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RESEARCH ARTICLE

Cerebrovascular Changes and Cerebral Atrophy in the Development of Dementia during Alzheimer's Disease

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ABSTRACT

Background: Alzheimer's disease (AD) is the world's number one cerebral neurodegenerative disease. Up to 80% of all dementia cases are due to this disease. AD occurs not only because of impaired metabolism of amyloid beta (Aβ) and tau protein in cerebral tissue, but also in connection with specific disorders of cerebral blood supply, manifested in dyscirculatory angiopathy of Alzheimer's type (DAAT).

Aims: The present research focuses on the clinical discovery of the sequence of development of dyscirculatory angiopathy of Alzheimer's type, cerebral atrophy, and dementia in patients with AD and their immediate family members.

Methods: 99 patients were selected for the research, of whom:

Test Group 1

93 (93.94%) suffered from various stages of AD and severity of dementia (age 34-79 (mean age 67): 32 (34.40%) men, 61 (65.59%) women).

Test Group 2

6 (6.06%) children aged 8-12 with a high probability of inheriting AD. Each of them had a parent diagnosed with AD with mild dementia (TDR-1), and a grandparent diagnosed with AD with moderate (TDR-2) or severe dementia (TDR-3). Each child complained of fatigue, memory loss, difficulty in remembering, difficulty in concentrating, and frequent headaches.

Results:

Test Group 1. According to the severity of dementia and atrophic changes in the temporal lobes, the patients were subdivided: preclinical stage TDR-0 - 10 (10.75%) people, mild stage AD TDR-1 - 26 (27.96%) people, moderately severe stage AD TDR-2-40 (43.01%) people, severe AD TDR-3 - 17 (18.28%) people. We identified dyscirculatory angiopathy of Alzheimer's type in all patients, regardless of their AD stage.

Test Group 2. There were no signs of dementia of cognitive disorders in any case. Initial involutive cerebral changes were detected in all 6 (100%) patients. Phenomena similar to DAAT were detected in all 6 (100%) patients.

Conclusion: Cerebrovascular changes manifested by dyscirculatory angiopathy of Alzheimer's type, regardless of the stage of the disease, are observed in all patients with AD, as well as in all their young offspring.

These changes affect amyloid beta metabolism in the brain and contribute to its deposition and accumulation in cerebral tissue, which leads to neurodegeneration and AD development.

The data obtained indicate that dyscirculatory angiopathy of Alzheimer's type is primary and, moreover, possibly congenital in AD development.

Keywords: Alzheimer's Disease; AD; Dyscirculatory angiopathy of Alzheimer's type; DAAT; CSVD; The Tomography Dementia Rating scale; TDR.

Introduction:

Diseases leading to neurodegenerative lesions of the brain are becoming more and more common among the population of different countries[1]. Alzheimer's disease (AD), Binswanger's disease (BD) and Parkinsonism are most widespread.

These diseases lead to the development of dementia, mental, cognitive disorders, decrease in daily life activities, which significantly complicate the life not only of the patient, but also of their relatives[1-4].

All these diseases are accompanied by distal cerebrovascular lesions caused by cerebral small vessel disease (CSVD)[5-8].

The brain requires powerful blood supply, and therefore, has angioarchitectonics particularities. 1 cubic centimeter of cerebral tissue contains 3-4 thousands of capillaries [9]. Cerebral blood supply disorders lead to a decrease in hemodynamics, hypoxia development, ischemic and neurodegenerative lesions [7].

Alzheimer's disease (AD) is the number one neurodegenerative brain damage. Over the past decades, there has been a steady increase in AD cases. Up to 80% of all dementia cases are related to this disease. In the US only, 6.5 million people, suffering from AD at the age of 65 and older, were registered in 2022. Younger patients were not taken into consideration. This suggests that the true number of patients with AD is much higher. Presumably, by 2060, in this country the number of patients will increase to 13.8 million people [1].

The etiology and pathogenesis of AD are complex and not fully understood [1-4,10]. The disease begins to develop secretly, primary cerebral changes appear 10-20 years before the primary clinical manifestations of the disease [1, 5-7]. In this regard, the preclinical stage of AD, in which patients do not present classical complaints, is rather difficult to identify, which greatly complicates the timely diagnosis [1,3,10]. AD is often hereditary, and therefore, for early diagnosis, it is necessary to conduct an examination of relatives and descendants of patients suffering from this disease [1,8].

When considering the causes of the development of AD, it should be taken into account that this disease occurs not only due to impaired metabolism of amyloid beta (Aβ) and tau protein in the cerebral tissue and vascular wall, but also because of specific disorders of cerebral blood supply [7-16].

In our earlier studies, we identified vascular and microvascular changes that appear in the brain in AD, which were named dyscirculatory angiopathy of Alzheimer's type (DAAT) [4, 7, 16]. DAAT relates to cerebral small vessel disease (CSVD) [4, 7, 16-18].

Dyscirculatory angiopathy of Alzheimer's type is manifested by increased tortuosity of the distal intracerebral arterial branches, specific reduction of the capillary bed in the temporal and frontoparietal regions, development of arteriovenous shunts, early discharge of arterial blood through them and into the venous bed, the development of abnormal large venous trunks, subsequent stagnation of venous blood [7, 8, 16, 18, 19, 20]. Our data are confirmed by the studies of other authors [5, 11, 12, 14, 15, 17, 21].

As a result, the cerebral blood supply is completely rebuilt, which leads to damage to tissue structures [7, 8, 14–16, 19, 22]. In the brain, the neurovascular unit (NVU) is damaged [12, 13, 23, 24]. In the cells of the smooth endoplasmic reticulum and the Golgi apparatus, synapses are destroyed, mitochondria die, and neurons degenerate and die [12, 13, 15, 19, 21].

Such degeneration of neurons is accompanied by impaired metabolism of amyloid beta, which leads to a decrease in its excretion and an increase in its accumulation [13, 23, 26, 27]. In its turn, the deposition of amyloid beta in the cerebral tissue and vascular wall reduces the elasticity of microvessels, causing an even greater narrowing of their lumen, which, secondarily, further reduces cerebral blood flow [28]. A decrease in blood flow contributes to an even greater deposition of amyloid beta, which jointly contributes to the development of progressive neurovascular dysfunction, neurodegeneration, cerebral atrophy, and dementia [7, 8, 19].

It should be noted that DAAT develops only in patients with AD and does not occur in other neurodegenerative and ischemic cerebral lesions [7, 8, 18, 19].

Also in our earlier studies, based on digital processing of CT and MRI images, a morphometric, digital scale of dementia stages in AD, the Tomography Dementia Rating scale, (TDR) was developed [29, 30]. This scale makes it possible to objectively determine the severity of dementia and the stage of AD by the severity of atrophic changes in the temporal lobes.

The present study is devoted to the clinical identification of the sequence of development of destructive cerebral changes, such as dyscirculatory angiopathy of Alzheimer's type (DAAT) and cerebral atrophy, leading to the development of dementia and cognitive impairment in patients with AD and their immediate relatives.

Methods

In this study, all examinations performed were performed with the written consent of the patients and their relatives, as well as with the approval of The Ethical Review Board (ERB) (Protocol No. 3 of 01-12-2003, Protocol No. 12 of 04-30-2014).

Patient selection criteria:

- consent of patients and their relatives for the examination;
- absence of concomitant diseases that could interfere with the examination;
- the somatic condition of patients, allowing for examination;
- patients' complaints corresponding to AD, signs of dementia and cognitive disorders corresponding to this disease;
- in the direct descendants of patients suffering from AD, signs of memory loss and signs of possible early cognitive disorders.

Patients' examination plan

Conducted:

- Clinically, dementia severity was assessed using the Clinical Dementia Rating scale (CDR)[31];
- Cognitive functions were assessed with the Mini-Mental State Examination (MMSE) [32];
- Cerebral blood flow and microcirculation were identified in static and dynamic modes using scintigraphy (SG);
- Cerebral perfusion blood filling was identified using rheoencephalography (REG);
- Structural cerebral changes were assessed using CT and MRI. To objectively determine the severity of dementia, the digital morphometric scale, the Tomography Dementia Rating scale, (TDR) was used [29, 30]. The studies were carried out upon admission of patients, as well as in the long-term period with an interval of 2-10 years.
- Intracerebral vascular and microvascular bed was determined using cerebral multi-gated angiography (MUGA), or MR angiography (MRA) with digital imaging.
- Laboratory tests were carried out in accordance with the principles and requirements of interventional neuroangiology;

99 patients were examined, of whom:

Test Group 1

93 (93.94%) people aged from 34 to 79 suffered from AD with various stages and severity of dementia (mean age 67 years), 32 (34.40%) men and 61 (65.59%) women.

Test Group 2

6 (6.06%) children aged from 8 to 11 with a high probability of inheriting AD. Each of them had a parent diagnosed with AD with mild dementia (TDR-1), and a grandparent diagnosed with AD with moderate dementia (TDR-2) or severe dementia (TDR-3). Each child complained of fatigue, memory loss, difficulty in remembering, difficulty in concentrating, and frequent headaches.

Results

Test Group 1.

According to clinical staging of dementia by CDR:

- Dementia at the level of CDR - 1 was detected in 26 (27.96%) cases;
- Dementia at the level of CDR - 2 was detected in 40 (43.01%) cases;
- Dementia at the level of CDR - 3 was detected in 17 (18.28%) cases;

According to clinical staging of cognitive functions by MMSE:

- A decrease in cognitive functions to the level of 26-28 points was detected in 10 (10.75%) cases;
- A decrease in cognitive functions to the level of 20-25 points was detected in 26 (27.96%) cases;
- A decrease in cognitive functions to the level of 12-19 points was detected in 40 (43.01%) cases;
- A decrease in cognitive functions to the level of 7-11 points was detected in 17 (18.28%) cases.

According to the data received with CT and MRI with digital image processing, in accordance with the TDR scale, the examined patients revealed specific, morphometrically substantiated atrophic changes in the temporal lobes corresponding to the stages of AD and dementia:

- 10 (10.75%) people - preclinical stage AD of TDR-0: atrophy of temporal lobes 4-8%, no signs of dementia, cognitive functions are reduced to the level of 26-28 points

according to MMSE (clinically, the patients showed increasing memory impairment, each had direct relatives suffering from AD) (Table 1);

- 26 (27.96%) people - mild stage AD of TDR-1: atrophy of temporal lobes 9-18%, clinical dementia corresponds to CDR-1, cognitive functions at the level of 20-25 points according to MMSE (Fig. 1 (C5)) (Table 1);
- 40 (43.01%) people - moderately severe stage AD of TDR-2: atrophy of temporal lobes 19-32%, clinical dementia corresponds to CDR-2, cognitive functions at the level of 12- 19 points according to MMSE (Table 1);
- 17 (18.28%) people - severe stage AD TDR-3: temporal lobes atrophy 33-62%, clinical dementia corresponds to CDR-3, cognitive functions at the level of 7-11 points according to MMSE (Fig. 2 (C5)) (Table 1).

Long-term (2-10 years) repeated cerebral CT and MRI with digital image processing showed a significant increase in atrophic changes in the temporal lobes, which were accompanied by an increase in dementia and cognitive deficit (Fig. 3(5)).

Cerebral multi-gated angiography with digital image processing revealed the following vascular and microvascular changes:

- Depletion of capillary blood flow caused by a decrease in the number of microvessels in the temporal and frontoparietal regions, with the formation of hypovascular zones, was detected in all 93 (100%) patients (Fig. 1 (A1), Fig. 2 (A1)) (Table 1);
- The formation of multiple arteriovenous shunts in the pools of the anterior villous arteries supplying the temporal regions, as well as in the pool of distal arterial branches supplying the frontoparietal regions, were detected in all 93 (100%) patients (Fig. 1(A2), Fig. 1(B2), Fig. 2(A2), Fig. 2(B2)) (Table 1);
- The formation of abnormally dilated lateral venous trunks, into which blood is discharged from arteriovenous shunts of the temporal and fronto-parietal regions, was detected in 84 (90.32%) patients (Fig. 1(B3), Fig. 2(B3)) (Table 1);
- Stagnation of venous blood at the border of the frontal and parietal regions, due to increased blood flow through arteriovenous shunts, was detected in 85 (91.40%) patients (Fig. 1(B4), Fig. 2(B4)) (Table 1);
- The formation of increased tortuosity of the distal intracranial arterial branches was detected in 74 (79.57%) patients (Table 1).

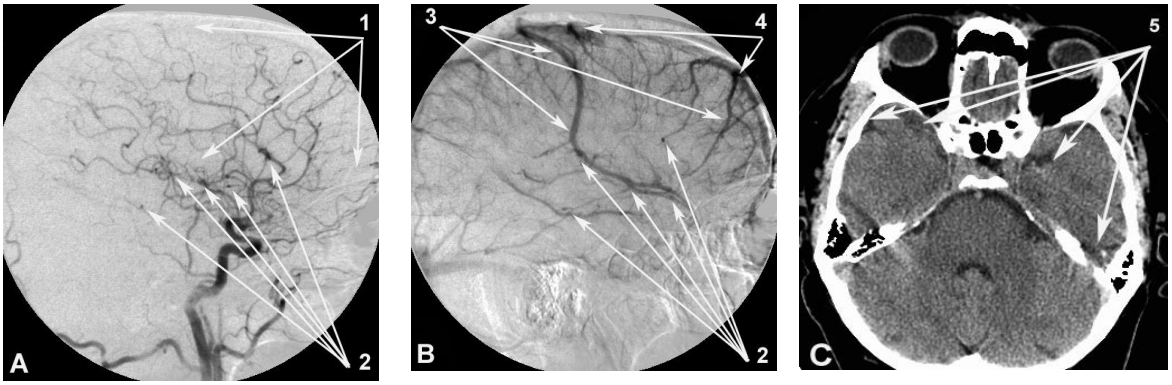

FIGURE 1. Patient C., 42 years old, male, AD (TDR-1): Left internal carotid artery MUGA & cerebral CT.

A - MUGA, arterial phase.

1 - Reduction in the number of capillaries with the formation of hypovascular zones in the temporal and frontoparietal regions.

2 - Multiple arteriovenous shunts.

B - MUGA, venous phase.

2 - Multiple arteriovenous shunts.

3 - Abnormally dilated lateral venous trunks.

4 - Stagnation of venous blood.

C - Cerebral CT

5 - Total atrophy of the temporal lobes is 18% of the total tissue volume

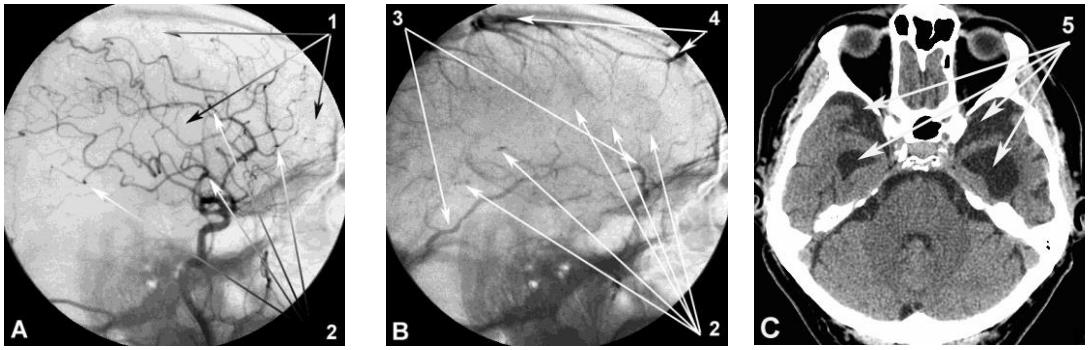

Figure 2. Patient C., 67 years old, male, AD (TDR-3): Left internal carotid artery MUGA & cerebral CT.

A - MUGA, arterial phase.
1 - Reduction in the number of capillaries with the formation of hypovascular zones in the temporal and frontoparietal region.
2 - Multiple arteriovenous shunts.
B - MUGA, venous phase.
2 - Multiple arteriovenous shunts.
3 - Abnormally dilated lateral venous trunks.
4 - Stagnation of venous blood.
C - Cerebral CT
5 - Total atrophy of the temporal lobes is 58% of the total tissue volume MSE – 10 points

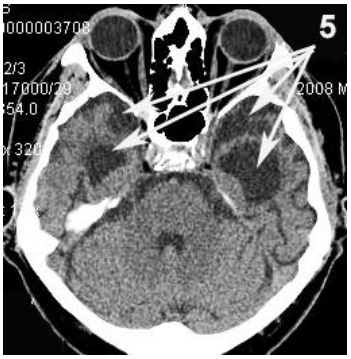

Figure 3. The same patient C., 69 years old, male, AD (TDR-3). Repeated cerebral CT in 2 years.

5 – Increasing atrophy. Total atrophy of the temporal lobes is 64% of the total tissue volume. Increasing dementia and mental disorders (MMSE – 7 points)

According to SG data, a decrease in blood flow in the cerebral hemispheres was detected in all 93 (100%) patients (Table 1).

According to REG data, a decrease in volumetric pulsed cerebral blood supply was detected in all 93 (100%) patients (Table 1).

According to laboratory tests, an increased level of lipids in the blood was detected in 35 (37.63%) patients, signs of hypercoagulability were detected in 39 (41.94%) patients.

As there are few patients in Test Group 2, to correctly apply the statistical criteria, we have to limit ourselves to only qualitative description of the results hoping that further research will allow to increase the number of the patients in this particular group and to statistically analyze the results obtained.

Test Group 2.

According to the clinical definition of the stage of dementia on the CDR scale, no signs of dementia were detected in any case.

According to the clinical definition of cognitive functions by the MMSE method, no signs of cognitive decline were detected in any case.

According to CT and MRI with digital image processing, initial involutive changes in the hippocampus and temporal lobes with a decrease in tissue volume by 4-7% were detected in all 6 (100%) cases (Fig. 4(C5)) (Table 1).

In contrast to patients from Test Group 1, repeated cerebral MRI with digital image processing in the long-term period (2-10 years) showed no signs of increasing involutive and atrophic changes in the temporal lobes in any case (Fig. 5(5)).

The research data are presented in Table 1.

Table.1 Results of patient examination.

CHANGES IDENTIFIED	Test Group 1 N - 93	Test Group 2 N - 6
Morphometric changes in temporal lobes according to CT and MRI data		
Initial involutive changes in temporal lobes	0	6
Atrophy of temporal lobes 4-8% - (TDR - 0)	10	-
Atrophy of temporal lobes 9-18% - (TDR – 1)	26	-
Atrophy of temporal lobes 19-32% - (TDR – 2)	40	-
Atrophy of temporal lobes 33-62% - (TDR – 3)	17	-
Assessment of cerebral blood flow according to SG data		
Decreased blood flow in cerebral hemispheres	93	6
Assessment of cerebral perfusion blood supply according to REG data		
Decreased volumetric pulse blood supply	93	6
Assessment of intracerebral vascular changes according to MUGA and MRA		
Development of increased tortuosity of intracerebral arteries	74	4
Reduction of capillaries in temporal regions	93	6
Development of hypovascular zones in temporal regions	93	6
Decrease in arterial inflow in temporal regions	93	6
Development of arteriovenous shunts in temporal regions	93	6
Development of abnormal large venous trunks	84	6
Development of venous stasis and impaired venous outflow	85	5

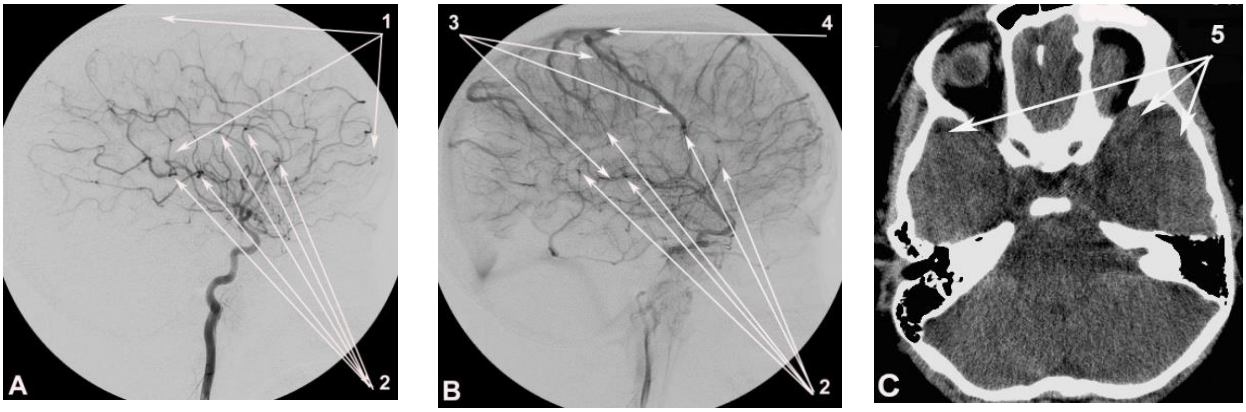

FIGURE 4. Patient C., 10 years old, male: Left internal carotid artery MUGA & cerebral CT.
A - MUGA, arterial phase.
1 - Reduced number of capillaries with the formation of hypovascular zones in the temporal and frontoparietal regions.
2 - Multiple arteriovenous shunts.
B - MUGA, venous phase.
2 - Multiple arteriovenous shunts.
3 - Abnormally dilated lateral venous trunks.
4 - Stagnation of venous blood.
C - Cerebral CT
5 - Involutive changes in temporal lobes is 6% of the total tissue volume.

Cerebral multi-gated angiography and MR angiography with digital image processing revealed the following vascular and microvascular changes:

- Depletion of capillary blood flow caused by a decrease in the number of microvessels in the temporal and frontoparietal regions with the formation of hypovascular zones was detected in all 6 (100%) patients (Fig. 4 (A1)) (Table 1);
- The formation of multiple arteriovenous shunts in the pools of the anterior villous arteries supplying the temporal areas, as well as in the pool of distal arterial branches supplying the frontoparietal areas, were detected in all 6 (100%) patients (Fig. 4(A2), Fig. 4(B2)) (Table 1);
- The formation of abnormally dilated lateral venous trunks, into which blood is discharged from arteriovenous shunts of the temporal and fronto-parietal regions, was detected in all 6 (100%) patients (Fig. 4(B3)) (Table 1);
- Stagnation of venous blood at the border of the frontal and parietal regions, due to increased blood flow through arteriovenous shunts, was detected in 5 (83.33%) patients (Fig. 4(B4)) (Table 1);
- The formation of increased tortuosity of the distal intracranial arterial branches was detected in 4 (66.67%) patients (Table 1).

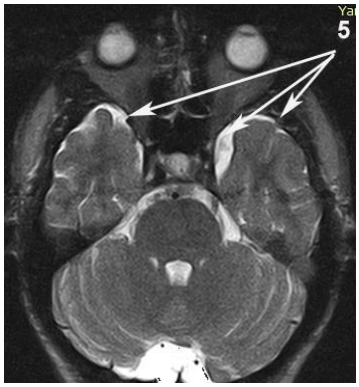

Figure 5. The same patient C., 20 years old, male, repeated cerebral MRI in 10 years.
5 - No increase in involutive changes in temporal lobes.

According to SG data, signs of reduced blood flow in the cerebral hemispheres were detected in all 6 (100%) patients (Table 1). According to REG data, signs of a decrease in volumetric pulsed cerebral blood supply were detected in all 6 (100%) patients (Table 1). According to the laboratory tests, elevated lipid levels and hypercoagulability in the blood were not detected in any case.

Discussion

As noted by many authors, the development of AD is accompanied by cerebrovascular changes proceeding in accordance with CSVD type [5, 11, 14, 21, 22, 25, 27]. Basically, these studies were carried out on the material of post-mortem autopsy of patients who died as a result of the development of the terminal AD stage. Studies of patients with earlier stages of the disease were not conducted. Moreover, there have been no studies of cerebral vascular changes in patients with preclinical AD stage and in close relatives of AD patients who have a high hereditary likelihood of developing the disease [15, 21]. A detailed intravital study of all vascular disorders developing at the level of the arterial, capillary and venous bed has not been conducted.

The present study is based on a lifetime examination of patients with preclinical AD stage of TDR-0, mild AD stage of TDR-1, moderately severe AD stage of TDR-2, and severe AD stage of TDR-3, as well as direct descendants of AD patients who have a high hereditary likelihood of developing the disease.

Considering the data obtained, it should be noted that cerebrovascular changes manifested by DAAT were detected in all 93 (100%) patients from Test Group 1.

This group includes 83 (89.25%) patients with clinical stages of AD (TDR-1, TDR-2, TDR-3) as well as 10 (10.75%) patients with preclinical stage of AD (TDR-0), in whom the disease has not yet developed and there is only a high probability of its development (Table 1).

In all patients from Test Group 1, regardless of the stage of the disease, the number of microvessels and capillaries in the cerebral temporal and frontoparietal parts of the hypocampus and limbic system is reduced, they are thinned, and further branching is not expressed. This leads to the formation of hypovascular zones in the corresponding cerebral areas with reduced capillary blood flow (Fig. 1A(1), Fig. 2A(1)). Difficulty in the passage of arterial blood due to the reduction of the capillary bed causes the opening of arteriovenous shunts through which arterial blood, without passing through the capillaries, is discharged into the venous bed (Fig. 1 A(2), Fig. 1 B(2), Fig. 2 A(2), Fig. 2 B(2)). The cerebral venous bed becomes congested, which leads to the development of large anomalous venous trunks (Fig. 1 B(3), Fig. 2 B(3)) and the development of venous congestion

(Fig. 1 B(4), Fig. 2 B(4)). As a result, blood circulation is reorganized in the brain, leading to AD-specific hypoxia and neurodegeneration. At the same time, the metabolism of amyloid beta is damaged, which leads to its accumulation in the cerebral tissue.

Both at the preclinical stage of AD TDR-0 and at the mild stage of AD TDR-1, moderately severe stage of AD TDR-2 and severe stage of AD TDR-3, the severity of arterial, capillary and venous changes in DAAT remains at the same level, without a clear increase in these changes depending on the severity of the disease. According to SG and REG data, in all patients from Test Group 1, there is a decrease in blood flow in the cerebral hemispheres and volumetric pulse cerebral blood circulation.

Our data are confirmed by studies by other authors, who showed that the incidence of AD development in the population depends on the initial state of intracerebral vessels and the level of reduction in cerebral blood supply [33].

According to the results of this study, all patients from Test Group 1, in accordance with the TDR scale, differ in the severity of cerebral atrophy, which leads to the development of a certain stage of dementia. If in patients with the preclinical stage of AD TDR-0, atrophy of the temporal lobes is 4-8%, then in patients with a mild stage of AD TDR-1, atrophy is 9-18%, in patients with a moderately severe stage of AD TDR-2 is 19-32 %, and in patients with severe AD TDR-3 is 33-62% (Table 1). The higher the degree of atrophy in the patient is, the more severe the stage of AD and the more pronounced dementia they have, as well as the more severe the cognitive deficit is.

Repeated CT and MRI studies in the long-term period (2 years or more) in patients from Test Group 1 showed an increase in cerebral atrophic changes, which led to growing dementia and cognitive deficit (Fig. 3 (5)).

Patients from Test Group 2 are direct descendants of patients suffering from AD, which does not guarantee the development of AD in the future, but indicates a high hereditary predisposition to the development of the disease.

When testing patients from Test Group 2 using CDR and MMSE, no signs of dementia and cognitive impairment were detected. However, patients complained of fatigue, memory loss, difficulty in remembering.

Cerebrovascular changes similar to DAAT were detected in all 6 (100%) patients from Test Group 2 (Table 1). Reduction of the capillary bed, development of hypovascular zones in the temporal and frontoparietal regions were detected in all 6 (100%) cases (Fig. 4 A(1)). The formation of arteriovenous shunts was detected in all 6 (100%) cases (Fig. 4 A(2), (Fig. 4 B(2)). The development of abnormally dilated venous trunks was detected in all 6 (100%) cases (Fig. 4 B (3)). Stagnation of venous blood was detected in 5 (83.33%) cases (Fig. 4 B(4)).

The severity of these cerebrovascular changes is similar to those found in patients from Test Group 1 suffering from various stages of AD (Table 1).

Considering the rather young age of patients from The Test Group 2, as well as their hereditary history, it can be concluded with confidence that vascular and microcirculatory changes according to the DAAT type are primary and are congenital, hereditary cerebrovascular disorders that potentially contribute to the further development of AD.

According to the SG and REG data, all patients from this group showed signs of a decrease in blood flow in the cerebral hemispheres and volumetric pulse cerebral blood supply.

According to CT and MRI data, all 6 (100%) patients from Test Group 2 showed signs of initial involutive changes in temporal lobes with a decrease in tissue volume by 4-7% (Table 1). However, repeated MRI conducted in the long-term period (2-10 years) showed no increase in cerebral involutive changes in patients from this group (Fig. 5(5)). This indicates that involutive and atrophic cerebral changes are secondary in the development of AD. According to repeated testing by means of CDR and MMSE, clinical signs of dementia and cognitive deficits were also not revealed.

Conclusions

The process of development of AD begins decades before the initial clinical manifestations of the disease.

The primary changes in the brain are DAAT, which is manifested by a specific restructuring of the arterial, capillary and venous bed. DAAT includes increased tortuosity of the distal intracerebral arterial branches, reduction of the capillary bed with the formation of hypovascular zones in the temporal and frontoparietal regions, the development of arteriovenous shunts, through which arterial blood is discharged into the venous bed, the development of abnormal large venous trunks with venous blood stasis.

As a result of the restructuring of the cerebral circulation, specific chronic cerebral hyporfusion and hypoxia develop, which over time lead to damaging of the metabolism of amyloid beta and its accumulation in the cerebral tissue.

Obviously, cerebrovascular DAAT type changes are congenital, possibly hereditary. The subsequent deposition of amyloid beta, the development of specific cerebral degeneration and atrophy are secondary changes that subsequently lead to the development of AD, dementia and cognitive deficits.

The time of development of AD depends on the compensatory capabilities of the human body, which allow compensating for cerebrovascular and microcirculatory disorders.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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