ELIMINATION OF MICROEMBOLIC SIGNALS BY COMBINED ANTICOAGULANT AND ANTIPLATELET THERAPY

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SUMMARY – The effect of antithrombotic treatment on cerebral microembolism detected by transcranial Doppler sonography (TCD) in a case of internal carotid artery siphon stenosis is reported. A 58-year-old man suffered acute visual impairment associated with acute transient right upper limb paresis and paresthesia. Ultrasound examination of the neck arteries, TCD and digital subtraction angiography showed stenosis of the siphon of the left internal carotid artery. The patient was administered aspirin as antiplatelet therapy for 40 days, followed by anticoagulant therapy. Subsequently, he experienced many recurrent cerebral ischemic events. TCD monitoring performed on 4 occasions revealed microembolic signals (MES) in the ipsilateral middle cerebral artery. Aspirin was added to anticoagulant therapy. Once the combined anticoagulant and antiplatelet therapy had been introduced, no recurrent events were recorded anymore and no MES were detected. In this case, the detected MES proved to be in close relationship with recurrent cerebral ischemia, and were eliminated by combined anticoagulant and antiplatelet therapy.

Key words: *Intracranial embolism and thrombosis, therapy; Brain ischemia, complications; Carotid stenosis, complications; Carotid artery diseases, complications; Ultrasonography, Doppler, transcranial; Case report*

Introduction

One of the main issues besides methodologic and technical aspects of the equipment and method of detection of microembolic signals (MES) by transcranial Doppler sonography (TCD) refers to the prognostic significance of MES in different clinical groups. Although MES are found in a great number of asymptomatic patients with various potential sources of cerebral embolism, several studies proved their significance for developing new cerebral ischemia[1,2]. We present a case where demonstrated MES turned out to be closely related to the progress of recurrent neurologic deficit, and were eliminated by combined antiplatelet and anticoagulant therapy.

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Case Report

A 58-year-old man with two stroke risk factors, i.e. habit of cigarette smoking and hypercholesterolemia, experienced acute visual impairment with light flashes and dark spots in the left eye for several minutes. During the next week he suffered four episodes of such impairment in the left eye as well as acute transient right upper limb paresis and paresthesia, each lasting for several minutes. He was admitted to our hospital for persistent weakness and numbness of the right arm after the last episode. The patient had no clinical data or prior history of cardiac disease. Electrocardiogram (ECG) and transthoracic echocardiography were normal. Computed tomography (CT) of the head showed a small fresh infarct in the subcortical area of the left middle cerebral artery. Magnetic resonance imaging (MRI) showed a small hypointense lesion consistent with ischemia. There was no hypercoagulopathy (blood counts, antithrombin, protein C and S, antiphospholipid antibodies). All other laboratory tests were normal.

Ultrasound (US) examinations of the neck arteries with continuous wave Doppler sonography and color Doppler duplex scanning, and of the basal arteries of the circle of Willis with TCD and TCD color sonography showed stenosis of the left internal carotid artery in the siphon area with slight flow velocity reduction in the upstream common carotid artery, moderately reduced flow velocity in the ipsilateral middle cerebral artery, and sufficient cross-flow *via* left posterior communicating artery. Angio IRM and digital subtraction angiography (DSA) demonstrated stenosis (70% - 80%) of the siphon of the left internal carotid artery and confirmed the cross-flow *via* left posterior communicating artery. The patient was placed on a regimen of 100 mg aspirin daily. One week upon admission, he complained of a sudden recurrence of upper right-sided paresthesia. Detection of MES was done for the first time. TCD recording of MES was made from the right and left middle cerebral artery by a computer-controlled Doppler ultrasound device (Multi Dop X4 TCD-8 DWL), according to the recommendation of the International Consensus Group on Microembolus Detection[3]. The left and right middle cerebral arteries were monitored simultaneously by use of a 2-MHz probe, 14 mm in diameter. Each artery was recorded simultaneously at two insonation depths (range 45 to 55 mm), with 5-mm intergait distance with axial extension of the sample volume, 8 mm for 45 minutes. Detection of MES was performed by use of automated emboli-detection TCD software for MDX version 8.0 K. The algorithm for signal intensity measurement uses the whole screen as background. A 64-point fast Fourier transform was used, with a 2-ms FFT length. The FFT time window overlap was set at 60%. The high-pass filter was set at 100 Hz, a scale at 100 sm/s. MES were identified according to the criteria of the Consensus Committee of the Ninth International Hemodynamics Symposium[4] (with a higher intensity threshold of 9 dB). Six MES were recorded in the left middle cerebral artery during the recording time. Anticoagulant therapy with heparin, followed by Sintrom (INR 2.6) was introduced. The patient was treated with Sintrom for 40 days. Upon the introduction of anticoagulant therapy, detection of MES was performed on 3 occasions at the same time of the day. No MES were revealed on the first recording, however, the next two recordings showed MES (5/45 min) in the left middle cerebral artery. At that time, the patient experienced monocular blindness again. On day 15, the patient suffered a new transient ischemic attack (TIA) accompanied by visual impairment in the left eye and right brachial paresis. Aspirin (100 mg/day) was added to the anticoagulant therapy with Sintrom, whereupon the patient became asymptomatic with no more ischemic events. Now, TCD monitoring showed no MES. One month later, no MES were detected on TCD monitoring either. The combined therapy was continued for six months.

Discussion

In our patient, the symptoms persisted upon the introduction of conventional antiplatelet therapy as well as upon the initiation of therapeutic doses of anticoagulant therapy. The recurrence of cerebral ischemic events was the only criterion for the introduction of combined anticoagulant and antiplatelet therapy. The patient turned asymptomatic (in terms of neurologic symptoms) upon the introduction of this combined therapy.

In this case, there were two interesting observations. First, during the period of recording MES, the patient experienced several recurrent ischemic episodes including monocular blindness, and TIA or RIND in the same affected vessel area where MES were recorded. Second, the introduction of combined anticoagulant and antiplatelet therapy led to disappearance of recurrent cerebral ischemic events and absence of MES recordings. In this particular case, MES as detected by TCD sonography served as an indicator of clinical cerebral embolism. Thus, it seems that therapy eliminating the risk of clinical cerebral embolism leads to MES elimination as well. However, it may be argued that our observation was due to a spontaneous course of cerebrovascular disease, where the absence of re-embolization resulted from the atherosclerotic plaque stabilization.

The effect of antithrombotic treatment on MES in patients with carotid artery diseases has not been established. The effect of antithrombotic therapy on the incidence of MES depends on the composition of the microembolic particles. Experience with the effect of medicamentous therapy on the prevalence of MES in such patients is limited and controversial. A great number of patients with carotid artery disease who show MES were on antiplatelet therapy at the time of TCD monitoring[5-8]. Only few studies report on the effect of antiplatelet therapy on MES[9-11] or on their elimination after intravenous infusion of acetylsalicylic acid[12]. Even under anticoagulation, clinically silent embolism of intracranial circulation may be common in atherosclerotic internal carotid artery disease[6,13,14]. Few studies have demonstrated the effect of anticoagulant therapy on the occurrence of MES[7,15] or have reported only non-significant trends[16]. Forteza *et al.* found

no significant difference according to the use of aspirin and anticoagulant between MES-negative and MES-positive cases[6]. Siebler *et al.* found no major differences between the subgroups of patients with and without antiplatelet or anticoagulant medication[14]. Koennecke *et al.* conclude that in patients with carotid disease, neither form of antithrombotic treatment appears to be related to MES detection[17]. However, we found two literature reports of similar MES abolishment with combined anticoagulant and antiplatelet therapy[8,18]. One refers to a patient with symptomatic carotid artery disease and recurrent amaurosis fugax, who was treated with warfarin and aspirin[8], and the other describes a patient with middle cerebral artery stenosis and recurrent hemispheric TIA who was administered ticlopidine and oral anticoagulants[18]. It seems probable that the addition of aspirin to anticoagulation with Sintrom acts on re-embolization by attacking simultaneously both platelet aggregation and coagulation system.

Confirmation of the prognostic value of MES for new cerebral ischemia and the effect of therapy – anticoagulant, antiplatelet or combined – on MES obviously are factors that will contribute to more efficient stroke prevention in patients with inoperable carotid stenosis.

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Sažetak

UKLANJANJE MIKROEMBOLIJSKIH SIGNALA KOMBINIRANOM ANTIKOAGULANTNOM I ANTITROMBOCITNOM TERAPIJOM

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U radu se izvještava o zapaženom utjecaju antitrombotskog liječenja na cerebralnu mikroemboliju, koji je otkriven transkranijskim Dopplerovim ultrazvukom (TCD) u slučaju stenoze sliva unutarnje karotidne arterije. U 58-godišnjeg muškarca nastupio je akutni poremećaj vida te akutna prolazna pareza i parestezija gornjeg desnog ekstremiteta. Ultrazvučni pregled vratnih arterija, TCD i digitalna subtrakcijska angiografija pokazali su stenozu sliva lijeve unutarnje karotidne arterije. Bolesniku je uvedena antitrombocitna terapija aspirinom kroz 40 dana, nakon čega je nastavio s antikoagulantnom terapijom. Naknadno je imao brojne opetovane moždane ishemijske ispade. Praćenje pomoću TCD provedeno u 4 navrata otkrilo je mikroembolijske signale (MES) u istostranoj središnjoj moždanoj arteriji. Antikoagulantnoj terapiji dodan je aspirin. Nakon što je uvedena kombinirana antikoagulantna i antitrombocitna terapija nisu više zabilježeni nikakvi opetovani ispadi niti su više otkriveni MES. U ovom slučaju se pokazalo da su otkriveni MES bili usko povezani s opetovanom moždanom ishemijom, a uklonjeni su kombiniranom antikoagulantnom i antitrombocitnom terapijom.

Ključne riječi: *Intrakranijska embolija i tromboza, terapija; Moždana ishemija, komplikacije; Karotidna stenoza, komplikacije; Bolesti karotidne arterije, komplikacije; Ultrasonografija, Dopplerova, transkranijska; Prikaz slučaja*