Analysis of Functional Connectivity When using Complementary Methods of Treatment in Patients with Asymptomatic Carotid Stenosis

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Abstract: Investigation of the mechanisms of neuroplasticity and detection of changes in the connectome in patients with asymptomatic carotid stenosis is relevant for the development of new preventive, therapeutic strategies and prediction of disease outcomes. Leech therapy (hirudotherapy, leeching) is one of the most well-known and studied methods of complementary medicine, with proven pathogenetic mechanisms, widely and justifiably used in patients with vascular diseases. Patients received a leech therapy course (10 sessions). All patients underwent resting state functional MRI, complaints and neurological status were evaluated before and after the course of leeching. After a leech therapy course, patients with asymptomatic carotid stenosis noted a significant improvement in their condition (reduction of headaches, dizziness, noise in the head and ears, optical and vestibular disorders, visual impairment). The connectivity of the main structures of the brain increased, which is an important morphofunctional indicator of improved brain function. The connectome study provides new approaches to understand the integrative brain function in health and disease, and to assess the effectiveness of the treatment.

ABBREVIATIONS

TIA – transient ischemic attack
ACAS – asymptomatic carotid stenosis
FC – functional connectivity
ICA – internal carotid artery

1 INTRODUCTION

Stenosis of the internal carotid artery without transient ischemic attack (TIA) or acute cerebrovascular accident is asymptomatic. Cognitive impairment has been described in patients with clinically asymptomatic stenosis (Wang, 2017; Lin, 2012; Lin, 2014; Cheng, 2012). The pathogenetic mechanism of the occurrence of these disorders in patients with asymptomatic carotid stenosis (ACAS) has not been fully studied. Patients with asymptomatic carotid stenosis are at an increased risk of developing acute vascular episodes, so the frequency of stroke and TIA in patients with stenosis of more than 70% reaches 40% over the next 2 years NASCET (Streffer, 1992).

The proven fact is that the disorders in functional connectivity (FC) are the basis of the most common cerebral pathology. Currently, in the development of pathophysiological models of cerebral pathology, not only the pathology of specific parts of the brain is evaluated, but also the characteristics of disorders of neural networks (Seung, 2014; Fornito, 2015). The basis of compensation of impaired functions of the nervous system are the mechanisms of neuroplasticity - the ability of nervous tissue to structural and functional restructuring after its damage. Several mechanisms of the functional connectivity reconstruction, which underlie neuroplasticity, are described: changes in the proportion of the connections, recombination, reconnection, and regeneration.

The use of multimodal neuroimaging techniques makes it possible to identify structural and functional disorders in patients with ACAS (Fornito 2015,

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Efimtsev A.Yu. et al. 2016). It is known that changes in the connections between neurons occur within three minutes after the onset of a stroke. Disruption of the functional connectivity may be associated with the loss of neurons or indirect effects in remote areas of the brain. Therefore, structural and interregional neuroimaging of the FC can demonstrate high clinical potential for ischemic brain damage (Gulyaeva, 2016).

The study of the mechanisms of neuroplasticity in patients with ACAS, the detection of changes of the FC in cerebrovascular diseases and during treatment is relevant for the development of new preventive and therapeutic strategies, as well as predicting the outcome (Bukkieva, 2015). As a result of the work, a high potential for the restoration of the disturbed connectome due to the activation of neuroplasticity processes was noted (Kublanov 2018, Kublanov 2018, Petrenko, 2019).

There is a decrease in the severity or termination of headaches, dizziness, noise in the head, flickering flies before the eyes in more than 70% of cases in patients with chronic cerebral ischemia and with ACAS during leech therapy (Konyrtayeva, 2015; Chernetsky 2003, Pospelova 2008).

2 PURPOSE

Connectome study in patients with asymptomatic carotid stenosis of more than 65% during leech therapy course for develop therapeutic and preventive strategies.

3 MATERIALS AND METHODS

3.1 Study Population

The study was conducted in accordance with the principles of the Helsinki Declaration. Under our supervision, there were 16 patients (10 women and 6 men, aged 61 to 81 years, average age 72.4 ± 3.4 years) with ACAS of one or both of the internal carotid artery (ICA) 60-75%. 3 patients underwent carotid enderectomy surgery from one internal carotid artery, with persistent stenosis of more than 65% of the contralateral ICA. All patients suffered from hypertension (disease duration from 3 to 20 years). 2 patients had diabetes (type II). The diagnosis of ACAS was made on the basis of anamnesis, complaints, and instrumental examination data.

All patients underwent ultrasound triplex examination of the brachiocephalic arteries on a Logiq Q7 Expert General Electric apparatus using B-mode, color and energy Doppler mapping, and pulse-wave Doppler. The study used a linear sensor with a frequency of 8.5-10.0 mHZ, a standard protocol with an assessment of the degree of stenosis of the lumen of the common and internal carotid arteries by area and diameter (European Carotid Surgery Trialists).

The study was approved by the ethics committee of the Federal State Budgetary Institution «National Medical Research Center V.A. Almazova» of the Ministry of Health of Russia (extract from the protocol No. 41 of 02/12/2018).

Criteria for exclusion of patients from the study were: 1. The presence of a history of psycho-organic pathology, epilepsy, brain tumors, injuries of the brain and spinal cord. 2. The presence of severe concomitant pathology (exacerbation of rheumatism, acute infections, cirrhosis, alcoholism, drug addiction, cardiomyopathy with thromboembolism in the arteries of the brain, acute myocardial infarction, heart failure 3-4 severity, blood diseases). 3. The simultaneous administration of drugs that can distort the results of treatment (anxiolytics, antidepressants, barbiturates, lithium preparations, narcotic analgesics, reserpine).

Patients complained of paroxysmal and / or persistent headaches of one- or two-sided localization, aching, pulsating; unsystematic and / or systemic instant, short-term or prolonged dizziness; noise in the head and / or in the ears; hearing loss; the inability to look at moving objects; flashing flies before the eyes.

In neurological status, the main symptoms were manifested by lethargy of pupil reactions - in 6 patients, convergence failure - in 4 patients, nystagmus with extreme leads - in 5, asymmetry of tendon reflexes - in 7, vegetative instability - in 8, tremor of fingers of extended arms - in 5, dynamic elements in 6 patients and static-locomotor ataxia in 5 patients.

Patients underwent a leech therapy course consisting of 10 sessions (2,5 months) according to their own patent of the Russian Federation No. 2327494 (Pospelova M.L., 2008). Leech therapy was carried out 1-2 times a week, once 2-6 leeches were placed. The most common points of the prefix: the occipital zone (along the edge of hair growth), the cervical spine (paravertebral), mastoid processes, lumbar, sacral spine (paravertebral), coccyx (in the gluteal fold), the region of the liver, spleen, heart, around the navel. Against the background of leech therapy, patients continued to take antihypertensive, antiplatelet, and lipid-lowering drugs.

Complaints (scale: yes/no) of subjective sensations and neurological status were evaluated before the start of leech therapy and after the end of the course of treatment (after 2-2.5 months).

Patients were instructed to lie with their eyes open (do not sleep), without fixing the gaze. Thus, for everyone there were identical conditions of a state of rest, and this had a minimal effect on the visual and auditory working networks of the brain.

3.2 MR Imaging Protocol

All patients underwent structural MRI with obtaining T1 and T2 weighted images and FLAIR (Fluid attenuated inversion) to exclude brain tumors, strokes and other pronounced pathological changes. All patients underwent functional resting state MRI at 2 time points - before and after the course of leech therapy. Pulse sequence data of a T1-weighted gradient echo (MP-RAGE – Magnetization Prepared Rapid Acquired Gradient Echoes) was collected to combine fMRI data with anatomical structures of the brain, slice thickness – 4.5 mm, number of slices – 29, the number of repetitions – 120, scan time – 6 minutes. The main feature of this sequence is its high resolution and 0.8 mm isotropic voxel. BOLD (Blood Oxygenation Level Dependent) were using with repetition time (TR) = 3000 ms, echo time (TE) = 50 ms, field of view (FOV) = 230 mm and matrix size 128*128, slice thickness – 4.0 mm, the number of repetitions – 120, scan time – 6 minutes.

3.3 Image Analyses

Analyzing the data of functional MRI, when performing an intergroup statistical analysis (two-sample t-test, comparing the resting state before treatment and after a course of leech therapy) with the choice of the medial prefrontal cortex (MPFC) as the region of interest.

3.4 Statistical Analyses

For statistical analysis, the non-parametric McNemar test for dependent binary indicators was used. Statistical processing and evaluation of the results of neuroimaging studies of each patient individually, as well as their group totality (resting state fMRI data) were carried out using the CONN v.18 software package (Functional connectivity toolbox), designed to determine the relationships between different parts of the brain, statistical mapping of activation zones, determining the structure of various resting state networks and functional networks of the brain.

3.5 Results

Against the background of the course of leech therapy in patients with asymptomatic carotid stenosis, a significant improvement was noted in the assessment of complaints. There was no deterioration in the condition of patients, adverse and allergic reactions during treatment. The improvement ranged from 16.67% to 100%, on average - 58.35%. Statistically significant changes in the state were observed according to the following indicators - aching, paroxysmal and aching, unilateral, bilateral, and overall headache; unsystematic, instantaneous, short-term, and generally dizziness; opto-vestibular syndrome and transient visual disturbances. Improvement in 100% of cases was achieved by the following indicators: throbbing, persistent headache; systemic, systemic in combination with non-systemic, prolonged dizziness.

Similar positive dynamics in evaluating complaints of headaches and dizziness, noise in the head and in the ears was noted by us and a number of other authors in patients with chronic vertebral-basilar insufficiency, hypertensive angioencephalopathy, posthypoxic encephalopathy (Portik O.A., Efimtsev A.Yu. et al, 2019; Pospelova M.L, 2010; Frolov 2006).

Analyzing the functional MRI data, when performing an intergroup statistical analysis (two-sample t-test, comparing the state of rest before treatment and after a course of leech therapy) with the choice of the medial prefrontal cortex (MPFC) as the ROI, we determined the enhancement of the positive functional connections of MPFC with zone 10, right cerebellum, with cerebellar vermis. Such changes of connectom correlate with clinical data on a decrease in the severity of vestibular disorders in this group of patients.

Region of interest - cerebellar area. Demonstrated positive FC with right and left hemisphere of the cerebellum (8 area), the vermis cerebellum, the precuneus, angular gyri and posterior divisions of the cingulate gyrus (part of the default mode network) (Figure 1).

When performing an analysis based on graph theory with global efficiency assessment after a course of leech therapy, stable functional relationships between the middle temporal gyrus (posterior, right), upper temporal gyrus (anterior, right) and lower temporal gyrus were determined comparing to the results of the study before the start

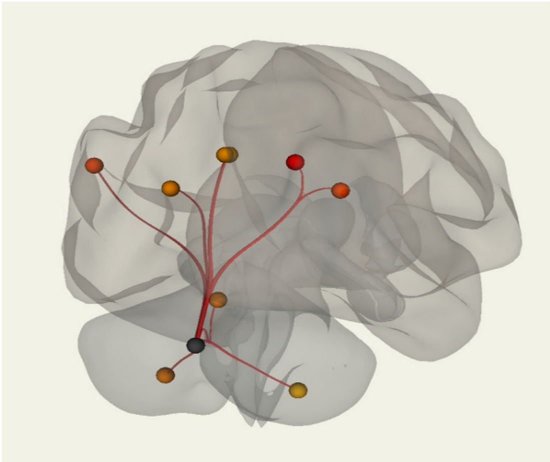

Figure 1: Cerebellar network. Intergroup comparison.

of treatment (temporal-occipital departments, left), lingual network, visual network, cerebellar vermi, zone 6 of the right hemisphere of the cerebellum, pole of the occipital lobe. At the same time, the degree of severity of activation of the lingual network (upper and lower frontal gyrus on the right) was decreased (Figure 2, Table 1).

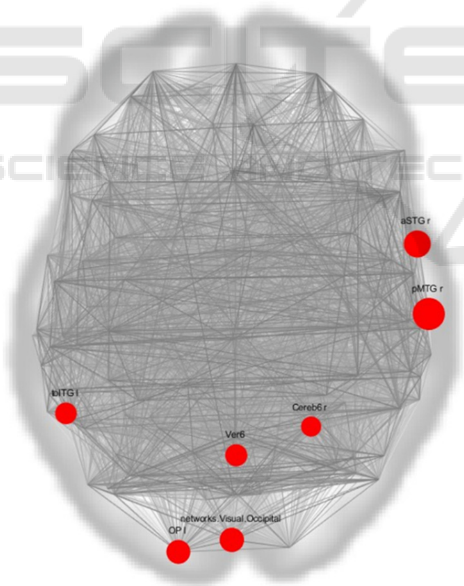

Figure 2: Maps of functional connectivity. Graph theory results.

There was an increase of the negative functional connections of MPFC with the left middle frontal gyrus and a weakening of the negative functional connections of MPFC with the right parahippocampal gyrus p<0.001 (Figure 3).

Table 1: The degree of activations severity.

ROI	beta	T	p-unc	p-FDR
Network	0.00	-0.98	0.822939	0.931425
pMTG r	0.05	2.95	0.008122	0.931425
aSTG r	0.07	2.48	0.017570	0.931425
Visual Occipital	0.05	2.24	0.026075	0.931425
OP l	0.03	2.19	0.028042	0.931425
Vermis 6	0.04	2.03	0.036683	0.931425
toITG l	0.06	1.98	0.039213	0.931425
Cereb6 r	0.05	1.85	0.048780	0.931425

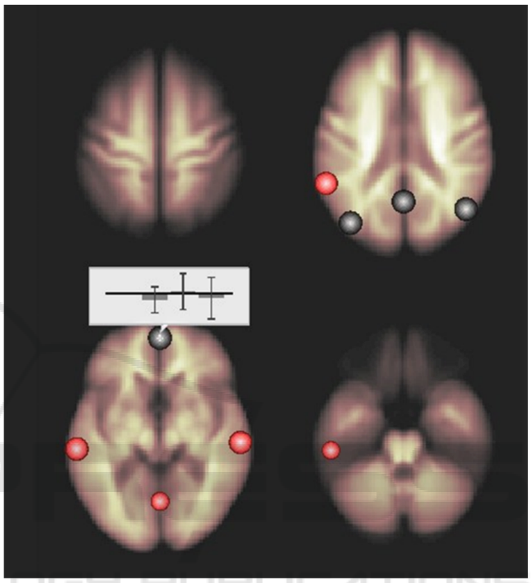

Figure 3: Intragroup comparison of the subjects before and after a course of treatment. The changes that occur after treatment are shown. Activation sites combined with anatomical images of the head — brain regions positively functionally associated with MPFC are mapped in red, and negatively functionally associated with MPFC are mapped in blue (p<0,001).

The analysis of functional MRI showed that after the course of leech therapy, the activation of the main structures of the salience network and the executive control network was noted. The functional connections of MPFC — the area of the brain responsible for controlling and making decisions with the cerebellum — increased, which was clinically manifested in a decrease in vestibular disorders, and the functional connections with the left middle frontal gyrus decreased, which may indirectly indicate a decrease in the inhibitory component of the network.

In patients with chronic cerebrovascular accident, cerebral microangiopathy, there is a gradual loss of inter- and intrahemispheric functional connections between the structures of the salience network and the executive control network, which is the functional

MRI equivalent of the disconnection phenomenon (Dobrynina, 2018). After a course of leech therapy, the connectivity of the leading structures of the brain significantly increased, which is a morphological and functional indicator of improving brain functioning and improving cognitive, emotional and behavioral disorders in patients with asymptomatic carotid stenosis.

When assessing the colorability and safety of the therapy, no hemorrhagic events during the treatment (hemorrhagic stroke, retinal hemorrhage, gastrointestinal bleeding, hemorrhoids, nose, uterine bleeding) were noted.

As a result, we can talk about a significant positive effect of the leech therapy course on the complex of complaints and indicators of brain connectivity in patients with asymptomatic carotid stenosis.

4 CONCLUSIONS

The study of connectome provides new approaches to the analysis of integrative brain function, and to assessment of the treatment effectiveness. A course of leech therapy significantly altered the functional connectivity of the brain in patients with asymptomatic carotid stenosis.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

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