all cases of Alzheimer's Disease [7]. Other than certain similarities in the clinical picture of dementia of the Alzheimer type and vascular type dementias, there are disease-specific changes which differentiate them. Besides symptoms included in the so-called cognitive sphere, a certain etiological difference in the process is exposed in the nature of behavior disturbances and psychotic symptoms which accompany dementia processes. For example, depressive disorders are more prevalent in vascular dementias, whereas psychotic symptoms are more often seen in Alzheimer's Disease. [8]. Therefore, it seems probable that the presence of a vascular component in the course of AD could affect both the clinical picture and the course of the disease.

The goal of our study was to evaluate the influence of a vascular component on the psychopathological picture in Alzheimer's Disease.

MATERIAL AND METHODS

The initial population was made up of people treated from 1.02 to 30.10. 2000 in the Clinic of Mental Illnesses or any Mental Health Counseling Centre in Gdańsk. The inclusion criteria for the study were the following:

- Patients' informed consent regarding participation in the study
- The possibility of obtaining detailed patient history from a caretaker who knows the patient well;
- Physical state which allows for a full clinical evaluation by means of clinical scales – thus, no eye condition, hearing disability, no locomotor, cardiovascular or respiratory problems;
- No past history of schizophrenia, affective disorder, schizoaffective disorder, substance dependency (including alcohol) or epilepsy. No symptoms of the aforementioned diseases and disorders present during the initial clinical evaluation.
- Diagnosis of dementia of the Alzheimer type made on the basis of DSM IV criteria for Alzheimer's Disease [9]; In accordance with the DSM IV diagnostic criteria , dementia of the Alzheimer type was diagnosed on the basis of both a clinical evaluation and several additional tests. 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, aminotransferases, electrolytes), 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.
- Score on the Hachinski scale (0 – 4 points) .
- Exclusion of other types of dementia

Once patients were accepted into the study the main examination was performed using the following scales:

- Alzheimer Disease Assessment Scale – cognitive part (ADAS – cog) [10];
- Alzheimer Disease Assessment Scale – noncognitive part (ADAS – ncog) [10]
- Montgomery-Asberg Depression Scale (MADRS) [11];
- Instrumental Activity of Daily Living (IADL) [12]
- The AMDP scale (Arbeitsgemeinschaft fur Methodik und Dokumention in der Psychiatrie**)**, which is actually more of a psychiatric evaluation system, was designed on the basis of many different research projects conducted since 1965 in German-speaking countries. The scale consists of several inventories : anamnesis I - demographic characteristics, anamnesis II - life events, anamnesis III - individual history of mental illness, psychopathology symptoms, somatic symptoms. A great advantage of this inventory, and the reason why we included it in our methodology, is that it enables clinicians to make very detailed records of patients' psycho-pathology. The fourth part of the scale "Psychopathology symptoms" includes the following elements: intellectual impairments, consciousness impairments, orientation impairments, concentration and memory impairments, formal thought disorder, phobias and compulsions, delusions, percep-

tion impairments, *ego* disorders, affect disorders, locomotor impairments, daily fluctuations in disorder symptoms & intensity, other disorders & impairments and other symptoms. Each category consists of a few or a few dozen well-defined symptoms (Tab. 1), which can be quantified on a scale from 0 (*the symptom is absent*) to 5 (*the symptom is very severe*). A great convenience is the possibility to analyze a given psychopathology profile with reference to a group of symptoms (a category) and with reference to a single symptom. It is also permitted to differentiate groups of disorders by grouping particular symptoms, e.g. it is possible to create a manic-depressive scale. In our study we used the Polish version of the scale adapted by M. Rzewuska, with the help of L. Welbel and K. Nurowska (1991). Research conducted by the Laboratory of Pharmacotherapy of the Institute of Psychiatry and Neurology in Warsaw confirmed the reliability and validity of the Polish version of the scale. In our study we used two inventories (mental state and somatic state) [14].

Clinical examination with ADAS and MADRS inventories was always done by a specialist in psychiatry or a clinical psychologist. Social workers and the nursing staff performed the MMSE and IADL inventories on their own and were also an important source of information about the patients, information which was essential for the specialist to carry out the AMDP scales.

In the end, 50 people with an average degree of cognitive dysfunction (32.074 points on the ADAS-cog scale) and mean age of 70.12 years of age were accepted into the study.

Based on scores on the Hachinski scale, participants were divided into two groups – minor involvement of vascular factors (0 – 1 points on the Hachinski scale) (n = 23) and major involvement of vascular factors (2 – 4 points on the Hachinski scale) (n = 27). With the help of the two-sample t-test we compared the two study groups with respect to the mean scores obtained on all clinical scales. The adopted level of significance was 0.05. Results for which the level of significance was equal to or lower than 0.05 ($p < 0.05$ or

Table 1. Symptoms comprising particular categories of dysfunction according to the AMDP scale.

Category of symptoms	Symptoms
Memory impairment	impaired comprehension, ability to focus attention, memorizing, permanence of memory, confabulations, paramnesis
Dysfunction of thought processes	inhibition of thought processes, bradyphrenia, excessive meticulousness, narrowing of thought content, perseverations, rumination, throng of thoughts, racing thoughts, incoherent thoughts, restraint, breakdown of thought processes, neologisms
Psychotic symptoms	suspicious mistrust, hypochondrical symptoms and attitude, phobias, compulsive behavior, obsessive thoughts, delusional mood, delusional perception of reality, delusions, illusions, hallucinations
Emotional disturbances	helplessness, a feeling of "devoid of feelings", poverty of feelings, decrease in vitality, depressed mood, negative perception of reality, fear, euphoria, dysphoria, irritability, anxiety, having many complaints, decreased self-esteem, increased self-esteem, guilt feelings, feelings of impoverishment, ambivalence, parathymia, emotional lability, emotional incontinence, emotional rigidity
Motor dysfunctions	decrease in psychomotor drive, motor inhibition, increase of psychomotor drive, motor agitation, parakinesis, mannerism, melodramatic behavior, speechlessness, logorrhea
Other dysfunctions	withdrawal from social relations, excessive sociability, aggressiveness, suicidal tendencies
Other symptoms	loss of will to live, asthenia, difficulty in falling asleep, intermittent sleep, shortened sleep duration, premature awakening from sleep, decrease or increase in appetite

p = 0.05) were considered significant, whereas the rest (p > 0.05) were considered to be insignificant. A two-way interval was adopted.

RESULTS

Table 2 shows mean scores on the ADAS scale (cognitive and non-cognitive part), the AMDP scale (particular categories of symptoms as listed in Tab. 1), and the MADRS scale. Statistically significant differences are marked with an asterisk (*).

Differences were found with respect to somatic symptoms and the following categories: orientation, dysfunction of thought processes, emotional disturbances, "other" symptoms (as listed in the AMDP scale).

DISCUSSION

Results of prior studies have shown vascular factors to be a serious risk factor in Alzheimer's Disease [1, 2]. However, as our study shows, vascular factors also have a significant influence on psycho-pathological symptoms in people diagnosed with Alzheimer's Disease. No major differences were noted with respect to the severity of dementia as evaluated by means of the ADAS-cog scale. The differences we found were mostly related to non-cognitive symptoms which occur in the course of dementia, known as behavioural and psychological symptoms of dementia (b.p.s.d.) Besides more intense physical symptoms reported by people with a vascular component, we noted greater problems in the area of thought processing, emotional well-being, as well as a set of symptoms categorized by the ADMP as "other" symptoms (withdrawal from social relations, compromised social relations, aggression, suicidal tendencies). Orientation dif-

Table 2. Mean scores obtained on the ADAS scale (cognitive and non-cognitive part), AMDP scale (particular categories of symptoms are shown in tab. 1), the Geriatric Depression Scale and MADRS in people with a minor (score on the Hachinski Scale - 0–1 points.) and a major vascular component (score on the Hachinski Scale 2–4 points.)

Variable	Hachinski 0 -1 n = 23		Hachinski 2 – 4 points n = 27	
	Mean	SD	Mean	SD
ADAS – cog	32.38	14.32	31.83	10.71
ADAS- ncog	5.96	4.51	8.15	5.49
Age	69.87	7.81	70.33	7.97
AMDP – SOM *	4.26	3.98	7.74	6.79
ORIENTATION *	6.64	3.26	4.41	3.61
MEMORY	6.50	2.92	6.96	2.68
THOUGHT PROCESSES *	0.77	1.11	2.04	1.97
PHOBIAS	0.14	0.35	0.15	0.36
DELUSIONS	0.23	0.61	0.76	2.05
HALUCINATIONS	0.00	0.00	0.11	0.58
EMOTIONALITY	2.27	2.35	6.33	6.29
LOCOMOTOR	0.64	0.95	1.22	1.15
OTHER DISORDERS *	3.09	3.41	5.62	3.75
MADRS	9.36	7.27	12.85	8.17

significant group differences (p< 0.05, test for two independent means)

ficulties also differentiated the study groups, but the obtained result (lower in case of an existing vascular component) is surprising and difficult to interpret. In order to show the differences in the psychopathology profile, we needed to use a tool as sensitive as the AMDP scale to evaluate the mental state of the participants. Symptoms noted by means of the non-cognitive part of the ADAS scale were only slightly more intense in the group with a vascular component, yet this result was not confirmed by means of statistical methods. As in vascular-based dementias, in people with Alzheimer's the sole existence of a vascular component brought about a marked increase in the intensity of emotional disturbances, mainly comprised of depressive symptoms. Some researchers link depressive disturbances in the course of vascular-based dementias with more severe somatic changes. [15]. Others believe they are caused by damage to the left hemisphere of the brain, which is typical for pathological changes occurring in the course of vascular-based dementias. [16]. In the light of the obtained results, it seems more likely that there is a link between depressive disorders and the presence of somatic ailments. We must also remember that b.p.s.d. may be caused by a biochemical imbalance. Lately, it is more widely assumed that the more frequent occurrence of b.p.s.d. symptoms in the course of dementia is caused by a dysfunction of the brain's neurotransmission systems [17]. According to Cummings et al. [18], hallucinations are related to decreased cholinergic transmission in the limbic system, cortex, and the thalamus. The limbic system, precisely its temporal and frontal parts, has also been linked with the occurrence of delusions through the cholinergic and dopaminergic system. [19]. Similarly, as in the case of delusions, a decrease in cholinergic transmission and disorders in dopamine turnover encompassing the whole limbic system are said to cause aggressive behaviors [20]. Lastly, according to Datt et al., sleep disorders, which are very often diagnosed in patients with dementia, are related to the decrease in cholinergic transmission within the brain stem. [21]. The cholinergic system of the brain is impacted by vascular changes observed in the course of Alzheimer's Disease. A few studies have proven that in the course of vascular-based dementias cholinergic transmission becomes impaired due to a decrease in the concentration of, for example, acetylcholinetransferase [22]. Vascular factors most probably play a role in the pathogenesis of Alzheimer's Disease by damaging the blood-brain barrier. Abundant evidence indicates damage of micro blood vessels and capillaries in the course of Alzheimer's Disease. Degeneration of smooth muscle cells [23] and focal narrowing of smooth muscles have also been noted [24]. Additionally, Kalaria et al. [25] found that people with Alzheimer's Disease have degenerative and necrotic lesions in the endothelial micro-circulation of the central nervous system (CNS). What is more, the basilar membrane of micro-circulation vessels showed signs of collagen accumulation which leads to destruction and changes in permeability of these vessels. [26]. The aforementioned changes damage the blood-brain barrier, allowing for the permeation of proteins which can cause inflammation if the immune system is compromised (e.g. due to a previous head injury). Such inflammation is accompanied by the production of cytokines and so-called acute phase proteins (alpha 1 antichymotrypsin and alpha 2 macroglobulin) which can contribute to the aggregation of beta-amyloid and consequently to the death of neurons, including cholinergic neurons. [27, 28].

It is impossible to overlook the major limitations of these studies, namely the fact that they are all based on Hachinski's Ischemic scale, which takes into account vascular risk factors. The studies did not directly confirm the existence of vascular-based changes in the CNS – they only evaluated diseases and particular disease symptoms which are thought to be the result or cause (hypertension, diabetes) of changes in the brain.

In summary, the presence of vascular factors does affect the clinical profile in Alzheimer's Disease. Studies indicate that vascular factors do not exacerbate the depth of dementia itself, but are related to the occurrence of b.p.s.d. (behavioural and psychological symptoms of dementia). Another issue which is very interesting from the clinical standpoint is the effect of vascular factors on the course of Alzheimer's Disease, however, this issue is the subject of another article. [29].

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