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Review Article

Cerebrovascular Reactivity in Multiple Sclerosis

Nevzat Uzuner* and Gülnur Tekgöl Uzuner

Department of Neurology, Eskisehir Osmangazi University, Turkey

Abstract

Multiple sclerosis (MS) is a chronic inflammatory, demyelinating and degenerative disease of the central nervous system. In addition a close relationship between MS lesions and the cerebral vasculature has long been recognized. The cerebral hypoperfusion is associated to the disease process. Additionally, impaired cerebrovascular reactivity might be considered in the pathogenesis of MS; however, the studies have inconsistent results. Another interesting point is impaired vasoneuronal coupling phenomenon in patients with MS. The results of the studies assessing vasoneuronal coupling in MS patients have showed hyperactivity at the occipital region to visual stimulation during attack, but not attack free period of the disease suggesting that demyelinization and axonal degeneration leads the surviving neurons hyperactive. Clinical relevance of these hyperactive neurons needs to be clarified.

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Corresponding author
Nevzat Uzuner, Department of Neurology, Faculty of Medicine, Eskisehir Osmangazi University, Meselik, 26480 Eskisehir, Turkey, Tel: +90 222 2392979/3650; Email: nevzatuzuner@gmail.com

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- Vascular reactivity
- Vasoneuronal coupling

ABBREVIATIONS

MS: Multiple Sclerosis; PPMS: Primary Progressive Multiple Sclerosis; SPMS: Secondary Progressive Multiple Sclerosis; NAWM: Normal-Appearing White Matter; PET: Positron-emission tomography; CBF: Cerebral Blood Flow; EDSS: Expanded Disability Status Scale; MSSS: Multiple Sclerosis Severity Score; ET-1: Endothelin-1; TCD: Transcranial Doppler

INTRODUCTION

Multiple Sclerosis (MS) is a chronic inflammatory, demyelinating and degenerative disease of the central nervous system. Inflammation is invariably present at all stages of MS. In primary progressive multiple sclerosis (PPMS) and secondary progressive multiple sclerosis (SPMS), active demyelination and neurodegeneration are also associated with inflammation [1]. The brains of patients with MS show focal, diffuse and global changes, including widespread inflammation, microglial activation, astrocytic gliosis, and mild demyelination and axonal loss in Normal-Appearing White Matter (NAWM) and in the normal-appearing cortex [2]. In addition a close relationship between MS lesions and the cerebral vasculature has long been recognized [3]. MS lesions contain evidence of vascular injury and vascular endothelial cell activation [4].

HYPOPERFUSION

Positron-Emission Tomography (PET) studies in MS patients found a widespread reduction in Cerebral Blood Flow (CBF) affecting both grey and white matter [5]. A recent study showed a decreased CBF throughout the NAWM in MS subjects [6]. These findings suggest that a decreased cerebral NAWM perfusion is an integral part of the disease process [7]. Reduced NAWM CBF has not shown any correlation with disability status measured by the Expanded Disability Status Scale (EDSS), or disease progression assessed by the Multiple Sclerosis Severity Score (MSSS) in MS subjects in the study was published very recently [8]. The same group has also shown that ET-1 plays a prominent role in the cerebral hypoperfusion in patients with MS. They have found higher levels of endothelin -1 (ET-1) in the internal jugular vein comparing to the peripheral vein suggesting that ET1-1 are released from the brain. Another result of their study was the source of ET-1 which was reactive astrocytes in MS plaques. They also report that this ratio was higher in patients with MS compare to control subjects [9]. It seems to the cerebral hypoperfusion is associated to the disease process more or less, however, clinical relevance of its still needs to be clarified.

Vascular reactivity

Apart from the hypoperfusion, impaired cerebrovascular reactivity might been considered another role in the pathogenesis of MS. Cerebrovascular reactivity can be examined by means of functional transcranial Doppler (TCD) [10,11]. TCD sonography allows for real-time investigation of flow velocities in the large cerebral arteries and velocity changes after vasodilatory stimulus such as acetazolamide, CO_2, or apnea [12]. Hypoxia caused by breath holding results in an autoregulatory_vasodilatation and an increase in CBF to the cortex [13]. The increased CBF can be evaluated by TCD and can provide information about the vascular reactivity [14]. Recently, normal cerebrovascular reactivity using breath holding test in MS patients was published

[15]. The authors have TCD examinations during attack, after high-dose intravenous corticosteroid treatment, and attack free period. They have not found any significant differences between patients with MS and controls. Another paper in which cerebrovascular autoregulation was examined in MS patients by transcranial Doppler during head-up tilt was published recently [16]. They have found significantly reduced mean CBF velocity in comparison with the baseline values in patients and controls after tilting up. More recently another group has examined cerebral autoregulation during head-up tilt table testing and the effects of high-dose intravenous corticosteroid treatment [17]. They have found no significant differences in the autoregulatory indices between patients and controls, or between pre- and post-steroid results. Although non-significant differences, they have concluded that cerebrovascular autoregulation impairments are detectable in MS.

Vasoneuronal coupling

There is a physiological relationship between neuronal activity and regional CBF related to metabolic demand, so-called vasoneuronal coupling of functional hyperemia [18,19]. TCD provides information about blood flow velocity changes in individual cerebral arteries as representation of cerebral blood flow to visual stimulation. Moreover, the TCD method is able to provide continuous information about the dynamics of the response [20,21]. There are a few studies working on the vasoneuronal coupling in patients with MS. The results of the studies assessing vasoneuronal coupling in MS patients have showed hyperactivity at the occipital region to visual stimulation during attack and after high-dose intravenous corticosteroid treatment, except attack free period [22-24]. They also correlated the velocity changes of the posterior cerebral artery with visual evoked potential data (latency and amplitude) obtained during the attack period, and concluded that this hyperactivity might be a result of long-term inhibition caused by axonal injury and demyelinization representing adaptive changes in occipital cortical neurons.

CONCLUSION

MS is a chronic inflammatory, demyelinating and degenerative disease of the central nervous system. The cerebral hypoperfusion is associated to the disease process. Impairment of cerebrovascular reactivity is still controversial. Finally impaired vasoneuronal coupling phenomenon was found in patients with MS, however, its clinical relevance needs to be clarified.

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