Medical Research Archives

ESMED
European Society of Medicine

OPEN ACCESS

Published: July 31, 2022

Citation: Ivan V. Maksimovich, 2022. Transcatheter Intracerebral Laser Photobiomodulation Therapy Reduces Dementia and Cognitive Impairment in Patients with Various Stages of Alzheimer's disease, Medical Research Archives, [online] 10(7). https://doi.org/10.18103/mra.v10i7.2938

DOI
https://doi.org/10.18103/mra.v10i7.2938

ISSN: 2375-1924

RESEARCH ARTICLE

Transcatheter Intracerebral Laser Photobiomodulation Therapy Reduces Dementia and Cognitive Impairment in Patients with Various Stages of Alzheimer's disease

Ivan V. Maksimovich*[1]

[1]Clinic of cardiovascular diseases named after Most Holy John Tobolsky, Building 2, Block 15, 6th Lazenki Str., 119619 Moscow, Russia

*carvasc@yandex.ru

ABSTRACT

Background: Alzheimer's disease (AD) is the leading neurodegenerative disease associated with dementia and cognitive impairment. A major achievement in AD treatment was the use of lasers with low output power of the red or near-infrared spectral region, which was named Photobiomodulation Therapy (PBMT).

Aims: This study investigates the effect of PBMT on regression of dementia and cognitive impairment among patients with various AD stages.

Methods: For the study, 97 patients with previously diagnosed AD, aged 34-80 (mean age 67.5), 34 (35.05%) men, 63 (64.95%) women, were selected. According to AD severity, the patients were subdivided: preclinical stage TDR-0 - 10 (10.31%), mild stage TDR-1 - 28 (28.87%), moderately severe stage TDR-2 - 42 (43.30%), severe stage TDR-3 - 17 (17.52%).

Test Group - 48 (49.48%) patients, 17 (35.42%) men, 31 (54.58%) women, underwent Transcatheter Intracerebral Laser Photobiomodulation Therapy (PBMT).

Control Group - 49 (50.32%) patients, 16 (32.65%) men, 33 (67.35%) women, underwent conservative treatment with Memantine and Rivastigmine.

Results:

Test Group. Due to angiogenesis and neurogenesis stimulation with Transcatheter Intracerebral Laser Photobiomodulation Therapy (PBMT), all the patients had an improvement in cerebral blood supply and microcirculation and a decrease in cerebral involutive changes. Consequently, all the patients showed reduced dementia and improved cognitive abilities. The vast majority of the patients began to correspond to the group of a milder AD stage.

Control Group. No persistent expressed positive dynamics. Partial improvement was obtained only among patients with early AD stages.

Conclusion: Transcatheter Intracerebral Laser Photobiomodulation Therapy (PBMT) is an effective, physiologically based method of stimulating cerebral angiogenesis and neurogenesis. As a result of such a complex impact, patients with various AD stages have cerebral capillary collateral revascularization, their tissue metabolism improves, and regenerative processes develop in the cerebral tissue. Tissue regeneration leads to an increase in the volume of the temporal and frontoparietal sections. Clinically, this leads to a stable decrease in dementia level, cognitive functions restoration, and improved quality of patients' life. The resulting clinical effect lasts for many years.

Conservative treatment with Memantine and Rivastigmine is not effective enough.

Keywords: Alzheimer's Disease; AD; Photobiomodulation Therapy; PBMT; Transcatheter Intracerebral Laser Photobiomodulation Therapy; Reducing dementia; Reducing cognitive impairment.

Introduction:

Alzheimer's disease (AD) occupies a leading position among neurodegenerative diseases accompanied by the development of dementia and cognitive disorders. AD accounts for 60% to 80% of all cases of dementia. In 2022, in the United States, 6.5 million patients aged 65 and older suffered from AD. Given the progress of the disease, it is estimated that in 2060 this figure may increase to 13.8 million people. It should be noted that the number of patients suffering from AD at a younger age was not taken into account. In 2019, 121,499 deaths from this disease were officially registered in the United States, in 2020 this figure increased to 133,382 [1, 2].

The development of this disease has a complex character, which has not been fully studied to date [3, 4, 5]. According to recent studies, it has been established that angioarchitectonics and microcirculation disorders in the brain play an important role in the development of AD [6-14]. It cannot be ruled out that these disorders may be congenital or hereditary [7, 11]. These changes in angioarchitectonics and microcirculation are related to cerebral small vessel disease (CSVD), but they occur only in patients with AD and are manifested in Alzheimer's type dyscirculatory angiopathy (DAAT) [7, 11, 12-18]. The development of DAAT leads to AD-specific changes in the arterial, microcirculatory, and venous bed. These changes contribute to the development of metabolic disorders of amyloid beta (Aβ) and tau protein [7-14, 15-19].

In AD, vascular and microcirculatory changes appear 20-30 years before the clinical manifestations of the disease and are observed even at an early age in patients' relatives and descendants [1, 11, 12, 20, 21].

The leading role in the development of DAAT is played by the reduction of cerebral capillaries [7-13, 16-18]. In the hippocampus and temporal region, and, further, in the frontoparietal regions of the brain, are observed thinning of capillaries, a decrease in their branching, and a decrease in their number, which causes the formation of hypovascular zones [7, 9–13].

These changes lead to a decrease in the arterial inflow in the cerebral tissue and cause AD-specific changes in hemodynamics [7, 10, 16-18]. The blood flowing through the arterial branches cannot pass through the reduced capillary bed, which causes increased "tortuosity" of the inracerebral arterial branches [7, 11]. Due to the reduction of the capillary bed in the cerebral tissue, large anomalous arteriovenous shunts open, through which arterial blood flows into the venous bed [7, 11, 21]. Consequently, the venous bed overflows in the temporal and frontoparietal regions, which causes the interruption of the venous outflow and the development of venous congestion. Due to the development of arteriovenous shunts and impaired venous outflow, the decrease in cerebral hemodynamics is even more pronounced [11, 21].

It is important to note that in other neurodegenerative and cerebrovascular diseases, a combination of such pathological changes in angioarchitectonics and microcirculation does not occur [11, 18, 21].

Such serious changes in the cerebral arterial, microcirculatory and venous bed lead to the development of hypoxia specific for AD, cause the death of mitochondria in the cells of the smooth endoplasmic reticulum and the Golgi apparatus, as well as the loss of synapses, degeneration and death of neurons [10, 11, 13, 16-18, 22-27]. As a result, it causes a complex lesion of the neurovascular unit (NVU) [8-10, 27, 28]. The combination of these changes lead to impaired permeability of the blood-brain barrier (BBB) [15, 28, 29].

AD-specific hypoperfusion and hypoxia get involved in amyloid beta metabolism. It leads to its impaired metabolism, a decrease in excretion and an increase in accumulation, which causes the deposition of amyloid beta in the cerebral tissue and vascular wall [8, 10, 14, 28]. Such changes cause a decrease in microvascular elasticity and the narrowing of the lumen of intracerebral capillaries, which reduces intracerebral blood flow and leads to an even greater increase in hypoxia and the development of AD-specific neurodegeneration[14, 22-27, 30]. Over time, these changes cause the development and progression of AD [21, 24, 25].

When developing new methods of treating AD, it is necessary to strive to improve capillary blood supply and stimulate regenerative processes in the cerebral tissue, which requires complex methods.

A major achievement in addressing the issue of complex treatment of AD was the idea of using laser with low output power of the red or near-infrared spectral region (600-1100 nm). This direction in medicine is called laser Photobiomodulation Therapy (PBMT) [31].

Experimental and clinical studies aimed at the treatment of AD and other neurodegenerative and ischemic cerebral lesions have shown that the use of lasers with low output power has a complex impact on the brain. PBMT stimulates metabolical processes in the cerebral tissue; restores the exchange of adenesine triphosphate (ATP) in the mitochondria of neurons; stimulates natural angiogenesis, thereby causing collateral capillary revascularization; simultaneously stimulate

neurogenesis, thereby restoring normal cerebral tissues. Clinically, this complex impact leads to a decrease in the level of dementia, the restoration of mental and cognitive functions, and improves daily life [32-39].

PBMT is subdivided into transcranial [32, 33, 36], intranasal (often combined with transcranial) [35, 38] and transcatheter intracerebral treatment methods [40].

In our previous research, to determine cerebral involutive changes in AD, we devised the ATAA (Advance Tomo Area Analysis) digital processing program for CT and MRI images. This digital program allows you to determine the percentage decrease in the volume of the tissue of the temporal lobes compared to their normal volume, which shows the severity of involutive and atrophic changes [7, 11, 41-43]. The digital scale "The Tomography Dementia Rating scale" (TDR) has also been developed, with the help of which, in accordance with the severity of atrophic changes in the temporal lobes detected by CT and MRI, the level of dementia in AD was morphometrically determined [42-44].

According to the TDR scale, the AD patients were divided into groups: TDR-0 preclinical stage AD (temporal lobes atrophy 4-8%), TDR-1 mild stage AD (temporal lobes atrophy 9-18%), TDR-2 moderately severe stage AD (temporal lobes atrophy 19-32%), TDR-3 severe stage AD (temporal lobes atrophy 33-62%) [44].

To determine changes in cerebral capillary blood flow during cerebral MUGA, a digital image processing program "Angio Vision" was developed. This program allows you to determine the density of capillary blood flow in the corresponding contrast phase [7, 11, 24, 40, 43].

The previously conducted research has made it possible to develop the Transcatheter Intracerebral Laser Photobiomodulation Therapy (PBMT) method, the essence of which is as follows [45, 46].

In a catheterization laboratory, under local anesthesia and fluoroscopic control, guiding catheters are placed, which are led to intracerebral arterial branches approaching hypovascular zones [11, 24]. Through these catheters, is coaxially passed a flexible laser fiber optic light guiding instrument, 25-100 micrometers in diameter and connected to a laser apparatus. Laser PBMT is performed using a helium-neon laser ULF-01 (Russia) [40, 45, 46]. Parameters of intracerebral laser exposure: wavelength of 632.8 nanometers; laser output power of 25-45 mW; fiber output power of 24-44 mW; the duration of the therapeutic effect of 1200-2400 seconds; the diameter of the laser beam in the vessel of 1-2 mm; the average dose during laser exposure of 29-106 J [41]. With the transcatheter intracerebral approach, the depth of penetration of laser energy into cerebral tissues is 20-40 mm. [41]. In this connection, the power density and energy density have a variable value [30, 41, 45, 46].

PBMT is performed on the right and left hemispheres. If necessary, a solution of a radiopaque agent (Omnipaque 350) is introduced in small doses for fluoroscopic control.

At the end of PBMT, repeated cerebral MUGA is performed using the digital image processing program "Angio Vision". This program allows assessing changes in cerebral arterial and capillary blood flow. The results of MUGA are used to assess the severity of intracerebral angiogenesis, the degree of collateral and microcirculatory revascularization [24, 40, 41, 45, 46]. The program "Angio Vision" in real time, in the appropriate contrast phase, automatically registers changes in the vascular image.

The clinical application of the method has shown that the Transcatheter intracerebral laser PBMT stimulates cerebral angiogenesis and neurogenesis, thereby improving blood circulation and inducing regenerative processes in the brain [30, 41, 45, 46].

The present study is devoted to the study of the effect of this treatment method on the reduction of dementia and cognitive impairment in patients with various stages of AD.

Methods

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

Patient selection:

- Consent of the patients and their relatives for examination and appropriate treatment;
- The absence of concomitant diseases that could, because of the severity of the condition, prevent the examination and treatment;
- A satisfactory somatic condition of the patients, allowing for the examination and treatment;
- The presence of cerebral involutive and microcirculatory changes in the temporal and frontoparietal regions corresponding to AD;
- The presence of signs of dementia and cognitive disorders corresponding to AD;

For the study, 97 patients previously diagnosed with AD and aged from 34 to 80 (mean age 67.5) were selected, men - 34 (35.05%), women - 63 (64.95%).

Test group - 48 (49.48%) patients.
Control group - 49 (50.52%) patients.
In all the selected patients in the test and control groups, the severity of dementia, the severity of cognitive impairment, physical condition were similar, in accordance with the stage of AD.
Data collection was carried out immediately upon admission of the patients to the clinic. Follow-up was carried out for 5 years for the control group and for 7-15 years for the patients in the test group.
The results data were processed statistically using the Statsoft Statistica 10 software (StatSoft Inc., USA). In the test and control groups, a contingency table analysis was made by means of the Chi-square test to compare the characteristics of Before / After treatment.

Patient examination plan.
Examinations of patients were carried out according to the following scheme:

- The clinical severity of dementia was assessed using The Clinical Dementia Rating scale (CDR) [47];
- Cognitive impairment was assessed using the "Mini-Mental State Examination" (MMSE) [48];
- Cerebral blood flow and cerebral microcirculation were assessed using scintigraphy (SG) in static and dynamic modes;
- Cerebral perfusion blood filling was assessed using rheoencephalography (REG);
- Laboratory examination was carried out in accordance with the criteria of interventional neuroangiology;

(The above examinations were carried out upon the patients' admission, then at discharge, then at intervals of 6-12 months for seven or more years).

- Cerebral structural and morphological changes were assessed using CT and MRI. The examinations were performed using the digital image processing program ATAA (Advance Tomo Area Analysis) and digital morphometric scale "The Tomography Dementia Rating scale" (TDR).

(CT and MRI were performed upon the patients' admission, then, to assess the dynamics of cerebral changes, with an interval of 6-12 months. The examination was carried out in independent laboratories);

- The intracerebral vascular and capillary bed was assessed using cerebral multi-gated angiography (MUGA) using the digital image processing program "Angio Vision". The primary investigation was conducted upon a patient's admission to the clinic, repeated immediately after PBMT (for the test group patients). Further studies were carried out at intervals of 2 to 7 years. In selected cases, MSCT angiography (MSCTA) or MR angiography (MRA) were used.

The examination results are presented in Table 1.

Patients Treatment Methods.
The test group - 48 (51.61%) patients: men - 17 (35.42%), women - 31 (54.58%) - underwent Transcatheter Intracerebral Laser Photobiomodulation Therapy (PBMT).
In patients with preclinical AD (TDR-0), the interventions were performed against the background of increased signs of memory loss. In patients with clinical stages of AD (TDR-1, TDR-2, TDR-3), the interventions were carried out in the period from 1 to 12 years from the date of AD diagnosis.
After Transcatheter Intracerebral Laser Photobiomodulation Therapy (PBMT), the patients received disaggregant, anticoagulant, antioxidant, vasodilating and nootropic therapy. The patients received: Aspirin, depending on the parameters of the blood coagulation system Heparin, indirect anticoagulants. Also, infusionally Pentoxifylline 100 mg, Complamin 150 mg., Inosin 200 mg., Nootropil (Piracetam) 1200 mg. (or Gliatilin 1000 mg.). The number of infusions was 10-15, with subsequent transfer to oral forms. In the subsequent period, the courses of pills were repeated twice a year. The patients did not receive the specific therapy intended for the treatment of AD.

The control group - 49 (50.52%) patients: men - 16 (32.65%), women - 33 (67.35%) - conservative treatment was carried out.
The conducted conservative treatment was performed according to generally accepted schemes [49, 50]. Patients in TDR-0 group received: Nootropil (Piracetam) 2400 mg per day (in courses of 3-4 months), or Gliatilin 1200 mg. per day (courses of 4-6 months). Patients from groups TDR-1, TDR-2, TDR-3 received Memantine 5-20 mg. per day, or Rivastigmine 3-12 mg. per day. Similarly, to the test group patients, the control group patients received Pentoxifylline 100 mg, Complamin 150 mg., Inosin 200 mg by infusion. The number of infusions was 10-15, with subsequent transfer to oral forms in courses of 2-3 months, which were repeated twice a year.

Table 1. Results of patient examination.

CHARACTERISTIC OF IDENTIFIED CHANGES	Test Group N - 48	Control Group N - 49
Clinical Dementia Determination		
CDR – 1	16	12
CDR – 2	21	21
CDR – 3	7	10
Cognitive Disorders		
Decrease to 26-28 MMSE points	4	6
Decrease to 20-25 MMSE points	16	12
Decrease to 12-19 MMSE points	21	21
Decrease to 7-11 MMSE points	7	10
Morphometric determination of dementia stages on the TDR scale according to CT and MRI data		
TDR – 0 (temporal lobes atrophy 4-8%)	4	6
TDR – 1 (temporal lobes atrophy 9-18%)	16	12
TDR – 2 (temporal lobes atrophy 19-32%)	21	21
TDR – 3 (temporal lobes atrophy 33-62%)	7	10
Assessment of cerebral blood flow according to SG data		
Decreased blood flow in cerebral hemispheres	48	49
Assessment of cerebral perfusion blood supply according to REG data		
Decreased volumetric pulse blood supply	48	49
Assessment of manifestation of Dyscirculatory angiopathy of Alzheimer's type (DAAT) according to MUGA		
Reduction of capillaries in temporal regions	48	49
Development of hypovascular zones in temporal regions	48	49
Decrease in arterial inflow in temporal regions	48	49
Development of arteriovenous shunts in temporal regions	48	49
Development of venous stasis and impaired venous outflow	44	43
Development of increased tortuosity of intracerebral arteries	38	38

Results

The Test Group.

Immediate results.

Immediately after Transcatheter Intracerebral Laser Photobiomodulation Therapy (PBMT), according to digital MUGA, a positive result, manifested in pronounced cerebral angiogenesis, collateral and capillary revascularization, as well as reduction of arteriovenous shunts and improvement in venous outflow, was obtained in all 48 (100%) patients (Fig. 1A, 1B, Fig. 3A, 3B).

There were no complications observed after Transcatheter Intracerebral Laser Photobiomodulation Therapy (PBMT).

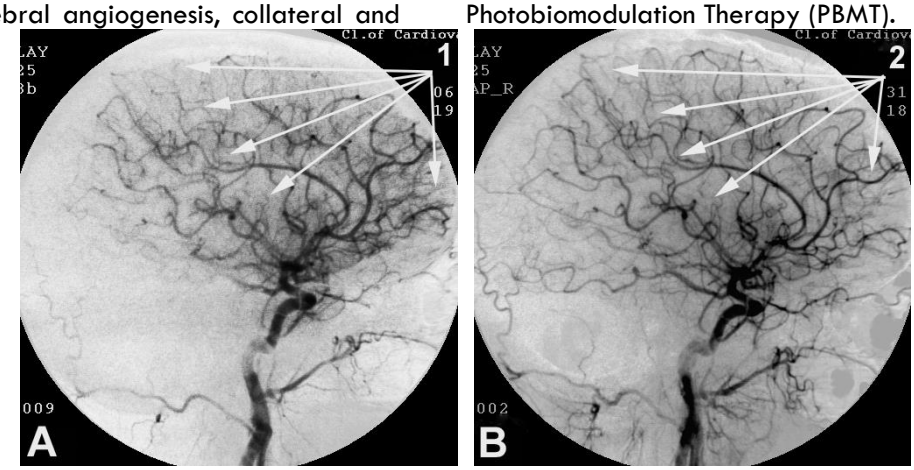


FIGURE 1. Patient P., 34 years old, female (TDR-0) Left internal carotid artery MUGA before and after transcatheter intracerebral laser PBMT.

A - Arterial phase before transcatheter intracerebral laser PBMT.

1 - Hypovascular areas in temporal and frontoparietal regions.

B - Arterial phase after transcatheter intracerebral laser PBMT.

2 - Stimulation of atheiogenesis, collateral and capillary bed recovery in temporal and frontoparietal region.

Early follow-up (1-6 months) after Transcatheter Intracerebral Laser PBMT.

Patients with preclinical AD stage (TDR-0).

According to CT and MRI with digital image processing, an increase in normal tissue and volume of temporal lobes, the narrowing of the Sylvian fissures, and the narrowing of the subarachnoid space were obtained in all 4 (100%) patients.

According to SG and PEG data, restoration of blood flow velocity, as well as pulse blood filling in the cerebral hemispheres, was obtained in all 4 (100%) patients.

Clinically, in all 4 (100%) patients, a positive trend was obtained, manifested by improved memory and restoration of cognitive functions to the level of 28-30 points according to MMSE.

Patients with mild AD stage (TDR-1).

According to CT and MRI with digital image processing, signs of an increase in normal tissue and volume of the temporal lobes, narrowing of the Sylvian fissures, and contraction of the subarachnoid space were obtained in all 16 (100%) patients.

According to SG and REG data, restoration of blood flow velocity, as well as pulse blood filling in the cerebral hemispheres, were obtained in all 16 (100%) patients.

Clinically, all 16 (100%) patients showed positive dynamics, manifested by a decrease in the level of dementia and restoration of cognitive functions. At the same time, in 6 (37.50%) cases, an improvement in cognitive functions was noted to the level of 25-26 points, and in 10 (62.50%) cases, to the level of 27-28 points according to MMSE.

Patients with moderately severe AD stage (TDR-2).

According to CT and MRI with digital image processing, signs of an increase in the normal tissue and volume of the temporal lobes, the narrowing of the Sylvian fissures, and the reduction of the subarachnoid space were obtained in all 21 (100%) patients.

According to SG and REG data, signs of restoration of blood flow velocity, as well as pulse blood filling in the cerebral hemispheres, were obtained in all 21 (100%) patients.

Clinically, in all 21 (100%) patients, a positive trend was obtained, manifested by a decrease in the level of dementia and the restoration of cognitive functions. At the same time, in 12 (57.14%) cases, an improvement in cognitive functions was noted to the level of 19-20 points, and in 9 (42.86%) cases to the level of 21-22 points according to MMSE.

Patients with severe AD stage (TDR-3).

According to CT and MRI with digital image processing, signs of an increase in normal tissue and volume of the temporal lobes, the narrowing of the Sylvian fissures, and a decrease in the subarachnoid space were obtained in all 7 (100%) patients.

According to SG and REG data, partial restoration of blood flow velocity and pulse blood filling in the cerebral hemispheres was obtained in all 7 (100%) patients.

Clinically, all 7 (100%) patients showed signs of positive dynamics manifested by a decrease in the level of dementia and an improvement in cognitive functions to the level of 11-12 points according to MMSE.

Long-term follow-up (1-7 years) after Transcatheter Intracerebral Laser PBMT.

Patients with preclinical AD stage (TDR-0).

According to CT and MRI with digital image processing 1 year after PBMT, normal tissue and volume of the temporal lobes were restored to the appropriate age norm, the narrowing of the Sylvian fissures and the restoration of the subarachnoid space were obtained in all 4 (100%) patients. In longer than one-year periods, positive dynamics persisted throughout the entire follow-up period in all 4 (100%) patients (Fig. 2A, 2B, 2C, 2D, 2E).

According to SG and REG data, 1 year after PBMT, normalization of blood flow velocity and pulse blood filling in the cerebral hemispheres was obtained in all 4 (100%) patients. In longer than one-year periods, positive dynamics persisted throughout the entire observation period in all 4 (100%) patients.

Clinically, 1 year after PBMT, all 4 (100%) patients received stable positive dynamics - complete recovery of memory and cognitive functions to the level of 28-30 points according to MMSE. In a more distant period of over 1 year, the obtained positive dynamics was maintained in all cases throughout the entire observation period. Based on this, all 4 (100%) patients were considered to be practically healthy people without dementia and cognitive disorders (Table. 2).

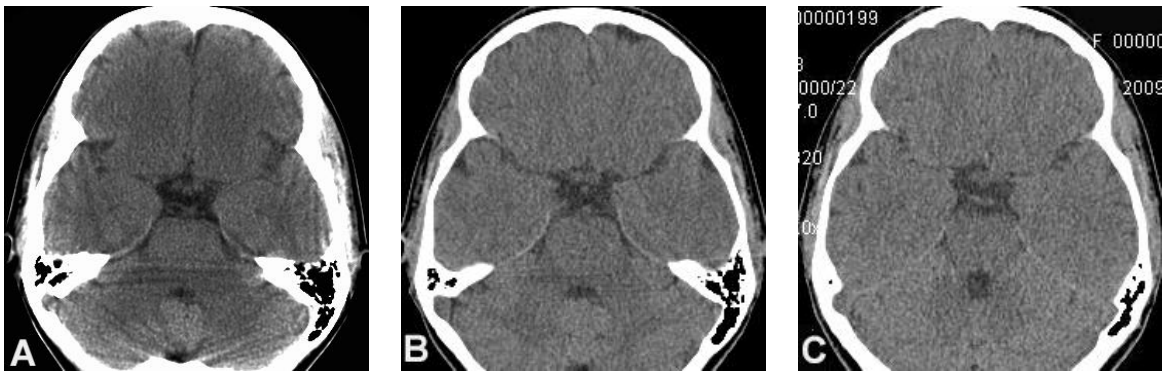
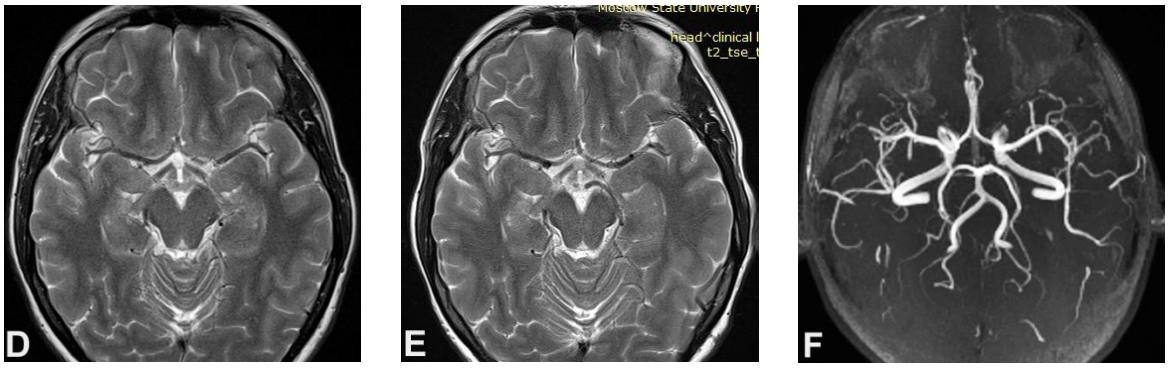


FIGURE 2. The same patient P., 34 years old, female (TDR-0): CT and MRI of the brain before and after transcatheter intracerebral laser PBMT.

A – CT before transcatheter intracerebral laser PBMT. Atrophy of the right temporal lobe - 9%, left - 7%.

B - CT 1 year after transcatheter intracerebral laser PBMT. Stimulation of neurogenesis, decrease in the atrophy of the right temporal lobe of up to 4%, left up to 3%, narrowing of the Sylvian fissures.

C - CT 2 years after transcatheter intracerebral laser PBMT. Progression of neurogenesis, restoration of the volume of the temporal lobes to the age norm, further narrowing of the Sylvian fissures.



D - MRI 6 years after transcatheter intracerebral laser PBMT. Complete restoration of the temporal lobes, the absence of negative dynamics.

E - MRI 15 years after transcatheter intracerebral laser PBMT. Complete restoration of the temporal lobes, the absence of negative dynamics.

F - MRA 15 years after transcatheter intracerebral laser PBMT. Normal blood supply to the brain.

Patients with mild AD stage (TDR-1).

According to CT and MRI with digital image processing, 1 year after PBMT, temporal lobe atrophy decreased by 8-10% in all 16 (100%) patients. After 2-4 years, a further decrease in the atrophy of the temporal lobes by another 4-5.5% was obtained in 13 (81.25%) cases, which led to an almost complete restoration of the volume of the normal tissue of the temporal lobes to the corresponding age norm. The narrowing of the Sylvian fissures and the restoration of the subarachnoid space accompanied the process.

According to SG and REG data, 1 year after PBMT, normalization of blood flow velocity and pulse blood filling in the cerebral hemispheres was obtained in all 16 (100%) patients.

Clinically, 1 year after PBMT, all 16 (100%) patients showed persistent positive dynamics, manifested in the absence of the signs of dementia, and persistent recovery of cognitive functions to the level of 27-28 points according to MMSE. In a more distant period of over 1 year, the obtained positive dynamics persisted throughout the entire observation period in all cases. Based on this, all 16 (100%) patients, in accordance with the criteria listed above, by definition, began to be related to TDR-0 group (Table. 2).

Patients with moderately severe AD stage (TDR-2).

According to CT and MRI with digital image processing, 1 year after PBMT, temporal lobe atrophy decreased by 5-10% in all 21 (100%) patients, which was accompanied by the narrowing of the Sylvian fissures and a decrease in the subarachnoid space. After 2-3 years, a further decrease in atrophy of the temporal lobes by another 4-5.5% was obtained in 12 (57.14%) cases (Fig. 3A, 3B, 3C). In 9 (42.86%) cases, no further pronounced reduction in involutive changes was obtained.

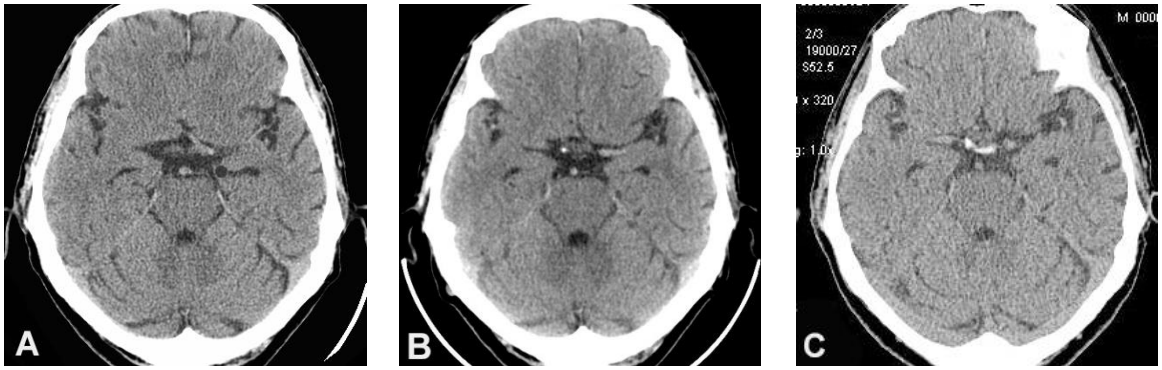
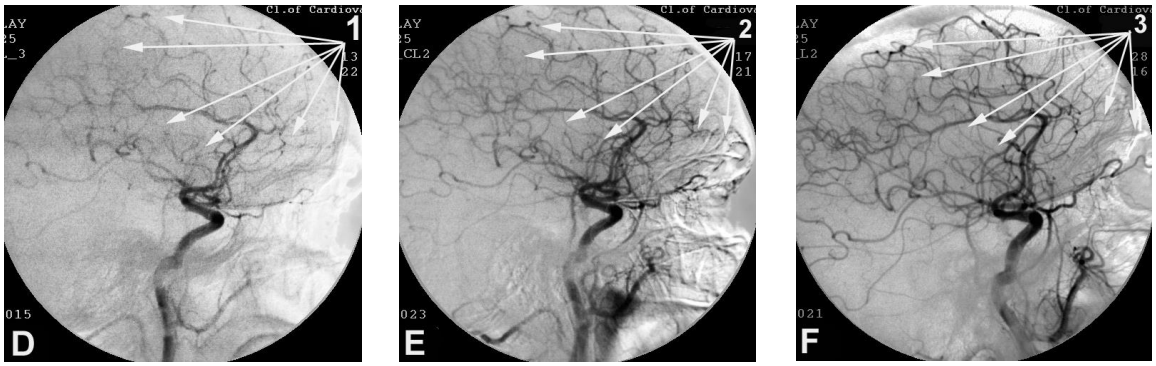


FIGURE 3. Patient T., 61 years old, male (TDR-2): CT scan of the brain and MUGA of the left internal carotid artery before and after transcatheter intracerebral laser PBMT.

A - CT before transcatheter intracerebral laser PBMT. Reduction in the volume of the temporal lobes: on the left by 22%, on the right by 28%.

B - CT 1 year after transcatheter intracerebral laser PBMT. Stimulation of neurogenesis, restoration of the volume of the temporal lobes: on the left by 10%, on the right by 12%.

C - CT 5 years after transcatheter intracerebral laser PBMT. Progression of neurogenesis, restoration of the volume of the temporal lobes to the age norm.



D - MUGA Arterial phase before transcatheter intracerebral laser PBMT.

1 - Hypovascular zones in the temporal and frontoparietal regions.

E - MUGA Arterial phase after transcatheter intracerebral laser PBMT.

2 - Stimulation of angiogenesis, restoration of the collateral and capillary bed in the temporal and frontoparietal regions.

F – MUGA Arterial phase 5 years after transcatheter intracerebral laser PBMT.

3 - Further progression of angiogenesis, strengthening of the collateral and capillary bed in the emporal and frontoparietal regions.

According to SG and REG data, 1 year after PBMT, positive dynamics of blood flow velocity and pulse blood filling in the cerebral hemispheres were obtained in all 21 (100%) patients.

Clinically, 1 year after PBMT, all 21 (100%) patients showed stable positive dynamics, manifested in a decrease in the level of dementia and an improvement in cognitive functions to the level of 21-22 points according to MMSE. After 2-3 years, a further decrease in the level of dementia and restoration of cognitive functions to the level of 23-25 MMSE points was obtained in 12 (57.14%) cases. Cognitive functions remained at the same level of 21-22 MMSE points in 9 (42.86%) cases (Table 2). In this regard, 16 (76.19%) patients, by definition, began to be related to TDR-1 group, 5 (23.81%) patients remained in TDR-2 group. Four years after the treatment, there was a tendency to a gradual decrease in cognitive functions in all 21 (100%) patients.

Patients with severe AD stage (TDR-3).

According to CT and MRI with digital image processing, 1 year after PBMT, a decrease in atrophy of the temporal lobes was obtained in all 7 (100%) patients, which was accompanied by the narrowing of the Sylvian fissures and the subarachnoid space. Of these, a decrease in the atrophy by 10-12% was obtained in 5 (71.43%) cases, by 6-8% - in 2 (28.57%) cases.

According to SG and REG data, 1 year after PBMT, the preservation of positive dynamics of blood flow

velocity and pulse blood filling in the cerebral hemispheres was obtained in all 7 (100%) patients. Clinically, 1 year after PBMT, all 7 (100%) patients showed persistent positive dynamics, manifested by a decrease in the level of dementia. The improvement in cognitive functions to the level of 11-14 points according to MMSE was obtained in 4 (57.14%) cases, to the level of 15-19 MMSE points was obtained in 3 (42.86%) cases. On this basis, 5 (71.43%) patients began to be related, by definition, to TDR-2 group, and 2 (28.57%) patients remained in TDR-3 group (Table 2). After 2-2.5 years after the treatment, there was a tendency towards an increase in dementia and a decrease in cognitive functions.

Repeated cerebral MUGA, MSCTA or MRA within 2 to 10 years after transcatheter intracerebral PBMT was performed in 10 (20.83%) patients from the test group. Preservation and further progression of angiogenesis, accompanied by cerebral collateral and capillary revascularization, was obtained in all 10 (100%) cases (Fig. 1A, 1B, 2F, Fig. 3D, 3E, 3F).

Table 2. Dynamics of changes in the severity of dementia and cognitive impairment in test group patients in the long-term period after the treatment.

Signs of dementia and cognitive impairment	**Before treatment n-48**	**After treatment n-48**	**p (chi-square)**
Practically healthy (MMSE - 29-30 points)	**0**	**4**	**p=0.00130**
TDR- 0 (MMSE - 26-28 points)	**4**	**16**	
TDR- 1 (MMSE - 20-25 points)	**16**	**16**	
TDR- 2 (MMSE - 12-19 points)	**21**	**10**	
TDR- 3 (MMSE - 7-11 points)	**7**	**2**	

Post-treatment indicators significantly differed from pre-treatment indicators in each group ($p < 0.05$). The statistical significance of the results was reliable in the test group (p=0,00130).

Control group

Immediate results.

Immediately after a course of conservative treatment, signs of improvement in cognitive functions were obtained in all 6 (100%) patients with preclinical AD (TDR-0) and in all 12 (100%) patients with mild AD (TDR-1). In patients with moderately severe AD stage (TDR-2) and severe AD stage (TDR-3), no clear positive dynamics was obtained.

Early observation period (1-6 months) against the background of conservative treatment.

Patients with preclinical AD stage (TDR-0).

According to CT and MRI with digital image processing, structural cerebral changes were not obtained in any of the 6 cases.

According to SG and REG data, signs of improvement in blood flow velocity and pulse blood filling in the cerebral hemispheres were obtained in all 6 (100%) patients.

Clinically, all 6 (100%) patients showed a tendency to memory improvement, as well as signs of restoration of cognitive functions to the level of 27-28 points according to MMSE.

Patients with mild AD stage (TDR-1).

According to CT and MRI with digital image processing, structural cerebral changes were not obtained in any of the 12 cases.

According to SG and REG data, signs of improvement in blood flow velocity and pulse blood filling in the cerebral hemispheres were obtained in all 12 (100%) patients.

Clinically, all 12 (100%) patients showed signs of stabilization.

Patients with moderately severe AD stage (TDR-2).

According to CT and MRI with digital image processing, structural cerebral changes were not obtained in any of the 21 cases.

According to SG and REG data, signs of improvement in blood flow velocity and pulse blood filling in the cerebral hemispheres were obtained in all 21 (100%) patients.

Clinically, 15 (71.43%) patients showed a tendency to a further increase in dementia and a decrease in cognitive functions. The absence of dynamics was observed in 6 (28.57%) cases.

Patients with severe AD stage (TDR-3).

According to CT and MRI with digital image processing, structural cerebral changes were not obtained in any of the 10 cases.

According to SG and REG data, signs of improvement in blood flow velocity and pulse blood

filling in the cerebral hemispheres were obtained in all 10 (100%) patients.
Clinically, all 10 (100%) patients showed a tendency to a further increase in dementia and a decrease in cognitive functions.

Long-term observation period (1-5 years) against the background of conservative treatment.

Patients with preclinical AD stage (TDR-0).
According to CT and MRI with digital image processing, in 2 years, no signs of increasing cerebral involutive changes were obtained in 1 (16.67%) case. Insignificant signs of an increase in the involutive changes were observed in 3 (50.00%) cases. A significant increase in involutive changes in the temporal lobes with a decrease in their tissue volume by 14-18% was observed in 2 (33.33%) cases.
According to SG and REG data, moderate positive dynamics of blood flow velocity and pulse blood filling in the brain persisted in all 6 (100%) patients.
Clinically, all 6 (100%) patients within 2 years after the start of the conservative treatment showed improvement in memory and stabilization of cognitive functions within 27-28 points according to MMSE. After 3-5 years, there were no obvious signs of dementia in 3 (50.00%) cases. The development of initial signs of dementia and a decrease in cognitive functions up to 24-25 points was obtained in 3 (50.00%) cases. On this basis, 3 (50.00%) patients remained in TDR-0 group, and 3 (50.00%) patients were by definition assigned to TDR-1 group of AD severity (Table 3).

Patients with mild AD stage (TDR-1).
According to CT and MRI with digital image processing after 3 years, no increase in cerebral involutive changes in temporal lobes was obtained in 2 (16.66%) cases. An increase in involutive changes with a decrease in the volume of the temporal lobes to 19-24% was observed in 10 (83.33%) cases. In this connection, 2 (16.66%) patients remained in TDR-1 group, 10 (83.33%) patients were transferred to TDR-2 group of AD severity (Table 3). In more remote periods, signs of an increase in involutive changes were observed in all 13 (100%) patients.
According to SG and REG data, weak positive dynamics of blood flow velocity and pulse blood filling was obtained in all 12 (100%) patients.
Clinically, in all 12 (100%) patients, stabilization of the level of dementia and cognitive functions was noted within 2-3 years after the start of the treatment. After 3 years, all 12 (100%) patients showed an increase in the signs of dementia and a decrease in cognitive functions. In 2 (16.66%) cases, there was a decrease in cognitive functions to the level of 20-21 points according to MMSE, in 10 (83.33%) cases, a decrease to the level of 18-19 MMSE points was noted. On this basis, 2 (16.66%) patients remained in TDR-1 group, 10 (83.33%) patients, by definition, became assigned to TDR-2 group of AD severity (Table 2).

Patients with moderately severe AD stage (TDR-2).
According to CT and MRI with digital image processing, in 3 years, an increase in involutive cerebral changes with a decrease in the volume of the temporal lobes of up to 34-40% were obtained in all 21 (100%) patients.
According to SG and REG data, a trend towards a decrease in the rate of cerebral blood flow and pulse blood filling was detected in 8 (38.10%) patients, a clear decrease in the rates of cerebral blood flow and pulse blood filling was observed in 13 (61.90%) patients.
Clinically, in all 21 (100%) patients in the period of 1-2 years after the start of the treatment, there was an increase in dementia and a decrease in cognitive functions of up to 11-12 points according to MMSE. After 3 years, all 21 (100%) patients showed a further increase in dementia and a decrease in cognitive functions to the level of 9-10 points according to MMSE. On this basis, by definition, all 21 (100%) patients were included in TDR-3 group of AD severity (Table 3).

Patients with severe AD stage (TDR-3).
According to CT and MRI with digital image processing, 1 year after the start of the conservative treatment, an increase in cerebral involutive changes, with a decrease in the volume of temporal lobes to the level of 40-45%, was obtained in all 10 (100%) patients.
According to the SG and REG data, a trend towards a decrease in the rate of cerebral blood flow and pulse blood filling was obtained in 7 (70.00%) patients, a clear decrease in the rates of cerebral blood flow and pulse blood filling was obtained in 3 (30.00%) patients.
Clinically, 1 year after the start of the conservative treatment, all 10 (100%) patients showed an increase in dementia and a decrease in cognitive functions to the level of 7-8 points according to MMSE (Table. 3).

Table 3. Dynamics of changes in the severity of dementia and cognitive impairment in control group patients in the long-term period after the treatment

Signs of dementia and cognitive impairment	**Before treatment n-49**	**After treatment n-49**	**p (chi-square)**
Practically healthy (MMSE - 29-30 points)	**0**	**0**	**p=0.00130**
TDR- 0 (MMSE - 26-28 points)	**6**	**3**	
TDR- 1 (MMSE - 20-25 points)	**12**	**5**	
TDR- 2 (MMSE - 12-19 points)	**21**	**10**	
TDR- 3 (MMSE - 7-11 points)	**10**	**31**	

Post-treatment indicators significantly differed from pre-treatment indicators in each group ($p < 0.05$), and the statistical significance of the results was significantly higher in the test group ($p = 0.00130$) than in the control group ($p = 0.01044$).

Discussion

AD is complex and has not been fully understood to date. Therefore, the treatment of AD should be pathogenetically substantiated, multicomponent, aimed at various pathological processes developing in the cerebral tissue, including the restoration of cerebral arterial and capillary blood supply, as well as the stimulation of regenerative processes. This situation requires the development of new effective methods of complex AD treatment.

Test group.

In the test group, SG, REG, MUGA, MSCTA and MRA before and in the immediate and long-term period after transcatheter intracerebral PBMT, showed that exposure to laser with low output power at a wavelength of 632.8 nanometers actively stimulates angiogenesis. Such stimulation leads to collateral and capillary revascularization and restoration of cerebral hemodynamics. As a result, arterial and capillary blood flow improves, pathological arteriovenous shunts close, venous congestion decreases, cerebral hypoperfusion decreases, and oxygenation is restored. Revascularization and collateral blood supply develop not only in the hypovascular zones of the temporal and frontoparietal regions, but also in other parts of the cerebral tissue, which improves the blood supply to the entire brain.

A similar mechanism of revascularization operates during transcatheter intracerebral laser PBMT in patients with Binswanger's disease (BD), vascular Parkinsonism (VP), and cerebral atherosclerosis [41, 49]. After the treatment, the effect of cerebral collateral and capillary revascularization persists for many years.

The results obtained in this research illustrate the mechanism of the effect of laser with low output power of the red spectrum on the vascular and microvascular system of the brain.

The same mechanism of stimulation of cerebral angiogenesis also works with other methods of PBMT. The data obtained in this research confirm the studies of many authors, who showed a decrease in hypoperfusion and an improvement in cerebral blood supply after transcranial or intranasal PBMT in AD and other neurodegenerative and ischemic cerebral lesions [31–38]. The difference lies in the fact that extracranial laser treatment requires a large number of sessions to obtain the desired therapeutic effect.

In the test group, CT and MRI with digital image processing before and at various times after transcatheter endocerebral PBMT showed that exposure to laser with low output power at a wavelength of 632.8 nanometers actively restores tissue metabolism, stimulates neurogenesis and regenerative processes. As a result, in all 48 (100%) patients of the test group, a stable decrease in cerebral involutive changes was obtained with an increase in the volume of the temporal and frontoparietal lobes. In this case, the cerebral tissue has a normal structure. The effect of restoration of cerebral structures persists for many years.

The results of this research are confirmed by the experimental and clinical studies of many authors, who showed that exposure to laser with low output power in the red or near-infrared region of the spectrum stimulates neurogenesis and causes regeneration of cerebral tissues [31-38].

Thus, Transcatheter Intracerebral Laser Photobiomodulation Therapy, as well as transcranial and intranasal PBMT, are minimally invasive, physiologically based methods for the

treatment of neurodegenerative and ischemic brain lesions.

The clinical effect after the stimulation of angiogenesis and neurogenesis during transcatheter intracerebral laser PBMT include a rapid recovery of memory, a stable decrease in the severity of dementia, and an improvement in cognitive functions. The primary positive reaction in all the patients of the test group, regardless of the stage of the disease, manifested itself in the first months after the intervention.

The severity and duration of the clinical effect depends on the stage of AD, the initial size of the affected cerebral tissue and the severity of dementia. In patients with preclinical stage TDR-0 and mild stage TDR-1, the absence of dementia and the recovery of cognitive functions were manifested during the entire follow-up period. In patients with moderately severe TDR-2 and severe TDR-3, a decrease in dementia and an improvement in cognitive functions were manifested within 4-4.5 and 2-2.5 years, respectively.

Control group.

According to SG and REG performed before and at various times during the conservative treatment, it was revealed that a moderate positive dynamics of cerebral blood flow and pulse blood filling was obtained in patients with the initial stages of AD in the early period of the treatment. In the later period, a gradual decrease in the indicators was noted.

According to MUGA, MSCTA or MRA performed before and at various times during the conservative treatment, there were no signs of improvement in cerebral circulation.

According to CT and MRI with digital image processing performed before and at various times during the conservative treatment, there were no signs of a decrease in cerebral involutive changes. In the vast majority of cases, an increase in atrophic changes in cerebral tissues was noted.

Clinically, improvement in memory, reduction in dementia and restoration of cognitive functions was obtained in a separate group of patients with the preclinical stage of CDR-0. In patients with the mild stage of CDR-1, temporary stabilization of the condition was obtained in the initial period of the treatment. All other patients in the control group showed progressive deterioration.

The conservative treatment of AD is not effective enough to reduce dementia and improve cognitive function. It is possible to briefly stabilize the condition of patients in the early stages of AD. In the later stages of the disease, conservative treatment is ineffective. The same results were obtained by other authors who conducted a similar conservative treatment of AD [50-51].

Conclusions

Transcatheter intracerebral laser PBMT is an effective method for stimulating cerebral angiogenesis. Intracerebral exposure to laser with low output power at a wavelength of 632.8 nanometers causes arterial and capillary collateral revascularization. Collateral blood supply actively improves cerebral hemodynamics and reduces hypoxia in AD.

Simultaneously, PBMT stimulates neurogenesis and induces regenerative changes in the brain. As a result of such laser exposure, involutive changes are reduced, the normal structure of the cerebral tissue is restored, and the volumes of the temporal and frontoparietal lobes increase to the age norm.

Such a complex impact leads to a decrease in the severity of dementia and the restoration of cognitive functions in patients with AD.

Conducting conservative treatment for AD does not actively affect the restoration of metabolic processes in the brain, does not stimulate regenerative processes and does not improve microcirculation. In patients of the control group, an improvement in cerebral blood supply was obtained only in the early stages of the disease, which was clinically accompanied only by temporary stabilization of the condition. In advanced stages of AD, conservative treatment is ineffective.

Declaration of Conflicting Interests

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

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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