OPEN ACCESS
Freely Available Online

International Journal of Multiple Sclerosis and Related Disorders
ISSN NO: Coming Soon

Research Article

DOI : Coming Soon

Neurovascular Reactivity After Repeated Attacks in Patients with Multiple Sclerosis

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ABSTRACT

Objectives: Increased neurovascular (NV) reactivity has been shown in patients with relapsing-remitting multiple sclerosis (RRMS) during the acute exacerbation period. However, the NV reactivity after several attacks is not known. We, therefore, have investigated the patients by transcranial Doppler (TCD) using simple visual stimulation after the repeated attack periods.

Patients and Methods: Thirty patients (22 females and eight males, mean age 40 years) with RRMS were examined at least two times. The average TCD examination interval was 26.7 months (range 4-120 months). Mean attack number was 3.8 (range 2-8 times), average disease duration was 57 months (range 4-124 months), and average Expanded Disability Status Scale (EDSS) value was 2.5 (range 1-5.5). We performed transcranial Doppler recordings from the P2-segments of both posterior cerebral arteries simultaneously during simple visual stimulation. The NV reactivity was defined as a relative increase of the blood flow velocities during visual stimulation.

Results: The NV reactivity to simple visual stimulation was significantly lower in the second test on both sides (31.5±9.2% and 29.2±7.2%; right and left side, respectively) from those of the first test (38.3±11.9% and 36.0±11.9%; right and left side, respectively) ($p<0.001$).

Conclusion: The present study is the first study examining neurovascular reactivity in patients with RRMS during repeated attacks using the transcranial Doppler to our best knowledge. Our results suggest patients with RRMS after repeated exacerbation periods have less reactive neurovascular units in the occipital cortex. The possible explanation might be the repeated demyelination, and insufficient remyelination with longer disease duration may lead glial dysfunction resulting neurovascular unit impairment. If so, functional TCD may be useful for the determining of the disease progression. However, the exact cut-off point is not known.

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Keywords: Multiple sclerosis, ultrasound, visual stimulation, neurovascular reactivity.

Received : May 18, 2017; **Accepted :** July 24, 2017; **Published :** Aug 10, 2017

Introduction

Multiple sclerosis (MS) is a chronic disease containing the inflammatory, demyelinating, and degenerative processes of the central nervous system [1]. The inflammation, microglial activation, astrocytic gliosis, demyelination, and somewhat axonal loss in white matter and grey matter was present in the brains of the patients with MS [2]. Moreover, MS patients presented a reduction in the cerebral blood flow (CBF) affecting both grey and white matter in positron emission tomography (PET) studies [3].

There is a physical relationship between the neuronal activity and regional cerebral blood flow (CBF) related to the metabolic demand [4,5]. Transcranial Doppler provides information regarding blood flow velocity changes in individual cerebral arteries as representative of CBF to visual stimulation [6,7]. Besides, the studies evaluating the NV in patients with RRMS have indicated hyperactivity to visual stimulation during the attack, and after high-dose intravenous corticosteroid treatment [8-10]. However, it is not known which is this reactivity is subject to change after several exacerbation periods of the disease. In the present study, we assessed the NV reactivity in patients with RRMS after the several repeated exacerbation periods, by the visually evoked CBF velocity changes in both posterior cerebral arteries (PCA) using TCD monitoring.

Patients and Methods: Thirty patients (22 females and eight males, mean age 40.1±8.7 years) with RRMS who were admitted to our Neurosonology laboratory during an exacerbation period of the disease were examined at least two times. An exacerbation was defined as a rapid worsening of the symptoms lasting for more than one day in a particular area. The diagnosis of RRMS was determined according to McDonald criteria [11].

All patients were examined clinically, and haematological investigations were performed on all of them. The Expanded DisabilityStatus Scale (EDSS) was also routinely calculated for all the patients [12]. The cerebral MRI examinations were conducted on all the patients. All subjects had a normal extracranial ultrasound examination. The evaluation of extracranial vessels was carried out by Duplex Color-coded ultra-sonography (Acuson X150, Siemens Medical Solutions, USA). The written confirmations from the Local Clinical Research Ethics Committee were received for this study.

The TCD examination was performed within the first three days of an acute exacerbation and before any treatment. All TCD and Duplex Sonography examinations were done by the same person (NU), and the same machine was used in this study. The examiner was blinded to disease characteristics of the patients and to study timeline at the time of the examination. Caffeine and nicotine use before TCD examination was not allowed. Although cardiovascular risk factors were not estimated according to the Framingham Cardiovascular Risk Score [13]. Subjects lay comfortably in a quiet room. We used a four-channel TCD (DWL Multidop X) with 2-MHz pulsed-wave Doppler transducers affixed to a headband. We performed transtemporal TCD recordings from the P2-segments of both PCAs simultaneously during visual stimulation. The vessels were identified according to the criteria described earlier [14]. Briefly, through the temporal bone both P2 segments of PCA's (flow direction away from the probe) were insonated at a depth of 58–68 mm. The verified PCA insonation was required to assess the velocity increase on both sides during the measurement of the visually evoked flow when the patients' eyes were open as opposed to being closed.

The simple visual stimulation was performed with a black and white checkerboard. The full instrumentation of the simple visual stimulation has been published elsewhere [15].

The analysis of the visually evoked flow response was performed offline. NV reactivity was defined as a relative increase of the blood flow velocities as a percentage change of the baseline values [NVR = 100*(Vs-Vr)/Vr]. Where Vs indicates the maximum velocity at stimulation (eyes open and stimulus on); the Vr, the minimum velocity at rest (eyes closed) (Fig 1). They are calculated by the special software of the TCD system that allows trigger-related blood flow velocity is averaging [16].

The mean number of the attacks were 3.8 (range 2-8 times), and the mean disease duration was 57 months (range 14-124 months) at the date of the Doppler examination. The EDSS values of the patients were 2.5 (range 1.0–5.5). Twenty patients had mono or hemiparesis, 2 had paraparesis, 8 had ataxia, 22 had sensory disturbances, 7 had optic neuritis, and 2 had diplopia. A combination of more than two symptoms was present in most patients. NV reactivity to simple visual stimulation of patients with optic neuritis only (2 patients) was not significantly different from those of other patients, and therefore, this data was not excluded in the analysis.

A paired t-test for the samples was applied for statistical analysis, where appropriate, and $p < 0.05$ was accepted as the statistical significance.

Results:

The visual stimulation led to a significant blood flow velocity increase (NVC) on both sides ($p < 0.001$) in all the subjects. All Doppler data for the visual stimulation group is given in Table 1.

The NV reactivity to simple visual stimulation was significantly lower in the second test on both sides (31.5±9.2% and 29.2±7.2%; right and left side, respectively) from those of the first test (38.3±11.9% and 36.0±11.9%; right and left side, respectively) ($p<0.001$).

Discussion

Normal brain activity is subject to a continuous supply of oxygen and glucose, and local brain activity has to be gone together with an increase in local CBF. The signalling from the neurones to the local vessels are necessary for the local CBF to increase. Also, glial activation plays a role in the neurovascular coupling; especially visual stimulation [5,17]. Endothelial cells and pericytes are also involved in the neurovascular reactivity [18]. However, the exact coupling mechanism of the neurovascular unit is not yet fully understood.
Also, neurovascular reactivity can be affected by different concomitant factors [13].

The cerebrovascular reactivity can be measured by TCD, which allows for the real-time investigation of the velocity changes after the breath holding test [19, 20]. Normal cerebrovascular reactivity using a breath-holding test or tilt-table test in MS patients was published [21, 22].

The results of the previous studies assessing NV reactivity in MS patients have shown hyperactivity to visual stimulation during an attack and just after a high-dose of intravenous corticosteroid treatment [8-10, 13]. Their conclusion was that this hyperactivity might be a result of the adaptive changes in the occipital cortical neurones due to long-term inhibition caused by axonal injury and demyelination.

To our best knowledge, the present study is the first one examining neurovascular reactivity in patients with RRMS after repeated attacks using the transcranial

Doppler. However, the small number of cases and the variation of the second test whether about the number of attacks or relation to the disease duration are the

Table 1: Doppler data of the patients

	First test	Second test	P value
Right-hand side			
Maximum velocity (cm/s)	49.6±12.0	45.4±10.2	0.086
Minimum velocity (cm/s)	36.2±9.9	34.8±8.9	0.478
Reactivity (%)	38.3±11.9	31.5±9.2	0.001
Left-hand side			
Maximum velocity (cm/s)	47.9±10.0	46.4±8.4	0.352
Minimum velocity (cm/s)	35.4±7.9	35.9±6.9	0.618
Reactivity (%)	36.0±11.9	29.2±7.2	0.001

Values are mean±SD, paired sample t-test

important limitations of our study. Nonetheless, our results suggest patients with RRMS after repeated exacerbation periods have less reactive neurovascular units in the occipital cortex. The possible explanation might be the repeated demyelination, and insufficient remyelination with longer disease duration may lead not only neuronal dysfunction but also the impaired glial dysfunction. Due to limitations of the present study, we recommend a larger study with an adequate number of patients to support our explanation.

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