Parfenov V.A.
Department of Nervous System Diseases and Neurosurgery, I.M. Sechenov First Moscow State Medical University, Ministry of Health of Russia, Moscow, Russia
11, Rossolimo St., Moscow 119021

Diagnosis and treatment of chronic cerebrovascular disease, use of pentoxifylline

Chronic cerebrovascular disease (CCVD) is one of the most common diagnoses in Russian neurology, by which is meant vascular cognitive impairment (VCI) in modern foreign literature. There are data available in the literature on the diagnosis and treatment of CCVD (VCI). The results of the author's studies show that CCVD often masks other diseases (anxiety and depressive disorders, primary headache, peripheral vestibulopathy, and Alzheimer's disease) that are unfortunately poorly diagnosed in our country, so patients do not receive effective treatment. To modify risk factors for stroke (smoking and alcohol cessation, sufficient exercise), to normalize blood pressure (the use of antihypertensive medications), to reduce blood cholesterol levels (statins), to perform antithrombotic therapy antiplatelet agents and anticoagulants), and to use cognitive enhancers are of key importance when treating patients with CCVD (VCI). There are data on the use of pentoxifylline in patients with CCVD, vascular dementia.

Keywords: *chronic cerebrovascular disease; dyscirculatory encephalopathy; vascular cognitive impairment; pentoxifylline.*
Contact*: Vladimir Anatolievich Parfenov;* ***vladimirparfenov@mail.ru***
For reference: *Parfenov VA. Diagnosis and treatment of chronic cerebrovascular disease. Nevrologiya, neiropsikhiatriya, psikhosomatika = Neurology, neuropsychiatry, psychosomatics. 2016;8(3):4–9.*
DOI: *http://dx.doi.org/10.14412/2074-2711-2016-3-4-9*

In Russian clinical practice, chronic cerebrovascular disease (CCVD), or discirculatory encephalopathy (DEP), is often diagnosed in patients both in outpatient clinics and at hospital [1]. In ICD-10 there is a code for "Other cerebrovascular disease", under which this disease is referred to in our country [2]. In modern foreign literature, such diagnosis as CCVD is practically not used. Previously, this diagnosis often implied vascular dementia or vascular cognitive impairment (VCI). For example, in articles published more than 20 years ago and devoted to the use of pentoxifylline in CCVDs, it was noted that patients with cognitive impairments caused by cerebrovascular pathology were included in the CCVD group [3, 4].

In Russian neurological literature, the term "chronic cerebrovascular disease" coincides with the term "dyscirculatory encephalopathy", which is regarded as a chronic cerebrovascular disease (CCVD), manifested by the disorder of brain functions [1, 5]. A characteristic feature of CCVD is the lacunae and rarefaction of the white matter of the brain (leukoareosis) observed in X-ray computed tomography (CT) or magnetic resonance imaging (MRI) around the ventricles (periventricular) and under the cerebral cortex (subcortical).

Vascular cognitive impairment

Modern foreign literature distinguishes VCIs, which are regarded as the main manifestation of CCVDs [6-8]. VCIs include mild and moderate VCIs, as well as vascular dementia, which ICD-10 defines as a consequence of cerebral infarct or as a cerebrovascular disorder due to arterial hypertension [2]. Vascular dementia encompasses vascular dementia of acute onset, multi-infarct dementia, subcortical vascular dementia and mixed dementia (indeterminate) [6]. Dementia of acute onset occurs within 1-3 months after the first or (more often) repeated infarcts or massive cerebral hemorrhage. Multi-infarct dementia usually develops gradually after repeated minor strokes. The subcortical form of vascular dementia is characterized by the presence of arterial hypertension and signs (clinical and instrumental) of cerebral white matter lesions (leukoareosis). In case of combined cerebral infarcts and cerebral white matter lesions, mixed vascular dementia is suggested. All types of vascular dementia, with the exception of dementia of acute onset, which occurs relatively rarely, are preceded by a period of VCIs that do not meet dementia criteria.

The criteria for the diagnosis of VCIs that do not meet dementia criteria are given in Table 1.

VCIs are manifested through various neurological disorders, often a combination of several neurological and neuropsychological syndromes is observed in one patient [6–8]. Localization and severity of brain damage play a major role in the development of these syndromes. Typical VCI syndromes include slow thinking, difficulty switching attention, judgement decline, continuously low mood and mood swings. Primary disorders of higher cerebral functions – aphasia, apraxia, agnosia, and others – develop with the localization of ischemic foci or a history of hemorrhages in certain parts of the brain responsible for higher cerebral functions. In the stage of vascular dementia gait apraxia often occurs: slow, short and uneven steps, difficulty in the start of movements, instability during turns and increased breadth of stance.

The initial manifestations of CCVD (Stage I DEP) correspond to mild VCIs, moderate manifestations of CCVD (Stage II DEP) correspond to moderate VCIs, expressed manifestations of CCVS (stage III DEP) correspond to vascular dementia. It is important to note that in clinical practice, on the one hand, other neurological or psychiatric diseases are often masked as CCVDs, while, on the other hand, quite often not only initial but also severe manifestations of CCVDs (DEPs) tend to be underdiagnosed [9]. Many elderly patients with hypertension do not seek medical advice in the event of memory and other cognitive functions impairment, considering them "standard age-related changes." In a neuropsychological study, and according to CT or

Table 1. *VCIs that do not meet dementia criteria*

VCI	Mild	Moderate
Complaints of the patient and (or) his/her relatives	Memory impairment and other cognitive disorders	
Neuropsychological study methods	Mild cognitive impairment present	Moderate cognitive impairment present
Anamnesis, clinical examination, CT scan or MRI of the brain	Risk factors, signs and manifestations of cerebrovascular disease; absence of data indicating other diseases, including AD	
Activities of daily living (ADL) assessment	Absence of severe impairment of daily activities and dementia	

Note. AD – Alzheimer's disease

Table 2. *Potential CCVD (DEP)*

A, C plus one of the supporting criteria B or D
A. The presence of cognitive impairments of non-amnestic nature: acute or gradual development of cognitive impairment for ⩾6 months in patient or his relatives (network) words; cognitive functions impairment according to the neuropsychological tests
B. Signs of cerebral vascular lesions as per MRI or CT data: previous infarcts or haemorrhages, asymptomatic lacunae, subcortical leukoarosis
C. Lack of clinical, anamnestic and neuroimaging data, indicative of other neurological diseases
D. Associated ischemic heart and peripheral arteries diseases

MRI data, these patients display typical manifestations of CCVD (DEP) [9].

In Table 2, you will find current criteria for CCVD (DEP) diagnosis.

CCVD diagnosis is based on the exclusion of other manifestations of cognitive impairment, among which AD is the most common one [5–8]. A characteristic feature of CCVD (VCI) is the lack of amnestic ("hippocampal") type of cognitive impairment, commonly associated with AD. In AD, memory impairments are observed, mainly regarding current day events (the "amnestic" type of cognitive impairment), characterized by progressive development that gradually leads to forgetting the names of family members and close friends, names of objects and events of the past. CT or MRI studies of AD patients reveal atrophic changes in the parietal and temporal lobes of the brain, while cerebral vascular lesions are absent or mild. In practice, it is often difficult to distinguish between CCVD and AD, the more often a combination of these diseases is observed in the same patient. In such cases, AD can be diagnosed based on the detected biological markers of the disease (higher concentration of amyloid-beta in the brain as seen on positron emission tomography; lower amyloid-beta content in the cerebrospinal fluid, etc.), as well as through genetic studies.

The presence of a headache and (or) vestibular vertigo is not characteristic of CCVD [6–8]. In cases when a CCVD patient has a headache and (or) vestibular vertigo, two options are possible. In the first case, this means a combination of CCVD and primary headaches (chronic daily headache, migraine, tension headache, drug-induced, or abusus, headache) and (or) a vestibular disease (benign paroxysmal positional vertigo, vestibular migraine, Meniere's disease or other peripheral vestibulopathy). In such cases most often a primary headache and (or) a vestibular disease motivate the patient to seek neurological advice, and during the examination cognitive impairments and signs of cerebral vascular pathology are revealed through CT or MRT studies. In the second case, the patient has only a primary headache and (or) a vestibular disease, and CCVD is misdiagnosed. Unfortunately, at present a large number of adult or elderly patients suffering from a primary headache and (or) vestibular vertigo are mistakenly diagnosed with a CCVD, and they do not receive effective treatment [9].

Patients' complaints of nonrotary vertigo, sleep disturbances, and decreased performance may be a manifestation of CCVD, but in most cases they are caused by primary depressive or anxiety disorders, in the diagnosis of which mental status assessment and a psychiatrist consultation are of great importance [9]. The combination of a CCVD with primary anxiety and depressive disorders is also possible; in such cases, the symptoms often are mutually intensified and both a neurologist and a psychiatrist or a psychotherapist should be involved in patient management.

Currently, CCVD is often overdiagnosed. In many respects this is because neither a neuropsychological examination, which allows to reveal cognitive disorders, nor otoneurologic (diagnosis of vestibular disorders), a special survey for the detection of primary headache, diagnosis of anxious and (or) depressive disorders, are performed. Only the presence of cognitive impairments serves as the basis for the CCVD (DEP) diagnosis and often a CCVD patient exhibits combined primary headache, peripheral vestibulopathy, primary anxiety and depressive disorders and other neurological diseases, and it is the manifestations of these disorders why the patient seeks neurological advice, and not the CCVD symptoms. In such cases, it is necessary to treat not only the CCVD, but also associated diseases, and the improvement of the patients' condition is more often achieved with the effective treatment of associated diseases. It should be noted that the treatment of CCVD in most cases is of major importance, because it helps to prevent the development of cerebrovascular accidents and cognitive impairments.

Treatment of chronic cerebrovascular disease.

Treatment of CCVD (VCI) patients is aimed at the prevention of cerebrovascular accidents and chronic cerebrovascular

pathology progression, as well as at cognitive functions improvement [6–8]. Cerebrovascular accidents prevention based on mitigating its risk factors (smoking, alcohol abuse, low physical activity, obesity), treatment of hypertension, diabetes and other diseases, is of major importance [10, 11].

Regular physical exercises are aimed at training the cardiovascular system and (or) the strength of the muscles, improving the functional capabilities of the patient; they reduce the risk of developing both a stroke [10, 11] and cognitive impairments [6–8]. The positive effect of regular physical activity can be attributed to a decrease in body weight and blood pressure (BP), increased glucose tolerance, and a decrease in serum cholesterol. At the same time patients, especially those with cardiovascular diseases may benefit from refraining from significant physical exercise.

Normalization of BP in patients with arterial hypertension is one of the most effective means of stroke and cognitive impairments prevention [10, 11]. The target level of BP, which should be achieved with antihypertensive therapy, is patient-specific; it is advisable to gradually reduce the BP, and in most cases it is not recommended to reduce it to <130/80 mm Hg. Art. [11]. The choice of a specific antihypertensive drug is largely determined by the associated diseases (diabetes mellitus, coronary heart disease, etc.). Various groups of antihypertensive agents, as well as their combinations can be used to reduce BP; diuretics and a combination of a diuretic with an angiotensine transforming enzyme inhibitor are considered as an optimal therapy for patients undergoing ischemic stroke [11].

After the transient ischemic attack (TIA) or ischemic stroke, antithrombotic therapy is required, as well as in most cases, which include the use of statins and in some patients, carotid endarterectomy is required. [10, 11].

After noncardioembolic ischemic disorders of cerebral circulation, anti-thrombocyte (antiplatelet) agents are used: acetylsalicylic acid (ASA) at a dose of 75 – 325 mg a day, clopidogrel (plavix) at 75 mg a day, or a combination of 25 mg ASA and 200 mg of sustained release dipyridamole (aggrenox) 2 times a day. After cardioembolic disorders of cerebral circulation, warfarin is used at a daily dose of 2.5 mg to 10 mg with a control over the international normalized ratio (target INR is 2–3); in the case of atrial fibrillation, new indirect anticoagulants (apixaban, dabigatran, rivaroxaban) can be used. If a patient refuses to take anticoagulants or if there are contraindications to their use, antiplatelet agents are recommended.

Most patients with CCVD (VCI), in the pathogenesis of which an atherosclerotic lesion of the cerebral arteries is assumed, are recommended to take statins [12]. The administration of statins to CCVD patients is justified in case of concomitant coronary heart disease, diabetes mellitus, ischemic stroke or TIA, high level of low-density lipoprotein (LDL) cholesterol in the blood serum. Statins are used in doses that reduce LDL cholesterol to 2.5 mmol/l; the use of statins at higher doses than standard ones, for example 80 mg of atorvastatin instead of 20 mg, may lead to an additional reduction of the cerebrovascular accidents risk, which is especially important in patients with high risk of developing ischemic stroke [11].

Carotid endarterectomy is recommended for the expressed stenosis (70–99% of the diameter) of the internal carotid artery (ICA) on the side of the relevant hemisphere in early periods (preferably in the first 2 weeks), but no later than 6 months after the ischemic stroke or TIA [10, 11]. Carotid endarterectomy can be recommended for patients who suffered from ischemic stroke or TIA, and who have a moderate degree of the ICA stenosis (50–69% of the diameter) in case there are additional stroke risk factors (for example, male sex) and no expressed co-morbidities. If the patient with CCVD did not have ischemic stroke or TIA or suffered from them relatively long ago (more than 6 months ago), then carotid endarterectomy is not recommended, conservative treatment with large doses of statins is indicated instead.

The results of our own observations indicate that in our country a relatively small proportion of patients with CCVD (DEP) are constantly taking antithrombotic drugs, statins, antihypertensives for the prevention of stroke and cognitive impairment. In most cases, patients are administered courses (or regular treatment) of medications that improve cerebral circulation and metabolic processes in the brain, but do not fully use effective means of preventing stroke and dementia.

In case of vascular dementia, to improve cognitive function and daily activity, administration of acetylcholinesterase inhibitors that reduce cholinergic deficiency and (or) a blocking agents of akatinol memantine glutamate receptors is indicated [6–8, 12]. Randomized placebo-controlled studies have proven the efficacy of donepezil and galantamine, while the efficacy of rivastigmine remains controversial [7, 8, 12]. Acetylcholinergic therapy starts with a small dose of the drug to avoid gastrointestinal complications (nausea, vomiting, diarrhea, loss of appetite), with its gradual increase (during several weeks) to a therapeutic dose, which is 10 mg/day divided into two doses for donepezil, and 16–24 mg/day divided into two doses for galantamine. During Week 1, memantine is prescribed at a dose of 5 mg/day once, at Week 2 at 5 mg twice a day, starting from Week 3 – at 10 mg twice a day. Various mental activity-stimulating exercises (cognitive stimulation) are recommended to improve cognitive functions.

The matter of the efficacy of medicines that improve cognitive functions in patients with VCIs that do not meet dementia criteria remains controversial [6–8, 12]. In our country, a large number of medicines are used in CCVD patients, but only a small part of them has been studied in placebo-controlled randomized trials with regard to the treatment of cerebrovascular diseases. One of these medicines is pentoxifylline.

Use of pentoxifylline

Pentoxifylline (trental), a methylxanthine derivative synthesized in Germany, has been widely used in clinical practice since 1970 and currently remains one of the leading medicines for patients with intermittent claudication syndrome caused by atherosclerotic lesion of lower extremity vessels [13, 14]. When administered at therapeutic doses (400 mg three times daily), pentoxifylline improves the rheological properties of the blood through several mechanisms: it reduces the viscosity of blood (largely due to a decrease in the level of fibrinogen), increases the elasticity (deformability) of erythrocytes, and reduces their aggregation [13, 14]. More recent studies have shown that pentoxifylline is able to suppress the activity of circulating mononuclear cells, neutrophils and T-lymphocytes, as well as inhibit the synthesis of pro-inflammatory cytokines, suggesting its protective effect against the damage of various tissues, including the brain and blood vessels [15]. Pro-inflammatory cytokines can play an important role in the development and progression of atherosclerosis [16], therefore pentoxifylline can inhibit the atherosclerotic process. An analysis of the results of pentoxifylline administration in various diseases and conditions showed its good tolerability and

low frequency of side effects. In case of pentoxifylline administration, the most frequently occurring gastrointestinal complications are observed in less than 3% of patients; side effects are more likely to occur in elderly patients, especially if they take a large number of various medicines [13].

At the start of pentoxifylline administration, it was widely used in the acute period of ischemic stroke and TIA. An analysis of four double blind placebo-controlled trials showed that when pentoxifylline is prescribed in an acute period of ischemic stroke, reduced mortality and disability trends are observable [17]. The latest North American guidelines for the management of patients with ischemic stroke indicate positive results of pentoxifylline administration, but they conclude that there are insufficient data to recommend it as yet, as well as other vasoactive, nootropic and metabolic drugs [18].

In our country, pentoxifylline is widely used in CCVD treatment, furthermore in recent years there has been a heightened interest in its use [19]. Several studies have shown that oral or parenteral administration of pentoxifylline significantly increases cerebral blood flow by an average of 20%, with a most significant increase in areas of the brain that have reduced blood supply [13]. Pentoxifylline improves blood flow to the brain in elderly patients (60–74 years), but this effect has not been proven for later life (75 years and older); moreover the use of pentoxifylline does not cause the "steal" syndrome [13].

The use of pentoxifylline in CCVD patients can reduce the risk of developing acute cerebral circulation disorders. In one study, patients who underwent reversible ischemic deficiency received pentoxifylline or only basic (antihypertensive, antidiabetic) therapy [20]. With prolonged follow-up (38 months), it was demonstrated that the frequency of recurrent cerebral ischemic events significantly decreased in patients taking pentoxifylline at 1,200 mg per day. Another study found that in patients who underwent TIA, the use of pentoxifylline at 1,200 mg per day as monotherapy or in combination with ASA significantly reduced the frequency of recurrent cerebral ischemic events than taking ASA alone or its combination with dipyridamole [21].

The efficacy of pentoxifylline as a medicine, which improves cognitive functions was noted back in 1979 [3]. In a double blind placebo-controlled study, 60 patients were diagnosed with "chronic age-associated cerebrovascular insufficiency" were administered pentoxifylline 400 mg 3 times daily or placebo for 2 months. The results of the study demonstrated a positive superiority of pentoxifylline over placebo according to a number of neuropsychological tests; its good tolerability was also noted. Similar results were obtained in two more recent studies evaluating the efficacy of pentoxifylline in patients with CCVD [4, 22].

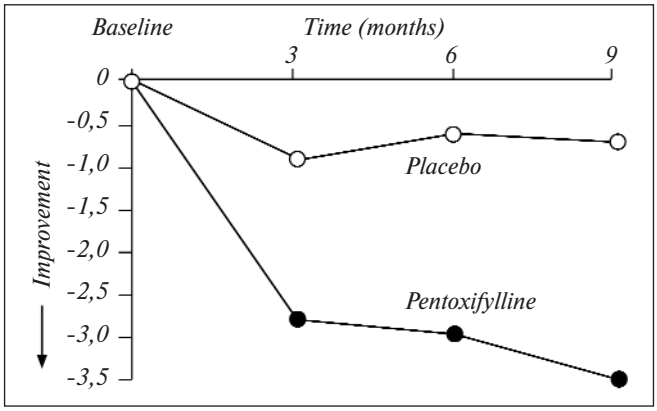

Fig. 1. *Cognitive functions trends (according to neuropsychological examination) in patients with severe VCI (multi-infarct dementia) who took pentoxifylline or placebo for 9 months*

The positive effect of pentoxifylline has been also confirmed by the results of a study, which included the largest patient population: when the medication was taken at 1,200 mg per day, memory and other cognitive functions (according to neuropsychological data) were improved in patients with severe VCIs caused by multi-infarct dementia [23]. The study included 289 patients who took pentoxifylline or placebo for 9 months. Cognitive functions were assessed every 3 months, and already after Month 3 there was a positive superiority of pentoxifylline over placebo (see Fig.1). The positive effect of improved cognitive functions was noted after 6 and 9 months of treatment.

A meta-analysis of several randomized controlled double-blind studies in patients with severe VCI (vascular dementia) showed a significant improvement in cognitive functions with the use of pentoxifylline [24]. Possible reasons explaining the improvement of cognitive function in VCI patients include improvement of cerebral blood supply, which was noted in many studies on the evaluation of blood supply to the brain before and after pentoxifylline therapy in standard doses [24].

Thus, CCVD is diagnosed not only on the basis of MRI or CT data, but also with the use of data from neuropsychological examination that can identify cognitive impairments of a non-amnestic type and rule out other diseases (AD, anxiety and depressive disorders, primary headache, peripheral vestibulopathy), which are often mistaken for manifestations of a CCVD. The management of stroke risk factors (quit smoking and alcohol abuse, sufficient exercise), blood pressure (antihypertensive medications), blood cholesterol levels (statins), antithrombotic therapy (antiplatelet agents and anticoagulants), and the use of cognitive enhancers are of key importance in treating CCVD (VCI) patients.

REFERENCES

1. Дамулин ИВ, Парфенов ВА, Скоромец АА, Яхно НН. Нарушения кровообращения в головном и спинном мозге. В кн.: Яхно НН, редактор. Болезни нервной системы. Руководство для врачей. Т.1. Москва: Медицина; 2005. С. 231-302. [Damulin IV, Parfenov VA, Skoromets AA, Yakhno NN. Circulatory disorders in the brain and spinal cord. In: Yakhno NN, editor. *Bolezni nervnoi sistemy. Rukovodstvo dlya vrachei* [Diseases of the nervous system. A guide for physicians]. Vol.1. Moscow: Meditsina; 2005. P. 231-302.]

2. Международная статистическая классификация болезней и проблем, связанных со здоровьем. Десятый пересмотр. (МКБ-10). Женева; 1995. [International statistical classification of diseases and problems related to health. Tenth revision. (IDC-10). Geneva; 1995.]

3. Harwart D. The treatment of chronic cerebrovascular insufficiency. A double-blind study with pentoxifylline ('Trental' 400). *Curr Med Res Opin.* 1979;6(2):73-84.

4. Blume J, RiIhlmann KU, de la Haye R, et al. Treatment of chronic cerebrovascular disease in elderly patients with pentoxifylline. *J Med.* 1992;23(6):417-32.

5. Шмидт ЕВ. Классификация сосудистых поражений головного и спинного мозга. Журнал невропатологии и психиатрии им. С.С. Корсакова. 1985;(9):1281-8.

[Shmidt EV. Classification of vascular lesions of the brain and spinal cord. *Zhurnal nevropatologii i psikhiatrii im. S.S. Korsakova*. 1985;(9):1281-8. (In Russ.)].
6. O'Brien J, Ames D, Gustafson L, et al, editors. Cerebrovascular disease, cognitive impairment and dementia. 2nd edition. Martin Dunitz; 2004.
7. Gorelick PB, Scuteri A, Black SE, et al. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2011 Sep;42(9):2672-713. doi: 10.1161/STR.0b013e3182299496. Epub 2011 Jul 21.
8. Levine DA, Langa KM. Vascular cognitive impairment: disease mechanisms and therapeutic implications. *Neurotherapeutics*. 2011 Jul; 8(3):361-73. doi: 10.1007/s13311-011-0047-z.
9. Неверовский ДВ, Случевская СФ, Парфенов ВА. Дифференциальный диагноз дисциркуляторной энцефалопатии в амбулаторной практике. Неврология, нейропсихиатрия психосоматика. 2013;5(2):38-42. [Neverovskii DV, Sluchevskaya SF, Parfenov VA. Differential diagnosis of dyscirculatory encephalopathy in outpatient practice. *Nevrologiya, neiropsikhiatriya psikhosomatika = Neurology, Neuropsychiatry, Psychosomatics*. 2013;5(2):38-42. (In Russ.)]. doi: 10.14412/2074-2711-2013-2411
10. European Stroke Organisation (ESO) Executive Committee; ESO Writing Committee. Guidelines for management of ischaemic stroke and transient ischaemic attack. *Cerebrovasc Dis*. 2008;25(5):457-507. doi: 10.1159/000131083. Epub 2008 May 6.
11. Kernan WN, Ovbiagele B, Black HR, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke*. 2014 Jul;45(7):2160-236. doi: 10.1161/STR.0000000000000024. Epub 2014 May 1.
12. Baskys A, Hou AC. Vascular dementia: Pharmacological treatment approaches and perspectives. *Clin Interv Aging*. 2007;2(3):327-35.
13. Frampton JE, Brogden RN. Pentoxifylline (Oxpentifylline) A review of its therapeutic efficacy in the management of peripheral vascular and cerebrovascular disorders. *Drugs Aging*. 1995 Dec;7(6):480-503.
14. McCarty MF, O'Keefe JH, DiNicolantonio JJ. Pentoxifylline for vascular health: a brief review of the literature. *Open Heart*. 2016 Feb 8;3(1): e000365. doi: 10.1136/openhrt-2015-000365. eCollection 2016.
15. Hohenberger P, Latz E, Kettelhack C, et al. Pentoxifyllin attenuates the systemic inflammatory response induced during isolated limb perfusion with recombinant human tumor necrosis factor-a and melphalan. *Ann Surg Oncol*. 2003 Jun;10(5):562-8.
16. Okazaki S, Sakaguchi M, Miwa K, et al. Association of Interleukin-6 with the progression carotid atherosclerosis (a 9-year follow-up study). *Stroke*. 2014 Oct;45(10):2924-9. doi: 10.1161/STROKEAHA.114.005991. Epub 2014 Aug 19.
17. Bath PM, Bath-Hextall FJ. Pentoxifylline, propentofylline and pentifylline for acute ischaemic stroke. *Cochrane Database Syst Rev*. 2004;(3):CD000162.
18. Lauch ES, Saver JL, Adams HP, et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the AHA/ASA. *Stroke*. 2013 Mar;44(3):870-947. doi: 10.1161/STR.0b013e318284056a. Epub 2013 Jan 31.
19. Широков ЕА. Второе пришествие пентоксифиллина в превентивную кардионеврологию. Русский медицинский журнал. 2013;(5):1-3. [Shirokov EA. The second coming of pentoxifylline in prevention cardioneurology. *Russkii meditsinskii zhurnal*. 2013;(5):1-3. (In Russ.)].
20. Ott E, Fazekas F, Valetitsch H, et al. The rationale of rheological pharmacological therapy. *Clinical Hemorheology*. 1986;(6):35-40.
21. Herskovits E, Famulari A, Tamaroff L, et al. Preventive treatment of cerebral transient ischemia: comparative randomized trial of pentoxifylline versus conventional antiaggregants. *Eur Neurol*. 1985;24(1):73-81.
22. Black RS, Barclay LL, Nolan KA, et al. Pentoxifylline in cerebrovascular dementia. *J Am Geriatr Soc*. 1992 Mar;40(3):237-44.
23. The European Pentoxifylline Multi-infarct Dementia (EPMID) Study Group. European pentoxifylline multi-infarct dementia study. *Eur Neurol*. 1996;36(5):315-21.
24. Sha M, Callahan C. The efficacy of pentoxifylline in the treatment of vascular dementia: a systematic review. *Alzheimer Dis Assoc Disord*. 2003 Jan-Mar;17(1):46-54.

Received 30.08.2016

This is a non-funded investigation. The author is fully responsible for submitting the final version of the manuscript for publication. The final version of the manuscript has been approved by the author.