

## TYPES OF TREMOR IN PATIENTS WITH CEREBROVASCULAR DISEASES AND CARDIOVASCULAR EVENTS

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**Abstract: Introduction:** Tremor can occur as a part of the clinical picture of cerebrovascular diseases. Many patients with cerebral stroke have cardiovascular diseases as a comorbidity or complication of stroke; sometimes cardiovascular events can lead to embolic stroke.

**Aim:** To present types of tremor in patients with cerebrovascular diseases and cardiovascular events and diabetes mellitus type 2, clinical characteristics of tremor and investigations used.

**Material and methods:** In our study we included 36 patients, 24 men and 12 women, that were examined and followed for 3 years, from 2012-2015. All patients were subjected to the following investigations: neurological examination, laboratory analysis, computerized tomography of brain, magnetic resonance imaging and electroencephalography. In cardiovascular patients we also performed Doppler sonography of carotid arteries, electrocardiography, cardiac ultrasound. The patients were examined and treated by cardiologists.

**Results:** Of all patients 22% had cerebral infarction, 41% atherosclerosis, 36% multiple lacunar infarctions and 28% diabetes mellitus type 2. Three patients with cerebral infarction had chorea, hemiballismus, dystonia and dystonic tremor, three had postural tremor and two cerebellar intention tremor. Atherosclerotic patients had atherosclerotic action tremor, while diabetic patients predominantly had with action-type tremor. Electroencephalography showed irritative basic brain activity with slow waves, while carotid arteries stenosis was diagnosed by Doppler sonography. Computerized tomography of the brain and magnetic resonance imaging revealed cerebrovascular diseases in certain areas. Patients with cardiomyopathy, rhythm disorders, high blood pressure, hyperli-

pidemia was investigated and medically treated by a cardiologist.

**Conclusion:** In cerebrovascular diseases different types of tremor can occur as a result of damage of the extrapyramidal system.

**Key words:** tremor, basal ganglia, atherosclerotic tremor, cardiovascular events.

### INTRODUCTION

Atherosclerosis of small blood vessels, multiple lacunar infarctions and ischemic lesions of the white matter due to atherosclerosis are the most common factors for the occurrence of abnormal movement disorders and parkinsonian symptoms. Atherothrombosis due to cardiac embolism, especially when caused by cardiac arrhythmia is also the cause of tremor and other movement disorders. Tremor can occur as a symptom of cerebrovascular insult, such as brain infarction predominantly or hemorrhagic stroke. In the post stroke patients not only tremor but also other dyskinetic movements can be presented (1). One of the most common type is cerebellar tremor that occurs in cerebellar infarction. Rubral tremor is a slow coarse tremor exacerbated by posture or voluntary movements. Three cases of rubral tremor were observed following stroke. Tremor was similar in all three cases. Lesions in some parts of the thalamus, midbrain and cerebellum can cause this tremor which responds well to levodopa therapy (2). Tremor can also occur in the infarction of the brain stem. Many patients with cerebral strokes also have cardiovascular diseases as a comorbidity or a complication of the cerebrovascular brain stroke. In these patients, in the acute period, many metabolic disorders and electrolyte disbalance can occur which causes the occurrence of tremor. Tremor is also present in

patients with diabetes mellitus associated with diabetic neuropathy that is the complication of diabetes. Vascular Parkinsonism is a special clinical entity which can occur in cerebrovascular diseases and post stroke patients; sometimes it is called atherosclerotic Parkinsonism when atherosclerosis is present mainly in the small and medium brain blood vessels and is manifested with parkinsonian symptoms predominantly on the lower extremities and postural tremor. Atherosclerotic Parkinsonism is typically presented in patients with long term hypertension and cardiomyopathy and diabetic patients when the tremor is more often present symptom (3, 4).

### AIM

The aim of the article is to present some types of tremor that occur in patients with cerebrovascular diseases, such as larger cerebral infarctions, small multiple lacunar infarctions and atherosclerosis with cardiovascular events and in diabetes mellitus type 2, and clinical characteristics of tremors that occurred in our patients and used investigations.

### MATERIAL AND METHODS

In our study 36 patients, 24 men and 12 women, were examined and followed at the Department for Movement Disorders, University Neurology Clinic in Skopje, during the period of 3 years, from 2012-2015. Among the studied patients, 8 (22%) of them had cerebral infarction, two cerebellar infarction (0.5%), 15 (41%) were with atherosclerotic changes of small and medium brain blood vessels and 13 (36%) had multiple lacunar infarctions of the brain. We also separated 3 patients from those with cerebral infarction, one with infarction in the putamen, one woman with infarction in the subthalamic nucleus and one in the globus palidus.

In this study all 36 patients had tremor as a part of the clinical picture of the cerebrovascular disease. In all patients a complete examination of neurological status was made, as well as laboratory analysis of blood glucose, neuromorphological investigations, CT-scan and MRI of the brain, while neurophysiological investigations involved electroencephalography (EEG) and Doppler sonography of the carotid arteries. Total serum lipids, cholesterol and triglycerides in the blood were also measured. Patients with cardiological diseases were examined and treated by cardiologists. Seven patients with atherosclerosis, three with cerebral infarctions and six with multiple lacunar infarctions had cardiomyopathy. EEG was performed on the 18-channel EEG apparatus using 4 standard montages in which the electrodes were placed on the scalp according to

the 10-20 international SI system. Doppler sonography of the common, internal and external carotid artery and vertebral arteries was performed in all patients with color duplex transcranial doppler in 2 patients. Doppler of the carotid arteries was performed on a color duplex sonography apparatus. Electrocardiography (ECG) was done in all patients as well as cardiac ultrasound. Most of the responders were investigated and medically treated by the cardiologist.

### RESULTS

CT scan revealed ischemic lesions of the white matter due to atherosclerosis in 15 patients with a slightly consecutive ventricular dilatation in two patients. CT also revealed multiple lacunar infarctions in the basal ganglia in the areas of the putamen, globus palidus and subthalamic nucleus and as well as multiple lacunar infarctions in the internal capsule, the brain stem mainly in the pons, thalamus and white matter. CT scan revealed cerebral infarction in another five patients. MRI findings were similar to those of CT and showed only more pronounced areas of ischemia in the white matter.

The women with subthalamic infarction, due to the lenticulostriate artery occlusion, had hemiballistic movements on the side contralateral to infarction. The movements were developed with a sudden onset and diminished in the follow-up period. MRI showed infarction in the subthalamic nucleus on the side contralateral of hemiballistic movements. The men with infarction in the putamen presented with choreic movements. His MRI revealed infarction on the side which was contralateral to the side of choreic movements. The third patient had dystonia and later on developed dystonic tremor. MRI of this patient also revealed infarction in the globus palidus on the contralateral side from dystonia. His dystonic tremor presented as oromandibular dystonic tremor that was irregular and disappeared when the patient touched the chin. In the 6-month follow-up period of a 6-month dystonia of the contralateral limb and dystonic tremor diminished but were still present.

EEG changes were registered in 16 patients with vascular Parkinsonism and three with cerebral infarction. Most common changes were irritative basic brain activity with slow waves in the posterior areas bilaterally and unilateral theta activity. On doppler sonography six patients showed stenosis of the common carotid artery bifurcation with hemodynamic changes in four, atherosclerosis of the external carotid artery in two and three were with stenosis of the common carotid artery without hemodynamic changes. In two patients transcranial color duplex sonography was performed which

**Table 1.** Presentation of the types of patients with cerebrovascular diseases with tremor

Types of cerebrovascular diseases	Number of patients total 36 (24 men and 12 women)	Percent (%)
Atherosclerosis	15	41
Diabetes mellitus type 2	10	28
Multiple lacunar infarctions	13	36
Cerebral infarctions	8	22

revealed hyperechogenicity of the mesencephalon right side without morphological and hemodynamic changes of the intracranial blood vessels. Laboratory tests showed increased total serum lipids, and the elevation of cholesterol fraction and triglycerides in all atherosclerotic patients and in 11 with lacunar infarctions.

Seven patients with atherosclerosis had a chronic ischemic cardiomyopathy established by the cardiologist. Dilated cardiomyopathy was revealed in three patients with cerebral infarctions and as well as in six with multiple lacunar infarctions.

Three of the patients (28%) with multiple lacunar infarctions and seven (46%) with atherosclerosis had a diabetes mellitus type 2 with diabetic neuropathy due to unregulated chronic hyperglycemia. They had chronic high glucose levels in blood and consequently signs of diabetic neuropathy. A laboratory test revealed high blood glucose level in all of them.

Three patients with cerebral infarction had irregular postural tremor; in two the tremor was in the legs which became more pronounced by walking and was associated with low-frequency muscle fatigue. Two patients with cerebellar infarction had cerebellar intention tremor of the same side with infarction. It was tremor at rest, more pronounced in posture and even more severe on intention. They had cerebellar infarction on CT and MRI scans. The patients with atherosclerosis (41%) and multiple lacunar infarctions (36%) presented signs of atherosclerotic vascular Parkinsonism, predominantly affecting the lower extremities. In these patients tremor at rest was not present except in one patient, but it was not pill-rolling tremor with a higher frequency.

All other patients with atherosclerotic Parkinsonism had atherosclerotic tremor which was a high-frequency action tremor, irregular, while patients with atherosclerotic changes in the cerebellar blood vessels had an additional intention tremor which became more pronounced by intention before reaching the goal of the movement. They had gait instability, bradykinesia and typical small step slow walking with brisk reflexes. The patients with diabetes mellitus type 2, due to

the diabetic neuropathy, had a diabetic tremor which occurred when they were tired and the tremor was predominantly action tremor. Tremor was presented in all our 36 patients (Table 1). All of 36 patients at the beginning were treated with standard antiparkinsonian therapy for tremor, but because of failed response to therapy, 77% of the patients with vascular tremor were treated with antiepileptic therapy later on and responded well. The tremor had specificity according to the involved area and tremor was predominantly atherosclerotic vascular tremor, cerebellar, dystonic and diabetic tremor.

## DISCUSSION

Vascular Parkinsonism developed later in the post-stroke period had a polymorphic clinical picture presented with Parkinsonian symptoms usually on the lower limbs and also sometimes with pyramidal and cerebellar signs. In our atherosclerotic patients the Parkinsonian symptoms were mainly present and we also found that the tremor at rest can occur, although rarely present; however it is not a typical pill rolling tremor. We also revealed that vascular tremor can developed in patients with larger cerebral infarctions as well. Vascular Parkinsonism presents as lower body Parkinsonism and the condition is the result of the development of the white matter lesions and lacunes in the brain (5).

Cerebrovascular disorders can lead to many cardiovascular events as a consequence of the stroke, as well such as elevated blood hypertension, cardiac tachycardia or arrhythmia, cardiomyopathy etc. Cardiac arrhythmia can be the factor leading to the occurrence of cardiac embolia and then occlusion of the brain arteries and development of the brain embolic infarctionion. As the result of the involvement of the basal ganglia, cerebellum and other brain structures, different types of tremor can occur in cerebrovascular disorders mostly in atherosclerosis, multiple brain lacunar infarctions and sometimes in large cerebral infarctions.

Diabetes mellitus can be the risk factor that can lead to development of atherosclerosis and consequently later on to the development of vascular Parkinsonism.

nism. In our 28% of the patients with diabetes mellitus type 2 and with a highly unregulated chronic level of glucose atherosclerosis and diabetic neuropathy lead to the occurrence of diabetic tremor. This type of tremor is mostly action tremor that is more pronounced when patients are tired. In hyperglycemia, tremor can occur similar to the coarse flapping tremor of asterixis, jerking and disorders of muscle tone have been described. With aging, diabetes can worsen rigidity and gait in elderly patients, but not in regard to change in bradykinesia and tremor (6). Arvanitakis Z. et al. in their study in 2004 reported that the presence of stroke reduced the association of diabetes with gait (7). Also, in our patients with atherosclerosis and diabetic tremor, with atherosclerotic vascular Parkinsonism, occurred at the later stage of the disease and was irregular postural or mostly action tremor with high frequency and low amplitude, and was refractory to antiparkinsonian therapy; however 77% of the patients responded well to antiepileptic therapy later on. Three of our patients with large cerebral infarctions had irregular postural tremor; in two of them the tremor was on the legs which became more pronounced by walking and when the muscles became tired with a low frequency. Two cases were presented with the myoclonic tremor caused by parietal cortical lesions manifesting tremulous finger movement provoked by action and posture. The tremor responded well to valproate and clonazepam (8).

In 2011 Andreas Puschmann et al. reported that progress was achieved in understanding the pathophysiology of tremor and that available options for the treatment of tremor in patients have increased. There is a more effective treatment for most forms of tremor and the underlying neurologic disorders that cause tremor (9). In accordance with this article, in our patients with atherosclerotic vascular Parkinsonism there was a good response of decreasing the tremor by antiepileptic therapy. In 2000, Deuschl G. reported that 25% of patients with cerebellar dysfunction had moderate to severe kinetic tremor with features of classical intention tremor. They concluded that intention tremor is a feature of essential tremor and that the cerebellum played the major role of its development (10).

Cerebellar tremor in our two patients occurred on the same side with the cerebellar infarction. Cerebellar tremor by its characteristics was an intention tremor in our patients, but it was also kinetic and postural tremor similar to the results of the mentioned author above. Classic cerebellar tremor presents as a low frequency, slow intention or postural tremor and is typically caused by multiple sclerosis with cerebellar plaques, stroke or brain stem tumors. Dystonic tremor is a rare tremor usually irregular and jerky and a certain arm position can extinguish the tremor (11).

In 2012 Netravathi M et al. reported that the underlying etiologies of pure dystonia, dystonia plus, tremor, tremor with dystonia, myoclonus and chorea in approximately 60% of patients was vascular, infections and space-occupying lesions (12). In 1997 Ghika-Schmid F. et al. concluded that hemihorea, hemiballism and hemidystonia were associated with stroke involving basal ganglia and adjacent white matter (13). In our study we also present three patients with infarction of the globus pallidus, subthalamic nucleus and putamen and our results are similar to the results of the cited authors. One of the characteristics of the vascular types of tremor and other movement disorders is that they can worsen over the time after stroke and many of this abnormal movement disorders can have a certain good response to antiepileptic therapy. Dystonic tremor is very similar to essential tremor but it differentiates from it by its irregularity; it mostly presents in the head or jaw as an oromandibular dystonic tremor, such as in our patient, and the patient was relieved from the tremor when touching the chin. The dystonic tremor can be produced by dystonic muscle contraction or the tremor associated with dystonia is the tremor positioned in one and dystonia in the other body part. Both forms of tremor in dystonia frequently resemble essential tremor or another pure tremor syndrome. New classification, primary tremor, is proposed and would be used for any disorder in which tremor is the sole or principal abnormality with no identifiable etiology (14). EEG findings in stroke patients and with atherosclerosis usually present with sharp irritative background activity associated with slow waves in the posterior areas of bilaterally and unilateral theta waves. The reason of the occurrence of slow waves is brain hypoxia as the result of atherosclerosis. Neuromorphological findings (CT and MRI scans) showed in our patients cerebrovascular insult, lacunar infarctions, atherosclerotic ischemic changes and infarctions in the basal ganglia.

## CONCLUSION

Our study highlights the spectrum of different types of tremor and their correlation with different cerebrovascular and cardiovascular etiologies. In this study we determined specifics of certain types of tremor, certain clinical characteristics and way of manifestations, depending on the type and localization of cerebrovascular disease, especially specifics of abnormal movements in patients with cerebrovascular basal ganglia lesions. We also determined the specifics of diabetic tremor.

This study opens the need for further research that could offer more effective treatments for different

types of tremor and a better understanding of diseases and neurologic disorders that cause tremor.

### Conflict of interest

The authors declare that there are no conflicts of interest.

### Sažetak

## VRSTE TREMORA KOD BOLESNIKA SA CEREBROVASKULARNIM OBOLJENJIMA I KARDIOVASKULARNIM INCIDENTIMA

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**Uvod:** Tremor može da se pojavi kao deo kliničke slike cerebrovaskularnih oboljenja. Mnogi bolesnici sa moždanim udarom imaju kardiovaskularna oboljenja kao komorbiditet ili je moždani udar njihova komplikacija; kardiovaskularni incidenti mogu ponekad da uzrokuju pojavu emboličnih moždanih udara.

**Cilj:** Cilj ispitivanja je da se prikažu vrste tremora: kod bolesnika sa cerebrovaskularnim i kardiovaskularnim oboljenjima, bolesnika sa dijabetes melitusom tipa 2. Da se prikažu i kliničke karakteristike tremora i primenjena ispitivanja.

**Materijal i metode:** Naše ispitivanje je obuhvatilo 36 bolesnika (24 muškaraca i 12 žena) koji su ispitivani i praćeni 3 godine, 2012-2015. Kod svih bolesnika primenjena su sledeća ispitivanja: neurološki pregled, laboratorijske analize, kompjuterizovana tomografija mozga, magnetna rezonanca i elektroencefalografija. Kod bolesnika sa kardiovaskularnim oboljenjima izvršili smo sledeća ispitivanja: Dopler sonografiju karotidnih arterija, elektrokardiografiju i kardiološki ultrazvuk. Ispitivanje i lečenje ovih bolesnika su sproveli kardiolozi.

### Abbreviations

CT — Computerized tomography of brain

EEG — Electroencephalography

MRI — Magnetic resonance imaging

ECG — Electrocardiography

**Rezultati:** Od svih bolesnika 22% su imali moždani udar, 41% aterosklerozu, 36% multipli lakunarni infarkt, a 28% dijabetes mellitus tip 2. Tri bolesnika sa moždanim udarom su imali horeu, hemibalizam, distoniju i distonični tremor, 3 su imala posturalni tremor, a 2 cereberalni intencioni tremor. Aterosklerozni bolesnici su imali aterosklerozni akcioni tremor, dok su bolesnici sa dijabetesom u većini slučajeva pokazivali akcioni tip tremora. Nalazi elektroencefalografije (EEG) registrovali su osnovne aktivnosti sa slabim talasima, dok je stenoza karotidnih arterija dijagnostikovana Doppler sonografijom. Kompjuterizovana tomografija mozga i magnetna rezonanca otkrila je cerebrovaskularna oboljenja izvesnih moždanih regiona. Bolesnici sa kardiomiopatijom, poremećajima ritma, povišenim krvnim pritiskom i hiperlipidemijom registrovani su nakon kardiološke obrade.

**Zaključak:** Kod cerebrovaskularnih oboljenja mogu da se pojave različite vrste tremora koji nastaju kao rezultat oštećenja ekstrapiramidnog sistema.

**Ključne reči:** tremor, bazalne ganglije, aterosklerozni tremor, kardiovaskularni incidenti.

### REFERENCES

1. Siniscalchi A, Gallelli L, Labate A, Malferrari G, Palleria C, Sarro GD. Post-stroke movement disorders: clinical manifestations and pharmacological management. *Curr Neuropharmacol*. 2012; 10(3): 254–62.
2. Berkovic SF, Bladin PF. Rubral tremor: clinical features and treatment of three cases. *Clin Exp Neurol*. 1984; 20: 119–28.
3. Zhang GP, He ML, Wang LL. Analysis of Clinical Features of Vascular Parkinsonism. *Chinese General Practice*. 2012; 24: 027.
4. Stojanović Z, Vukadinović-Stojanović S. Correlation analysis between depressive manifestations and morphological

lesion characteristics in patients with stroke. *Sanamed*. 2014; 9(1): 31–40.

5. Korczyn AD. Vascular Parkinsonism-characteristics, pathogenesis and treatment. *Nat Rev Neurol*. 2015; 11(6): 319–26.

6. Morres CA, Dire DJ. Movement disorders as a manifestation of nonketotic hyperglycemia. *J Emerg Med*. 1989; 7(4): 359–64.

7. Arvanitakis Z, Wilson RS, Schneider JA, Bienias JL, Evans DA, Bennett DA. Diabetes mellitus and progression of rigidity and gait disturbance in older persons. *Neurology*. 2004; 63(6): 996–1001.

8. Balci K, Utku U, Cobanoglu S. Two patients with tremor caused by cortical lesions. *Eur Neurol*. 2007; 57(1): 36–8.

9. Puschmann A, Wszolek ZK. Diagnosis and treatment of common forms of tremor. *Semin Neurol.* 2011; 31(1): 65–77.

10. Deuschl G, Wenzelburger R, Loffler K, Raethjen J, Stolze H. Essential tremor and cerebellar dysfunction clinical and kinematic analysis of intention tremor. *Brain.* 2000; 123(Pt 8): 1568–80.

11. Crawford P, Zimmerman EE. Differentiation and diagnosis of tremor. *Am Fam Physician.* 2011; 83(6): 697–702.

12. Netravathi M, Pal PK, Indira Devi B. A clinical profile of 103 patients with secondary movement disorders: correlation of etiology with phenomenology. *Eur J Neurol.* 2012; 19(2): 226–33.

13. Ghika-Schmid F, Ghika J, Regli F, Bogousslavsky J. Hyperkinetic movement disorders during and after acute stroke: the Lausanne Stroke Registry. *J Neurol Sci.* 1997; 146(2): 109–16.

14. Elble RJ. Defining dystonic tremor. *Curr Neuropharmacol.* 2013; 11(1): 48–52.

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