Journal of Behavioral and Brain Science, **2011, 1, 57-68**
doi:10.4236/jbbs.2011.12008 Published Online May 2011 (http://www.scirp.org/journal/jbbs)

Dyscirculatory Angiopathy of Alzheimer's Type

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Received March 15, 2011; *revised March* 30, 2011; *accepted April* 2, 2011

Abstract

Purpose*:** We assess the significance of dyscirculatory angiopathy of Alzheimer's type (DAAT) in identifying the predisposition to the development and diagnosis of Alzheimer's disease (AD) different stages. ***Methods*:** 108 patients took part in the research:1) 49 aged 34-79 suffering from AD or running an increased risk of its development (those not diagnosed with AD but having growing memory disorders without any manifestations of dementia or specific cognitive impairments, and having 2 or more immediate relatives with AD) - ***Test Group; 2) 59 aged 28-78 suffering from different types of brain lesions accompanied by dementia but not suffering from AD or corresponding to their age norm - ***Control Group***. All the patients underwent MRI, CT with subsequent calculation of the temporal lobes atrophy degree, brain scintigraphy (SG), rheoencephalography (REG), and MUGA. ***Results*:** Characteristic features of patients with an increased risk of AD as well as at its various stages are: 1) Temporal lobes and hippocampus atrophy ranging from 4% among those with an increased risk of AD to 62% among those at its advanced stages; 2) DAAT manifestations: reduction of the capillary bed in the temporal and frontoparietal regions with the development of multiple arteriovenous shunts of the same localization and correspondent early venous discharge accompanied by venous stasis on the border of the frontal and parietal region; 3) DAAT phenomena equally develop both among those with an increased risk of developing AD and those at various AD stages. Similar changes are not observed among Control Group patients with other brain lesions, regardless of the severity of dementia, as well as among practically healthy people of the corresponding age group. ***Conclusion*:** Timely identification of the abovementioned changes can reveal a predisposition to AD development long before its initial manifestations, and it allows differentiating AD from other diseases attended by dementia. In both cases, timely diagnosis allows beginning timely treatment and thus achieving more stable results.

Keywords: Alzheimer's Disease, Dementia, Hippocampus, Temporal Lobes Atrophy, Dyscirculatory Angiopathy of Alzheimer's Type

1. Introduction

Alzheimer's disease (AD) is becoming more widespread each year. According to the Alzheimer's Association, in 2007, 5.1 million cases were registered only in the United States [1]. In 2009, the number of cases increased to 5.3 million [2], and in 2050 it will approximately increase to 13.5 million [3]. In 2010, there were 35.6 million patients around the world, and it is estimated that by 2050 this figure will approach 115.4 million [4]. It all suggests that AD is becoming a global problem of mankind. One of the important issues in solving this problem is early diagnosis of the disease and timely visualization of changes and processes in the brain during disease development [5]. Another issue of no less importance is the differentiation of AD from other diseases that are characterized by the development of dementia [6-8].

A great step in the diagnosis of AD was the introduction of CT and MRI which made it possible to visualize the brain and to detect changes developing in the tissues of the temporal lobes and the hippocampus [9-12]. However, using standard CT or MRI techniques does not always allow differentiating AD from other diseases associated with dementia [13]. The introduction of PET has made it possible to carry out not only structural but also functional studies of the hippocampus [14-17] which consequently led to the development of fairly complex integrated visualization techniques [18]. The next achievement in AD diagnosis was the emerging of biomarkers and the development of various methods of their use, but

this extremely promising research is still under study [19].

There are certain problems in the diagnosis of early stage disease accompanied by mild dementia and Mild Cognitive Impairment (MCI) [16,17]. It is even more difficult to diagnose pre-clinical stages when the disease has not yet developed, there are no manifestations of dementia, and its development is only probable [13,19, 20].

Despite the fact that it was in the 1930s when F. Morel found out that AD was accompanied by dysoric or drusoidal angiopathy, the state of the brain vascular system in Alzheimer's disease has received insufficient attention. Until recently, medical literature had only some isolated reports on this subject [21-24]. The research was mostly carried out by means of ultrasound and MRI techniques which did not always give a clear picture. Accordingly, hemodynamic changes of the brain [25] and the development of perfusion abnormalities [26,27] have been looked at from the functional side to a greater extent, and vascular disorders were seen in terms of location of amyloid deposits and amyloid angiopathy [28-30], but not in terms of vascular pathology. Visualization of arte- rial, capillary and venous blood flow of the brain, as well as their correlation in AD, has yet received insufficient attention.

2. Materials and Methods

The whole research was made with the approval of the Ethics Committee and with the consent of the examined patients and their relatives. Our objective was to identify specific structural defects and their correlation with angioarchitectonic changes appearing in the brain during AD development, as well as the identification of these changes among patients with a predisposition to AD development, and their comparison with cerebral and cerebrovascular changes that occur in the control group of patients of the same age who suffer from other lesions of the brain accompanied by the development of dementia or not accompanied by the development of dementia. To carry out complete differential diagnosis of all the patients was not the objective of this research.

108 patients aged from 28 to 79 (average age 67) were examined during the research.

The Test Group included 49 patients aged from 34 to 79 (average age 65), 18 men (36.7%) and 31 women (63.3%).

43 patients suffering from AD were subdivided according to one of the most common classifications proposed by J. C. Morris in 1993 (The Clinical Dementia Rating /CDR/) [31]:

- *CDR*-1 - Group with mild dementia, mild cognitive impairment, had previously been diagnosed AD, medical history did not exceed 2 years - 15 (30.6%) patients;
- *CDR*-2 - Group with moderate dementia, quite persistent cognitive impairment, had previously been diagnosed with AD, history of the disease ranged from 2 to 6 years - 20 (40.8%) patients;
- *CDR*-3 - Group with fairly severe dementia, gross cognitive impairment, had previously been diagnosed with AD, history of the disease ranged from 7 to 15 years - 8 (16.3%) patients;
- A separate group of 6 (12.2%) included the patients' relatives with a high risk of developing the disease who wished to have an examination. They were all fairly young, aged from 34 to 42, had growing memory disorders without any manifestations of dementia or any specific cognitive impairment.

The Control Group included 59 patients aged from 28 to 78 (average age 68), 36 (61.0%) men and 23 (39.0%) women.

Control Group patients either had different types of brain lesions with varying degrees of severity accompanied by signs of dementia and cognitive impairment, but did not suffer from Alzheimer's disease or considered themselves healthy; they did not have any specific complaints and their brain changes were seen as age-corresponding and normal.

Those patients were divided into the following groups:

- A group at the initial stage of chronic cerebrovascular insufficiency of atherosclerotic genesis without any signs of dementia or cognitive impairment; usually those patients, regardless of age, had some complaints which were considered normal taking into account age-related changes of the brain - 17 (28.8%) patients;
- A group with sufficiently severe chronic cerebrovascular insufficiency of atherosclerotic genesis without gross occlusive vascular lesions; they had incipient mild dementia and initial cognitive impairment - 12 (20.3%) patients;
- A group with multiple atherosclerotic lesions of the brain, severe vascular dementia and cognitive impairment, with a history of recurrent small focal strokes - 6 (10.2%) patients;
- A group with atherosclerotic (vascular) Parkinsonism and signs of dementia - 14 (23.7%) patients;
- A group with Binswanger's disease and manifestations of dementia - 6 (10.2%) patients;
- A group with Parkinson's disease and manifestations of dementia 4 (6.8%) patients.

The research plan included: computed tomography of the brain (CT), magnetic resonance imaging (MRI), scintigraphy of the brain (SG), rheoencephalography (REG),

multi-gated angiography (MUGA).

CT was preferred over MRI in the research, as it was necessary to better visualize calcium deposits in the vascular wall in atherosclerotic lesions and to identify the nature of vascular pathology. The main goal of the research was study of the changes in the temporal lobes and the hippocampus, as they are the first to suffer from the development of AD [9-12,16,17], as well as the fact that they are easily enough visualized on the scans by bone formations.

CT of the brain was performed on apparatus "Somatom" (Siemens), "HiSpeed" (GE), "Tomoscan" (Philips) by the following procedure: the patient was placed according to the classical pattern, the boundary of the first scan took place on the orbital-miotal line, producing scans 2.5 mm thick with an interval of 2.5 mm. The boundaries of cerebral fosses on both sides were ascertained by bone marks. A consistent two-side measurement of cerebral fosses region and measurement of the size of the substance of the right and left temporal lobes of the brain for each scan were made with computer program "Advanced Tomo Area Analysis" (ATAA). Next, the area of the lower horn of lateral ventricle and the area of the sulci were subtracted and then compared with the area of the corresponding cranial fossa at the same level. The ratio of these quantities makes it possible to compare the state of brain tissue both in its normal condition and during the development of atrophic process. Reduction of the size of the brain tissue area at each scan corresponds to the severity of atrophic changes at this brain level. Then the above mentioned quantities were automatically recalculated by the thickness of each scan and each interval between the scans, and the volume of the right and left temporal lobes of the brain was determined, and thus the mass of brain tissue in the surveyed areas was calculated. Next, the masses of tissue of left and right temporal lobes were summed up. The results of the research automatically showed both the normal amount of tissue for the corresponding age group and the percentage decrease of the volume of the temporal lobes of the brain. The percentage ratio of those values determined the severity of atrophic changes in the temporal regions of the brain and, consequently, in the hippocampus tissue [12,32]. The data showed a tendency to develop Alzheimer's disease or the stage of its development in the experimental group and also pointed at the pres- ence or absence of atrophic changes in the temporal lobes of the brain in the control group of patients.

Due to the fact that examined patients belonged to different age groups, the study took into account age-related changes in brain tissue [32,34]. For example, the fact that patients aged 60 and older had common atrophic changes of the brain, along with a decrease of the size of the temporal lobes of up to 5%, was regarded as natural age-related changes and equal to normal [33].

SG of the brain was carried out on a gamma camera (*Ohio Nuclear*, U.S.) following the classical method in dynamic and static mode using the TC 99M pertechnetat 555.

REG was conducted by means of "Reospektr-8" (*Neurosoft*, Russia) in accordance with the standard automated method with the determination of pulse volume abnormalities.

MUGA of the brain was performed on apparatus "Advantx" (*GE*) following the classical method of transfemoral access. 10 - 12 ml of *Omnipack* 350 was introduced intra-carotidally and 7 - 8 ml intra-vertebrally. Registration was carried out in direct and side projections in constant subtraction mode at a speed of 25 frames per second.

3. Results

Since all classifications of stages and types of AD are functional in nature [6,8,18] and are not based on morphological changes, we have slightly modified the previously used classification proposed by J. C. Morris (The Clinical Dementia Rating) [31] and added a morphological component to it. Thus, the patients were divided into groups in accordance with the degree of severity of atrophic changes in the temporal lobes of the brain, as well as the degree of severity of dementia, cognitive impairment and the severity and duration of the disease.

Analyzing the results obtained, we introduced Group *CDR*-0 (as opposed to the method proposed by J. C. Morris where the earliest stage was represented by Group *CDR*-0,5). In our research, this group included relatives of patients with AD, *i.e.* people aged from 34 to 42 who had not been diagnosed with AD but who had growing memory disorders without any manifestations of dementia or any specific cognitive impairment and who had 2 or more immediate relatives suffering from AD. These patients were identified as a group running a high risk of acquiring the disease or a group with a possibility of its inheritance.

In the Test Group of patients, CT revealed the following main types of changes in brain tissue (**Table 1**):

- In Group CDR-0: 4 (66.6%) patients had atrophy of the temporal lobes of the brain with a decrease of tissue mass of 4% - 8% (**Figures 1(a)**, **1(b)**). 2 (33.4%) patients did not have any atrophic changes at the time of the examination, so they were withdrawn from those with a possible inheritance of AD;
- In Group CDR-1: 15 (100%) patients with mild dementia, mild cognitive impairment, early clinical stage of the disease and a history of up to 2 years had atrophy of the temporal lobes with a decrease of

tissue mass of 9% - 18% (**Figures 2(a)**, **2(b)**);

- In Group CDR-2: 20 (100%) patients with moderate dementia, persistent cognitive impairment, middle clinical stage of the disease and a history of 2 to 6 years, had atrophy of the temporal lobes with a decrease of tissue mass of 19% - 32% (**Figures 3(a)**, **3(b)**).
- In Group CDR-3: 8 (100%) patients with severe dementia, gross cognitive impairment, late-stage clinical AD and a history of 6 to 15 years had gross atrophy of the temporal lobes accompanied by a decrease of tissue mass of 33-62%; in some cases those changes were accompanied by formation of rather extensive cavities in the tissue (**Figures 4(a)**, **4(b)**).

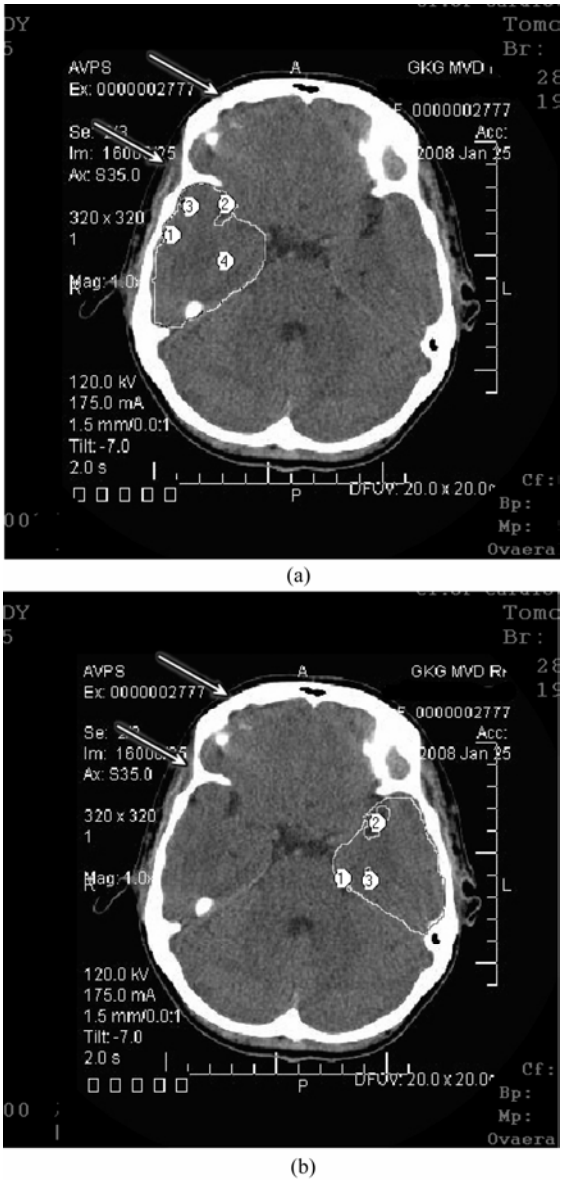


Figure 1. Tomograms of patient P. (36 years old, female) with an increased risk of AD development. (a) 7% atrophy of the right temporal lobe (zones 1 - 4); (b) 8% atrophy of the left temporal lobe (zones 1 - 3). Arrows indicate dilation of Sylvius fissure and subarobchnoidal space.

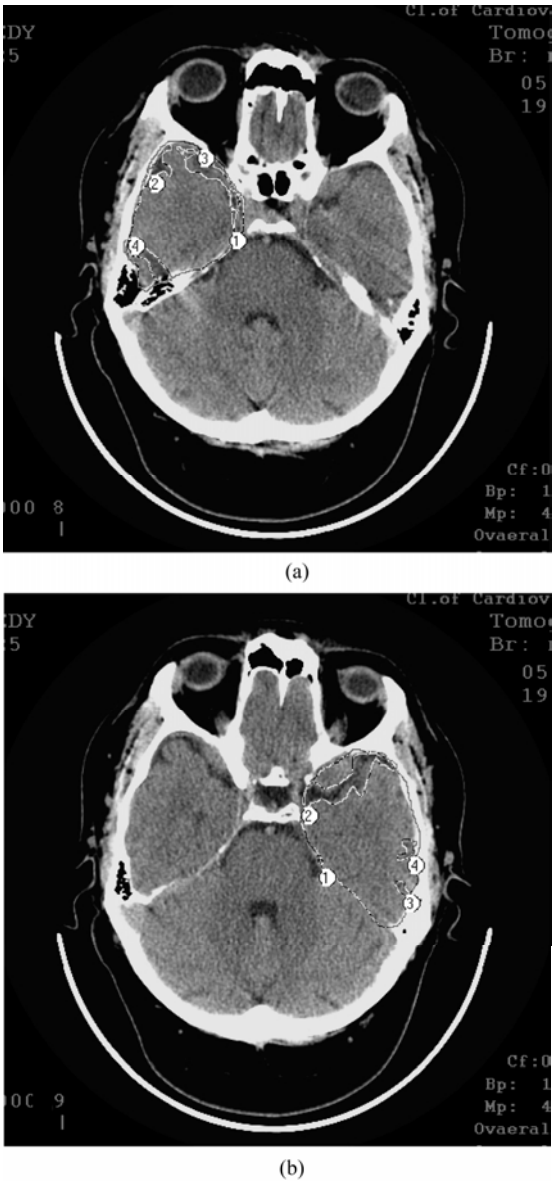
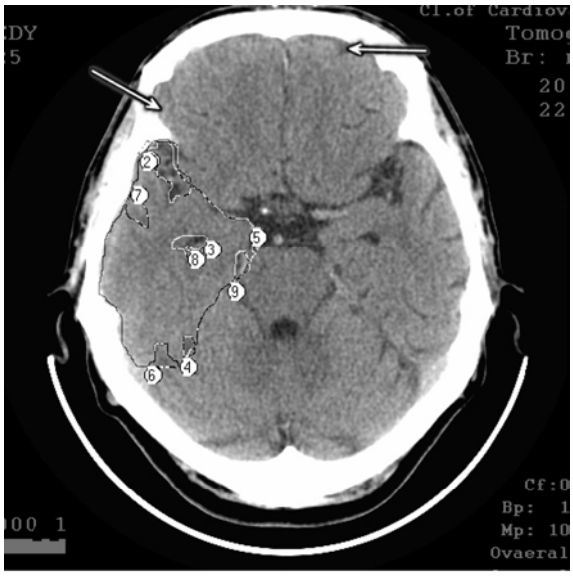


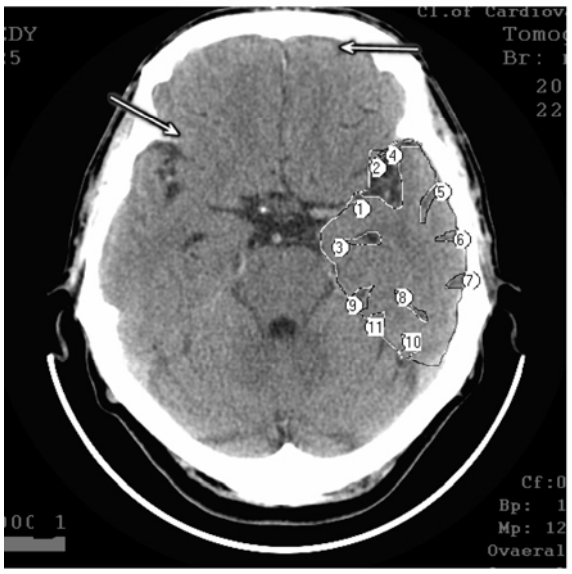
Figure 2 Tomograms of patient S. (42 years old, male); 2-year anamnesis of the disease. (a) 18% atrophy of the right temporal lobe (zones 1 - 4); (b) 17% atrophy of the left temporal lobe (zones 1 - 4).

Simultaneously, patients of the Test Group had the following:

- Absence or insignificant amount of calcium salts deposits in the walls of cerebral vessels - 47 (100%) patients;
- Dilation of Sylvian fissure (**Figures 1-4**) associated with atrophic changes, mainly of the temporal and partially frontal lobes of the brain - 47 (100%) patients;

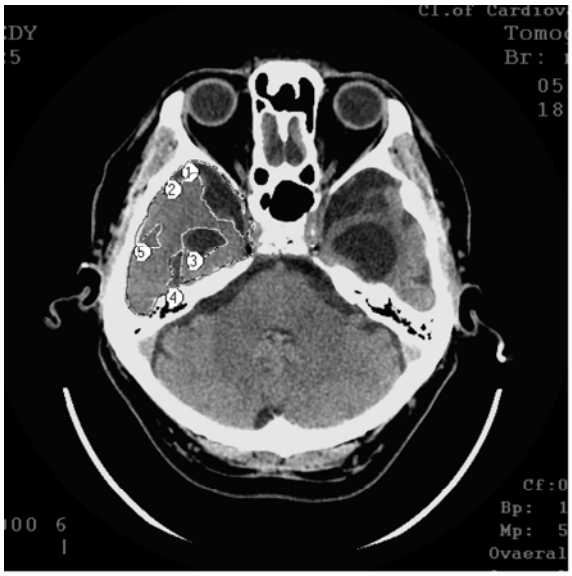


(a)

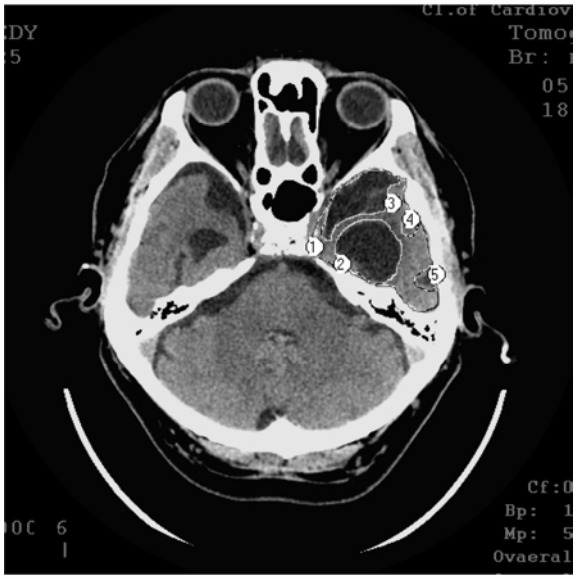


(b)

Figure 3. Tomograms of patient T. (58 years old, male); 6-year anamnesis. (a) 20% atrophy of the right temporal lobe (zones 1 - 9); (b) 22% atrophy of the left temporal lobe (zones 1 - 11). Arrows indicate dilation of Sylvius fissure and subarochnoidal space.



(a)



(b)

Figure 4. Tomograms of patient S. (67 years old, male); 12-year anamnesis. (a) 41% atrophy of the right temporal lobe (zones 1 - 5); (b) 62% atrophy of the left temporal lobe (zones 1 - 5).

- Local involutive changes of the cerebral cortex associated with the dilation of the sulci of up to 1.5 - 5.0 mm, and dilation of subarachnoid space of convexital surfaces of the temporal and frontal-parietal regions - 47 (100%) patients;
- General invalutive changes of the cerebral cortex - 18 (38.3%) patients;
- Signs of unocclusive hydrocephalus - 29 (61.7%) patients;

CT revealed the following features of Control Group patients' brain tissue (**Table 1**):

- Local atrophic changes in the temporal lobes were not detected in any case;
- General atrophy of the brain among patients aged from 60 to 78 accompanied by atrophy of the temporal lobes, with a decrease of tissue mass of 5% (which corresponds to the age norm), were detected among 26 (44.1%) patients [33];
- Multiple calcium deposits in the walls of intracranial vessels - 55 (93.2%) patients;
- Dilation of Sylvian fissure associated with general

atrophic changes - 41 (69.5%) patients;

- General involutive changes of the cerebral cortex associated with the dilation of the sulci of up to 1.5 - 2.0 mm, and dilation of subarachnoid space of convexital surfaces - 35 (59.3%) patients;
- Signs of unocclusive hydrocephalus - 35 (59.3%) patients.

Simultaneously, Control Group patients had the following:

- Single postischemic macrocysts (5 - 10 mm) – 7 (11.9%) patients;
- Single postischemic microcysts (3 - 5 mm) – 25 (42.4%) patients;
- Multiple postischemic microcysts (3 - 5 mm) – 9 (15.3%) patients;
- Manifestations of leucoaraiosis – 18 (30.5%) patients.

In the Test Group, SG showed blood flow slowdown in the cerebral hemispheres of up to T max 9 - 10 s., T 1/2 10 - 11 s. in 31 (66.0%) cases, of up to T max 12 - 13 s., T 1/2 15 - 20 s. – in 16 (34.0%) cases.

In the Control Group, according to SG, blood flow slowdown in the cerebral hemispheres of up to T max 10 - 12 s., T 1/2 11 - 13 s. was observed in 37 (62.7%) cases, of up to T max 14 - 15 s., T 1/2 15 - 20 s. – in 22 (37.3%) cases.

In the Test Group REG showed a decrease in pulse blood filling volume in the carotid system of 15% - 20% in 28 (59.6%) cases, 40% - 50% – in 19 (40.4%) cases.

In the Control Group, according to REG data, a decrease in pulse blood filling volume in the carotid system of 20-35% was detected in 35 (59.3%) cases, of 45% - 60% – in 24 (40.7%) cases.

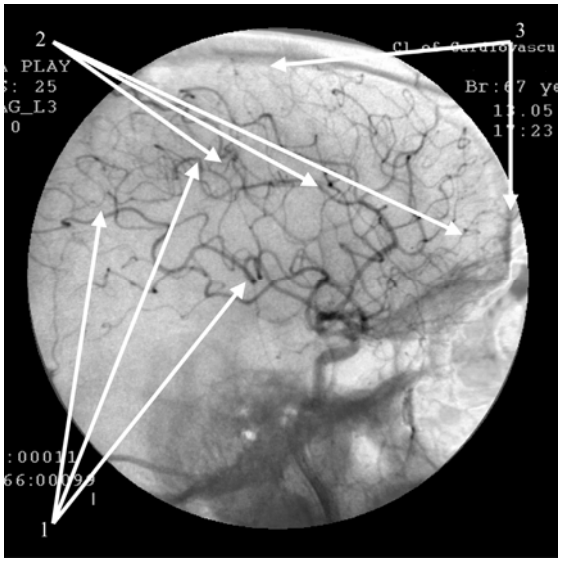
MUGA in the Test Group revealed (**Table 2**):

- Absence (or they were poorly expressed) of atherosclerotic changes of extra and intracranial arteries - 47 (100%) patients;
- Increased looping of the distal branches of intracranial arteries - 37 (78.7%) patients (**Figure 5**);
- Reduction of capillary contrast phase in a cone-shaped microvascular area in the frontoparietal regions and the projection of the hippocampus - 47 (100%) patients (**Figure 6**);

Table 1. CT data obtained by means of ATAA program.

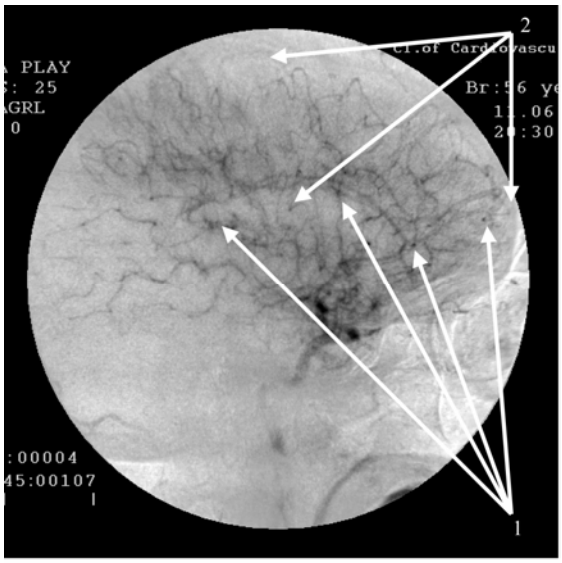
Signs	Test group (Alzheimer's disease)	Control group (brain disorders other than Alzheimer's disease)	p (chi-square)
Number of patients	47	59	
Multiple calcium salt deposits on the walls of intracranial vessels	0	55	< 0.005
Scattered postischemic macrocysts (5 - 10 mm)	0	7	0.015
Scattered postischemic microcysts (3 - 5 mm)	0	25	< 0.005
Multiple postischemic microcysts (3 - 5 mm)	0	9	0.0051
Manifestation of leucoaraiosis	0	18	< 0.005
Reduction in the size of the temporal lobes of the brain of 4 to 8%	4	0	0.022
Reduction in the size of the temporal lobes of the brain of 0 to 5% among patients older than 60	0	26	< 0.005
Reduction in the size of the temporal lobes of the brain of 9 to18%	15	0	< 0.005
Reduction in the size of the temporal lobes of the brain of 19 to 32%	20	0	< 0.005
Reduction in the size of the temporal lobes of the brain of 33 to 65%	8	0	< 0.005
Dilation of Sylvius fissure	47	41	< 0.005
Local involutive changes of the cerebral cortex in the temporal regions of the brain	47	0	< 0.005
General involuntary changes in the cerebral cortex	18	35	0.031
Signs of nonocclusive hydrocephaly	29	35	0.803 (no)

The differences between the groups were identified by the analysis of the relevant contingency tables 2 × 2 by means of Pearson's chi-square test. The corresponding values of p are shown in the last column of the table. P-value = 0.05".



1. Multiple loop formation; 2. Multiple arteriovenous shunts in frontoparietal and temporal regions; 3. Development of hypovascular region.

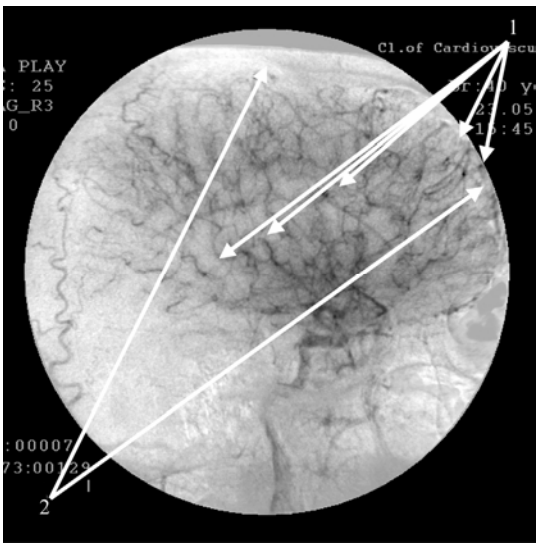
Figure 5. Angiogram of the left internal carotid of a 67-year old patient (12-year anamnesis); side projection; arterial opacification phase.



1. Multiple arteriovenous shunts; 2. Reduction of capillary opacification in the form of hypovascular zone in the frontoparietal and temporal regions.

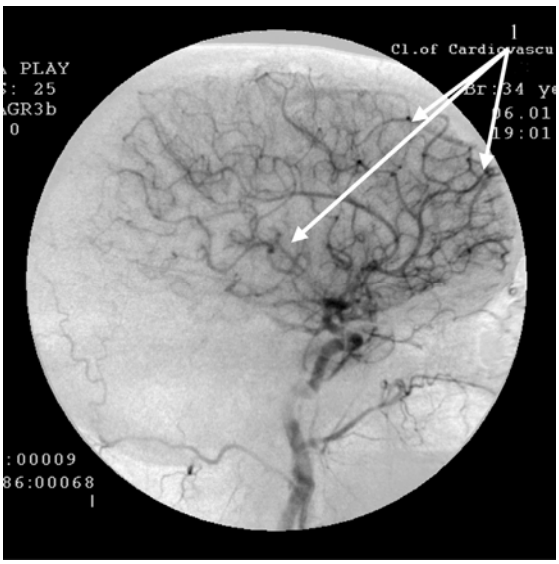
Figure 6. Angiogram of the left internal carotid of a 56-year old patient (7-year anamnesis); side projection; capillary opacification phase.

- Multiple arteriovenous shunts in the region of the arterial branches supplying the frontoparietal cortex, and in the region of the anterior choroid artery supplying the hippocampus, accompanied by early venous shunts - 47 (100%) patients (**Figures 6**, **7** and **8**).



1. Multiple arteriovenous shunts; 2. Development of hypovascular region.

Figure 7. Angiogram of the right internal carotid of a 40-year old patient (2-year anamnesis); side projection; capillary opacification phase.



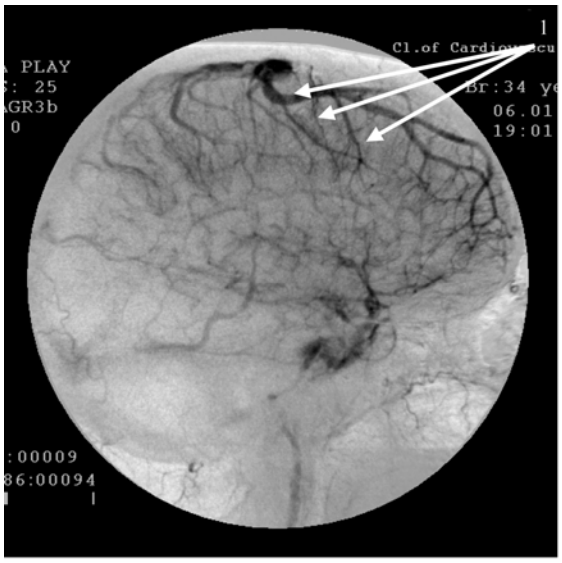
1. Multiple arteriovenous shunts.

Figure 8. Angiogram of the right internal carotid of a 34-year old patient (high-risk group); side projection; late arterial opacification phase.

- Anomalous venous congestion at the border of frontal and parietal lobe - 43 (91.5%) patients (**Figure 9**, **10**);
- The development of abnormal lateral veins in the frontoparietal region - 42 (89.3%) patients (**Figure 11**, **12**).

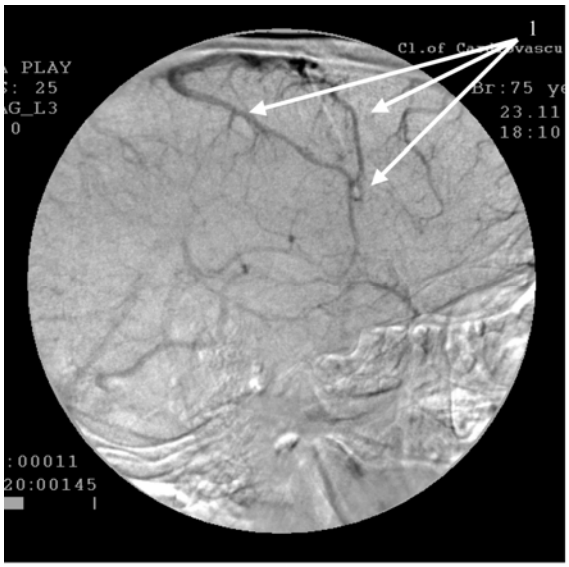
MUGA in the Control Group revealed (**Table 2**):

- Atherosclerotic changes in intra- and extracranial vessels - 57 (96.6%) patients;



1. Development of anomalous venous trunks in the frontoparietal region.

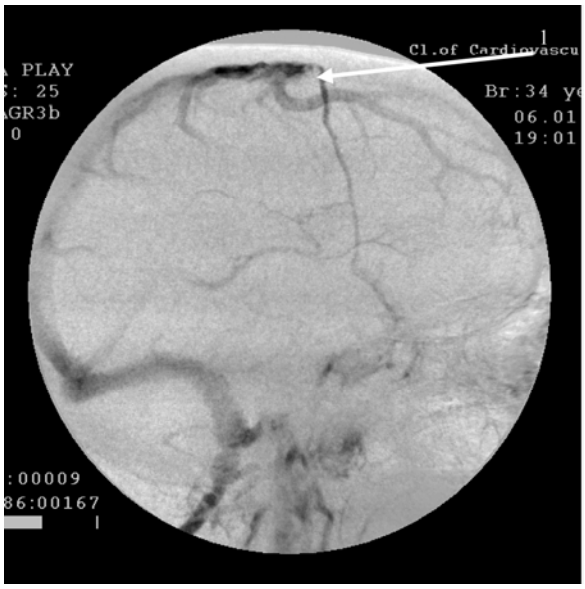
Figure 9. Angiography of the right internal carotid of a 34-year old patient (increased risk of AD development); side projection; venous opacification phase.



1. Development of anomalous venous trunks in the frontoparietal region.

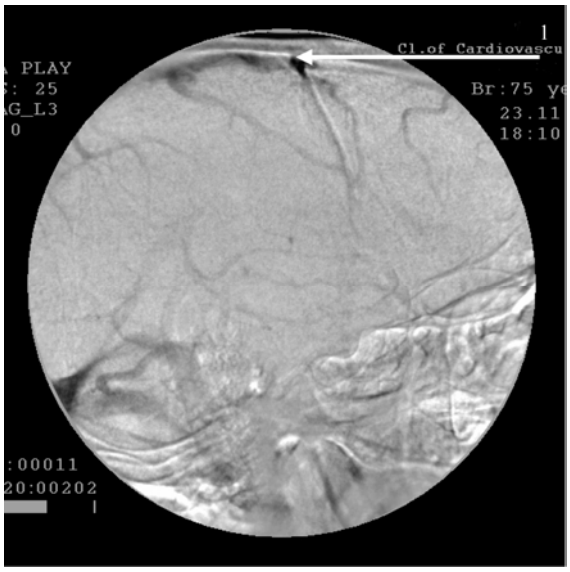
Figure 10. Angiography of the left internal carotid of a 75-year old patient (15-year anamnesis); side projection; venous pacification phase.

- A tendency towards increased looping of distal branches - 3 (5.1%) patients;
- Reduction of capillary contrast phase in the frontoparietal regions and hippocampus projection with formation of hypovascular zones was not detected in any case;
- Local arteriovenous shunts in the frontoparietal and temporal regions were not revealed in any case;
- Early venous discharge in the frontoparietal and temporal regions were not identified in any case;
- Existing arteriovenous shunts were scattered in nature, located at the level of the white substance of the brain and detected in 27 (45.8%) cases;



1. Development of congestion on the boundary of the frontoparietal region.

Figure 11. Angiography of the right internal carotid of a 34-year old patient (increased risk of AD development); side projection; venous opacification phase.



1. Development of congestion on the boundary of the frontoparietal region.

Figure 12. Angiography of the left internal carotid in 75-year old patient (12-year anamnesis); side projection; venous opacification phase.

Table 2. MUGA data.

Signs	Test group (Alzheimer's disease)	Control group (brain disorders other than Alzheimer's disease)	p (chi-square)
Number of patients	47	59	< 0.005
Atherosclerotic changes	0	57	< 0.005
Increased looping in distal regions of intracranial vessels	37	3	< 0.005
Reduction of capillary blood flow in frontoparietal region	47	0	< 0.005
Multiple arteriovenous shunts infrontoparietal and temporal regions	47	0	< 0.005
Multiple scattered arteriovenous shunts at the level of the white substance of the brain	0	27	< 0.005
Premature venous shunts in frontoparietal and temporal regions	47	0	< 0.005
Scattered premature venous shunts	0	28	< 0.005
Venous congestion on the boundary of frontal and parietal regions	43	0	< 0.005
Development of anomalous lateral veins in parietal region	42	0	< 0.005

The differences between the groups were identified by the analysis of the relevant contingency tables 2 × 2 by means of Pearson's chi-square test. The corresponding values of p are shown in the last column of the table. P-value = 0.05".

- Early venous shunts were diffuse in nature depending on the localization of arteriovenous shunts and were detected in 28 (47.5%) cases;
- Anomalous venous congestion at the border of frontal and parietal lobe was not detected in any case;
- Anomalous lateral veins in the frontoparietal region were not detected in any case;

Specific disorders of blood circulation and microcirculation in the hippocampus and frontoparietal cortex revealed among patients of the Test Group were named the "dyscirculatory angiopathy of Alzheimer's type" [33].

Interestingly, the severity of these disorders does not depend on the timing of the development of AD symptoms and severity of dementia, it is almost equally observed both among those running a risk of developing the disease and groups at its early and late clinical stages.

4. Discussion

The data obtained show that examined patients of the Test and Control Groups have clear differences of morphological and structural defects, as well as changes in angioarchitectonics and microcirculation in the brain.

Patients running a high risk of acquiring AD, as well as patients at different stages of the disease ranging from early to late ones have specific structural changes of atrophic character developing in the temporal lobes of the brain.

These changes are characterized by a decrease in pulp tissue of the temporal lobes and the hippocampus of 4% - 62% [10,12]. At early stages it is manifested in re- gional atrophy, and at late ones, atrophy leads to forma- tion of cavities. Besides, these changes are accompanied by local dilation of Sylvian fissure and subarachnoid space due to atrophy of the temporal and frontal lobes [13,16]. The degree of these changes is directly depend- ent on the stage of disease, the severity of dementia, and cognitive disorders [11,18,19].

Similar atrophic changes, localized in the temporal lobes of the brain, do not occur among patients of the Control Group with other lesions of the brain accompanied by the manifestations of dementia; similarly, they do not occur among patients of the Control Group who correspond to their age norm.

Simultaneously, AD leads to the development of some specific cardiovascular and microcirculatory abnormalities in the brain which we have named dyscirculatory angiopathy of Alzheimer's type [33]. These abnormalities are characterized by increased looping in the distal parts of intracranial arteries, reduction of capillary blood flow in the frontoparietal and temporal regions with the formation of hypovascular zones [22,32], the development of multiple arteriovenous shunts in the same brain regions. These changes lead to local early venous shunts and to simultaneous venous congestion on the border of the frontal and parietal regions [21,24]. The venous congestion is caused by impaired blood flow from the temporal and frontal-parietal regions which are caused by the reduction of the capillary bed. In turn, this leads to the formation of specific abnormal venous trunks [32].

All these changes lead to failure of blood supply in the

abovementioned brain regions and, consequently, to specific microcirculatory hypoperfusion [25,26] that may contribute to the deposition of abnormal proteins in brain tissue or the violation of their removal [28,29].

There is an opinion that at early stages of AD hyperperfusion occurs in the frontoparietal and temporal brain regions against the background of hypoperfusion [27]. These data were obtained in MRI studies. In fact, the authors observed no true hyperperfusion but an active discharge of blood through arteriovenous shunts which is a consequence of hypoperfusion caused by reduction of capillary blood flow.

We cannot exclude that the lesion of microvascular bed is associated with the symptoms of amyloid angiopathy and Morel's angiopathy [28], or possible paravasal amyloid deposits [21,23]. However, the discirculatory violations identified in the research affect not only the capillaries as they were described by F. Morel, but also arteries and veins. The severity of these abnormalities does not depend on the timing of symptoms, the severity of dementia or cognitive disorders. These abnormalities are observed both among patients running a high risk of acquiring the disease who have no clinical symptoms and among patients at early and late clinical stages of AD. This fact does not allow stating with certainty that the development of AD begins with amyloid deposition in the vascular wall, and only then its deposition in the brain tissue begins [24,33,35].

As a result, the question of what is primary arises: if it is congenital, or by some reason acquired, disorders of blood circulation and microcirculation that promote the development of AD, or if it is the disease itself that causes similar changes of the distal arterial, microcirculatory and venous bed in the brain [33]?

Atherosclerotic changes of intracranial blood vessels accompanied by calcium deposits in the walls of the arteries, the development of stenotic and occlusive lesions causing ischemic manifestations with the development of micro-and macro-cysts and the phenomena of leucoaraiosis are not characteristic for AD and practically never occur [24,33]. These changes with varying but high enough frequency and severity are found in the Control Group both among patients who correspond to their age norm and among those suffering from other types of atherosclerotic lesions, vascular dementia or Binswanger's or Parkinson's disease [33,36].

Control Group patients hardly ever have increased looping of distal intracranial arteries, or it is quite rare (5.8%) [13]. Besides, they do not have local reduction of the capillary bed with the depletion of the capillary blood flow in the temporal and frontoparietal regions with the formation of hypovascular zones in the same regions.

Early arteriovenous shunts do occur among patients of the Control Group, but they are not localized in the frontoparietal and temporal regions being scattered at the level of the white substance of the brain, and early venous discharge occurs in the same regions. Neither did patients of the Control Group have any marked venous stasis [33].

General changes among patients of Test and Control Groups are the signs of nonocclusive hydrocephaly and general atrophy of the cerebral cortex which are age-characteristic [34].

The research conducted has shown that such common and simple methods as SG of the brain and REG have their own place in the diagnosis of AD, but they prove not to be sufficiently effective for the differentiation from other pathological conditions of the brain.

On the contrary, CT combined with ATAA program and MUGA of the brain makes it possible to achieve significant results in diagnosing the disease. It is interesting to note that the use of CT, unlike MRI, is more promising as it provides a better opportunity to visualize calcium deposits in atherosclerotic tissues which to some extent allows differentiating the nature of the vascular lesion.

5. Conclusions

AD is characterized by a specific number of structural brain disorders which includes morphological changes of atrophic nature developing in the temporal lobes of the brain and the hippocampus, as well as violations in angioarchitectonics and microcirculation. These can be divided into the following sections:

1. Atrophic phenomena:
   - Atrophy of the temporal lobes of the brain and the hippocampus reaching in some cases up to 62%;
   - Dilation of Sylvian fissure mainly due to atrophy of the temporal lobes;
2. The phenomena of dyscirculatory angiopathy of Alzheimer's type:
   - Reduction of the capillary bed in the temporal and frontal-parietal regions of the brain;
   - The development of multiple arteriovenous shunts in the same regions;
   - Early venous discharge in the same regions;
   - Venous stasis with the development of abnormal venous trunks on the border of the frontal and parietal region;
   - Large looping of the distal branches of intracranial arteries.

These changes can be traced not only among patients at advanced stages of the disease but also among those at its earliest and preclinical stages. Timely detection of these changes is of great importance for examining pa-

tients with a high risk of acquiring AD and patients at early clinical stages, as it will make it possible to begin treatment sooner and thus achieve more pronounced and persistent results. Besides, detecting these changes is important for the differentiation of AD from other pathological conditions of the brain accompanied by cognitive impairment and dementia.

A combination of CT of the brain with ATAA program and cerebral MUGA can quite easily be used in a modern hospital, and they have a low cost.

A relative disadvantage of the proposed method is the usage of a fairly complex invasive multi-gated angiography (MUGA) requiring a percutaneous arterial puncture, catheterization of carotid and vertebral arteries with subsequent introduction of radiopaque substance. MUGA is the "golden standard" for diagnosis of the brain vascular system yet. However, in future, improved CT, MRI and PET will allow receiving high-quality, high-resolution angiographic images of arterial, capillary and venous contrast phases by means of less invasive and simpler and more benign methods.

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