Received: 2015.05.05
Accepted: 2015.05.25
Published: 2015.11.12

Vascular Factors and Cognitive Dysfunction in Alzheimer Disease

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Statistical Analysis C
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Manuscript Preparation E
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Source of support: Departmental sources

Background: The purpose of the present study was to assess the influence of vascular factors on the degree of intensity and rate of progression of cognitive disorders in the course of Alzheimer Disease (AD).

Material/Methods: The research group consisted of 39 persons, all of whom were diagnosed with AD according to the NINCDS/ADRDA criteria. We divided these patients into 2 subgroups, based on the vascular factors measured by the modified Hachinski Ischemic Scale (Ha-mod): group A, without the vascular component (HA-mod score of 0–1 point), and group B, with the vascular component (a score over 1 point). Cognitive functions were evaluated at baseline and again 2 years later, using the Cognitive Part of the Alzheimer Disease Assessment Scale (ADAS-cog).

Results: We found that the patients from subgroup B, with the stronger vascular component, demonstrated the highest intensity of cognitive disorders at baseline, both in terms of the overall ADAS-cog score, and in the subscores for ideational praxis, orientation, spoken language ability, comprehension of spoken language, and word-finding difficulty in spontaneous speech. Another variable which was connected with the intensity of dementia was age. After 2 years, however, the rate of progression of cognitive disorders was not significantly different between the 2 groups.

Conclusions: The severity of vascular factors correlates directly with the intensity of cognitive disturbances. At the 2-year follow-up examination, however, no correlation was observed in the research group between greater vascular involvement and more rapid progression of cognitive disorders, as measured by the ADAS-cog scale.

MeSH Keywords: **Apraxias • Comprehension • Language • Orientation**

Full-text PDF: <http://www.medscimonit.com/abstract/index/idArt/894550>

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Background

The presence of vascular factors constitutes a risk factor for degenerative processes in the brain. In some prospective studies it has been shown that high blood pressure and stroke are risk factors for Alzheimer disease (AD) [1,2]. Cardiac ischaemia is also thought to increase the risk of developing AD [3]. Vascular lesions are observed in about a third of patients with AD [4]. Moreover, some vascular lesions (amyloid angiopathy, periventricular leukoencephalopathy) are observed to occur in almost all investigated cases of AD [5].

The co-participation of vascular factors in the cerebral pathology in AD seems to be a factor intensifying the clinical symptoms of dementia [6]. At the same time, the role of vascular factors in the progression of cognitive dysfunction remains an open question. Some studies have suggested that they affect the progression of cognitive symptoms, especially in case of patients already having a dementia [7]. In research on the natural history of AD, the rate of progression in vascular dementia was observed to be similar to that of AD [8]. Nevertheless, in controlled experiments conducted in accordance with strictly defined diagnostic criteria, only minor progression of cognitive dysfunction disorders is observed [9].

The aim of our study was to assess the influence of the presence of vascular factors on the degree of intensity of the cognitive disorders and their progression in AD.

Material and Methods

The initial population consisted of individuals who were residing, as of 2 September 2005, in the Social Welfare House in Gdynia (n=188). The first step was to measure the patients' risk factors for AD, using the MMSE [10]. All patient, who scored 24 or less points in this scale were then examined further to determine whether there were other symptoms of AD. The second step, then, produced the research group of 39 individuals (24 women and 15 men), all of whom were diagnosed with potential AD on the basis of the NINCDS/ADRDA criteria [11].

The third step was to evaluate the presence and intensity of vascular factors according to the modified Hachinski Scale (Ha-mod; see Table 1). Two research subgroups were selected: those without vascular aggravation (a score of 01 point), and those with vascular aggravation (any score greater than 1 point).

The fourth step was to evaluate cognitive functions, at baseline and after 2 years (the period between the baseline and follow-up examinations ranged from 22 to 26 months), using the 11-element Cognitive Subscale of the Alzheimer Disease Assessment Scale (ADAS-cog) [13]. ADAD-cog. This instrument

Table 1. The assessment of the intensity of vascular factors according to the Ha-mod.

Assessed factor	Score
Declared hypertension	1
Stroke	2
Symptoms of arteriosclerosis	1
Neurological subjective symptoms	2
Neurological focal symptoms	2
Coronary heart disease	1
Hypotension	1
Heart rhythm disorders	1
Diabetes	1

After Hachinski 1974 [12].

assesses the quality of speech, comprehension of spoken language, recall of test instructions, difficulties in finding appropriate words during spontaneous speech, understanding commands, naming objects and fingers, mapping figures, ideomotor activities, orientation, word recall, and word recognition. ADAS-cog can range from 0 to 70 points, where 0 indicates no difficulties, and 70 – a profound dementia.

The pharmacotherapy being administered to the patients at the time was taken into account. Pro-cognitive drugs and other psychotropic medicines administered for at least 14 days of constant treatment were noted. Information from the medical staff served to clarify the dosage of such drugs and the period of their administration.

Exclusion criteria

The initial procedure of including an individual in the research group involved obtaining the patient's consent to participate in the study, and assessing the exclusion criteria, which consisted in the presence, at the time of the study or during the interview, of at least 1 of the following:

- clinical or radiological features that would suggest a vascular foundation for the disease;
- affective disease, schizophrenia, alcoholism, drug or psychoactive substance addiction, epilepsy, Parkinson's disease, or intellectual handicap;
- disturbances of consciousness;
- illnesses affecting the motor organs, vision or hearing, that could significantly impair the patient's compliance with the commands and procedures included in the clinical scales being used;
- other serious somatic diseases.

Table 2. Mean values obtained in the research population of house residents with a diagnosis of AD (n=39).

	Mean	Minimum	Maximum	SD
ADAS	22.13	14.00	32.00	5.80
Vascular factors	1.67	0.00	4.00	1.24
Age	77.38	61.00	93.00	8.38
MMSE-sum	16.08	12.00	19.00	2.42

Table 3. Comparison of age and ADAS-cog scores in patients from group A (no vascular involvement) and group B.

No.	Feature	Group A n=18 mean	SD	Group B n=21 mean	SD	t	P
1.	Word recall task	3.83	1.54	4.71	1.90	-1.57	0.12
2.	Following commands	1.06	0.64	1.48	0.87	-1.69	0.10
3.	Naming objects and fingers	0.83	0.71	1.24	0.89	-1.55	0.13
4.	Constructional praxis	2.06	0.73	2.52	0.98	-1.67	0.10
5.	Ideational praxis	0.78	0.73	1.57	0.60	-3.73	0.00
6.	Orientation	0.72	0.57	1.52	1.21	-2.57	0.01
7.	Word-recognition task	5.28	1.18	4.76	2.10	0.93	0.36
8.	Recall of test instructions	0.56	0.78	0.71	0.72	-0.66	0.51
9.	Spoken language ability	1.28	0.46	1.67	0.48	-2.56	0.01
10.	Comprehension of spoken language	0.94	1.06	1.81	1.03	-2.58	0.01
11.	Word-finding difficulty in spontaneous speech	1.61	1.29	2.86	1.11	-3.25	0.00
	ADAS-cog global	18.94	5.25	24.86	4.84	-3.66	0.00
	Age	74.11	7.48	80.19	8.24	-2.40	0.02

Inclusion criteria

All patients from the research group met the diagnostic criteria for dementia of the Alzheimer type. The inclusion criteria here were a score of 11–23 points on the MMSE and a score above 4 points on the Hachinski scale [12]. Due to the need for cooperation from the patient, only those patients with a light or moderate dementia were qualified to the research group.

The presence of vascular factors was assessed again in the case of patients included in the research group. The presence of vascular factors was assessed on the basis of selected elements of the Hachinski scale that refer directly to vascular pathology, while maintaining the original scoring scheme of the scale. We also looked for coronary disease, heart rhythm disturbances, and diabetes. Table 1 presents all the assessed elements, together with the scoring system.

Statistical analysis

Statistical analysis was done using the test for 2 independent methods with the introduction of a bilateral interval. Multiple regression analysis was also done (the overall result of the ADAS-cog scale and the rate of progression of cognitive dysfunction were assumed to be dependent variables). The level of statistical significance was assumed to be $p \leq 0.05$. The Chi-square test was used to verify the assumption of normal distribution of the investigated feature in the general population (when doing the tests for 2 means), and the assumption of the equality of variances was verified with the test for 2 variances.

The rate of progression of dementia was calculated on the basis of the difference between the ADAS-cog scores at baseline and at follow-up.

Table 4. Comparison of age and ADAS-cog scores at baseline and follow-up (n=26) between patients without vascular complications (Ha-mod score 0–1 point) and those who had such complications (score above 1 point).

	Group A n=10 mean	SD	Group B n=16 mean	SD
ADAS-cog global (baseline)	18.10	4.25	23.56	4.72
ADAS-cog global (follow-up)	27.70	7.27	35.00	8.49
PROG	9.60	4.48	11.44	5.56
Age	73.70	7.44	80.19	9.09

Table 5. Comparison of mean scores in the ADAS-cog scale (at follow-up), age and the overall ADAS score patients taking and not taking cholinesterase inhibitors (ChEIs) during the study.

	Participants in follow-up			Group A			Group B		
	ChEI n=17 mean	Non-ChEI n=9 mean	t	ChEI n=6 mean	Non-ChEI n=4 mean	t	Mean ChEI n=11	Mean non-ChEI n=5	t
Age	76.88	79.22	−0.63	72.83	75.00	−0.43	79.09	82.60	−0.70
ADAS-0	20.65	23.00	−1.10	16.67	20.25	−1.37	22.82	25.20	−0.93
ADAS-2	30.82	34.78	−1.11	25.83	30.50	−0.99	33.55	38.20	−1.02
PROG	10.18	11.78	−0.75	9.17	10.25	−0.36	10.73	13.00	−0.75

The research methodology was fully accepted by the patients, all of whom expressed in writing their full agreement to participate in the study. Permission to conduct this research was obtained from the local Bioethics Commission.

Results

Due to the lack of any statistically significant differences in terms of cognitive dysfunction between the men and the women in our research group, further analysis will be conducted without reference to gender.

The average age, the presence of vascular factors according to the Ha-mod) and the results of the ADAD-cog and MMSE scales are presented in Table 2.

The assessed variables were compared in group A (without vascular factors, i.e. Ha-mod score of 0–1 point) and group B (with aggravated vascular features, i.e. Ha-mod score above 1 point; see Table 3). The individuals with the greatest intensity of vascular factors were older and demonstrated more advanced cognitive disorders. However, not all the elements of the ADAD-cog scale differentiated the 2 groups. The functions that showed significant differences included orientation, ideational

praxis, spoken language ability, comprehension of spoken language, and word-finding difficulties in spontaneous speech.

Due to the possible connection between age and the intensity of cognitive disorders, multiple regression analysis was done for the variables of age and the Ha-mod score, which indicated a significant role for age in the variance of the overall ADAS-cog score (the dependent variable). Both the determination coefficient ($R^2=0.340$) and the age correlation coefficients (beta=0.316) and the Ha-mod scores (beta=0.377) reached the level of statistical significance.

The follow-up examination was conducted with a group of 26 patients (16 women and 10 men), with an average age of 77.69 (SD=8.94), and an average ADAS-cog score at follow-up of 32.19 (SD=8.69). The mean difference between the follow-up study and baseline ADAS-cog scores was 10.73 (SD=5.16). The follow-up examination was not conducted in 13 cases because of death (n=8), or a significant deterioration of physical health rendering further participation in the study (n=4), or termination of cholinesterase inhibitors (ChEIs) just before the examination (n=1).

The individuals in Group A differed significantly from those in Group B in terms of the overall -cog score, both at baseline

and at follow-up) (Table 4). However, the rate of progression did not differ significantly between the 2 groups.

The multiple regression analysis for the ADAS-cog score at baseline, age, and the Ha-mod score did not explain at a significant level the variance in the rate of progression (the dependent variable). The determination coefficient was 0.269; the beta regression coefficients for the ADAS-cog score at baseline was 0.199; for age, 0.322; for the Ha-mod, 0.117.

During the 2-year interval between baseline and follow-up, 17 patients were given ChEIs, donepezil (5–10 mg; n=14) and rivastigmine (3–9 mg; n=6). The number of people treated with donepezil and rivastigmine is greater than 17 because some of the patients were administered both drugs. The patients taking procognitive medicines were compared in terms of the ADAS-cog score with those who were not undergoing any treatment. The patients were not differentiated by either age or ADAS-cog scores (Table 5).

Discussion

Alzheimer's disease is usually thought of as a condition caused by primary damage to neurons. Nevertheless, there is increasing evidence that the degenerative lesions that appear in the CNS in the course of AD may be preceded by, or at least coexist with, vascular lesions.

Vascular problems are counted among the risk factors for developing AD [2,14]. Damage to minor blood vessels may constitute a significant factor facilitating the intensification of degenerative lesions. One hypothesis assumes that, due to the increased permeability of the blood-brain barrier in the aging organism, preceded by the prior immunization of the system (e.g. due to a cranial injury), there occur immunological reactions that lead to the destruction of brain cells. One proof offered to support this hypothesis is the claim that the number of damaged vessels in microcirculation correlates with amyloid inclusions in the cortex [15].

Vascular lesions are observed in a significant number of patients with AD [4]. The destruction of capillary vessels occurs in almost every patient with AD [16]. Lesions in the capillary vessels are located, at least in the first phase of the illness, primarily in the hippocampus [17]. As one might expect, these lesions cause increased permeability of the blood-brain barrier [18]. Experiments on animal models have thrown some light on what causes the lesions in the capillaries and other minor vessels of AD patients. The animals undergo a long-term hypoperfusion caused by the occlusion of the carotid arteries. Within 1 year the animals developed lesions very similar to those encountered in AD [19].

Apart from the hypothetical participation of vascular factors in the neurodegenerative process itself, it is worth noting that the presence of these factors intensifies cognitive dysfunction [6]. Already at baseline examination, the patients from Group B, with greater vascular aggravation, demonstrated a greater intensity of cognitive disorders. However, this relation does not pertain to all the elements of the ADAS-cog scale (Table 3). AD and vascular dementia (VaD) differ to some extent in terms of the kinds of cognitive disorders that occur. Patients with VaD perform worse in tests that are influenced by frontal and subcortical mechanisms [20]. AD patients are more impaired than those with VaD in terms of episodic memory, while patients with VaD are more impaired in terms of semantic memory, executive and attentional functioning, and visuospatial and perceptual skills [21].

While some consensus exists that vascular factors influence the degree of intensity of cognitive disorders, their effect on the progression of dementia is not so clear.

No relation was observed in our research group between greater vascular aggravation and more rapid progression of cognitive disorders, as assessed on the ADAS-cog scale.

This observation is in accordance with the results of previous research, carried out according to a different methodology and pertaining to earlier phases in the development of dementia, where it was shown that vascular factors increase the risk of developing dementia, but do not speed up the progression of cognitive disturbances [22].

The results reported in the present study can be explained by referring to the process of symptom formation in the development of dementia, where memory plays the most important role. This can be explained by referring to the synchronic model of memory, which has been worked out on the basis of microgenetic theory and process neuropsychology (Figure 1). The model refers to the holographic model of the universe, which, according to Peat [23,24] confirms the synchronicity of reality. The spatial configuration of the model makes it possible to present, on the x and y axes, the relationship between the overall structure of the attention and memory systems in terms of the number, content, and complexity of the elements being processed and the time needed to complete the processing. It is assumed, following Pribram [25], that by changing the angle at which light beams from 2 lasers operate on a photographic image, one can obtain multiple images on the same surface. Thus the synchronic pattern of the model (the dotted lines) reflects the holographic interaction of waves, corresponding to what happens in the brain: the pulsing of mental states and neuroplasticity (changes in neuronal connections and new connections in the brain).

Figure 1. The synchronic model of memory. Explanation in the text. After: Pačalska, Kaczmarek & Kropotov [26] with modification.

Consciousness and self-consciousness have been represented here as a separate circle, since this is what conditions the existence of cognitive processes, including memory and emotional processes. The outside (yellow) spiral refers to the fractal concept of consciousness and self-consciousness in relation to the mind, and to the synchronic image of reality formed by the self in relation to the world and the universe.

The tunnels through which the small spheres are flowing reflect different kinds of working and long-term memory, which allow the individual to form their own, synchronic reality, in the self-to-world relation. Thanks to plasticity and new connections in the brain, a form of dependency is created between events, in which every causal connection is possible. The large yellow spheres are the buffers of (1) attention, (2) working memory, (3) long-term memory, and (4) perception.

When dementia begins to develop, the cognitive systems are destabilized. Dementia cannot contribute anything new to behavior, but rather affects behavior by removing essential components. The famous Soviet neuropsychologist A.R. Luria [27,28] stated that damage to the brain leads to a certain splitting of the layers of behavior, which makes it possible to see into its deeper structure. The particular activities comprising its components, which in normal behavior occur without visible effort, are revealed. This can be seen most clearly in disturbances of speech, where we can observe difficulties in forming or comprehending utterances, or word-finding problems. In the process of maturation in the brain, as specific neuronal networks take shape, complex dynamic systems are created¹, consisting

Figure 2. Changes in connections and destabilization of systems in persons with a neurodegenerative disease.

of many diverse subsystems. On the one hand, this complexity complicates its operation; on the other, it enables the brain to rebuild a given subsystem when parts of it are damaged [26].

However, a dynamic system of this sort can be easily destabilized. We observe this, for example, in a state of extreme fatigue, or when falling asleep, or by one's own volition when using psychoactive substances, of which alcohol is the most popular. Another example of a more serious threat to the system's stability would be the consequences of a neurodegenerative disease. This happens because brain damage not only changes the existing connections, but also imposes new rules for functioning on the existing systems. In biological terms, this is manifested by neurological and cognitive disturbances; in social terms, by the patient's inability to function in their previous social roles; and in personal terms, by personality changes.

At a certain stage in the development of a neurodegenerative disease, the motor, cognitive, and emotional systems are destabilized (Figure 2).

The process of system destabilization in the brain poses diagnostic problems, since the same pathomechanism can manifest itself in various forms, depending on the task the patient is asked to perform. As a result, one researcher may describe a different set of symptoms than another, who used a different test battery dictated by the stated purpose of the given research project. This phenomenon can be observed in research on the prefrontal cortex, when various studies have described different disturbances of memory, speech and language, attention, perception, and behavior in the course of "frontal syndrome" – hence the phrase, once a kind of commonplace, "the mystery of the frontal lobes" [26,29–33].

Among the significant methodological limitations of this study we should mention the fact that vascular complications were

¹. When we speak of a system, we should be aware that a system is not only the sum of the functions of its components, but forms a completely new quality [26]. In other words, complex neuronal networks form an essentially dynamic system, which can easily be destabilized.

assessed only on the basis of clinical criteria. No direct assessment of the presence of the angiogenic lesions in the CNS was included in the research. We only assessed the states and symptoms that are theoretically considered to have some connection with vascular pathology.

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Conclusions

We found that the severity of vascular factors is related to the intensity of cognitive disturbances at baseline. At 2-year follow-up, however, no relation was observed in the research group between greater vascular aggravation and faster progression of cognitive disorders, as assessed on the basis of the ADAS-cog.