

Correlation of Cerebral Blood Flow Velocities and Event-related Potentials in Patients with MS

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Abstract

Objective: Studies on the relationship between cerebral blood flow velocities and event related potential (ERP) changes in non-dementia multiple sclerosis (MS) are completely lacking. The aim of the present study was to evaluate the association between cerebral blood flow velocities and ERP parameters in MS patients.

Methods: 30 patients (8 male, 22 female,) with a mean age of 37 ± 8 years (range: 21-56) with a diagnosis of relapsing remitting MS according to Mc Donald's criteria were included. Their mean EDSS score was 1.8 ± 1.7 (range: 0-5.5) and mean duration of disease was 70 ± 64 (range: 3-228) months. The patients were subdivided according to their mean disease duration. The group with the shorter disease duration comprised 15 MS patients who had been diagnosed with MS for less than 5 years (MS-short), and the group with the longer duration comprised 15 patients with disease durations exceeding 5 years (MS-long)

Results: In the MS patients, the N200 potentials recorded from the frontal, central, and parietal regions were prolonged relative to the controls and the differences were significant. The P300 latencies recorded from the frontal, central and parietal regions were significantly longer in patients with disease durations exceeding 5 years. The mean middle cerebral artery (MCA) blood flow velocities did not differ from those of normal controls.

Conclusion: Although there was a negative correlation between MCA velocity and frontal and parietal N100 latencies, there was no clear correlation between MCA blood flow velocity and ERP parameters. An important finding of this study is a positive correlation between MCA blood flow velocity and Mini Mental State Examination scores. This is the first study to evaluate the relationship between ERP and cerebral blood flow velocity using transcranial Doppler ultrasound. No definite relationship was shown.

Keywords: Cerebral blood flow; Middle cerebral artery (MCA); Event-related Potentials; P300; Transcranial; Doppler Ultrasonography (TCD); Multiple sclerosis; Cognitive dysfunction

Introduction

Cognitive dysfunction can be found in up to 65% of multiple sclerosis (MS) patients even though only small percentage of MS patients present with severe dementia. [1,2]. The most frequent cognitive deficits are present in recent memory, information processing speed, executive function, and visuospatial perception although no abnormalities are detected in general intelligence, language, short term, and implicit memory. However, little information is present concerning the natural history of cognitive dysfunctions during the course of the disease. Clinical studies on this field have revealed that some MS patients show neurobehavioral changes, even in the early phases of the disease, whereas others never develop such changes or complain about it [3]. Large percentage of MS patients who show intact mental capacity on neurological examination are however shown to be actually impaired [4].

Considerable interest exists in the utilization objective and easily administered measures of cognitive dysfunction that can be used to follow patients and also to demonstrate the clinical benefits of various therapeutic interventions [5]. Event related potential (ERP) records electrical manifestations of the brain's perception and response to external stimuli [6].

P300, is one of the most commonly recorded and studied type of ERP [7] and is an electrical signal produced by the brain during the performance of various cognitive tasks [8]. P300 recording has been used to evaluate brain mechanisms underlying cognition and to characterize information processing in normal subjects as well as patients with neurological disorders [9]. Specific studies on P300 ERPs

have been conducted [7] and, although the source of P300 generation has not been clearly shown, multiple areas in bilateral cerebral hemispheres such as the medial part of temporal lobe, temporoparietal junction, prefrontal area, inferior parietal lobe, midbrain, hippocampus thalamus, and basal ganglia have been considered to be important and believed to have a potential role in P300 generation [9].

In general, P300 latency measures the stimulus classification and speed while reflecting the capacity of memory processing [10]. Because P300 peak latency increases systematically with increases in cognitive dysfunction, it has been used as an objective electrophysiological method for determining the degree of demanding process, to measure the stimulus classification speed, and to evaluate the attention and memory processes [11]. Electrophysiological investigations of ERPs have proven to be useful for clinical assessment of attention skills. In MS, the most commonly studied component was P300; which is elicited by target stimulus in active oddball paradigms. Increased P300 latency in these studies was considered as an index of slowing of controlled information processing [5,12-14].

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Transcranial Doppler ultrasound is a noninvasive technique and allows physicians and technicians to study velocity, direction, and other properties of blood flow in cerebral arteries by means of a pulsed ultrasonic beam. Flow velocities have been shown to be proportional to direct invasive flow measurements [15,16].

Studies on the relationship between cerebral blood flow velocities and ERP changes in non-dementia MS are completely lacking. So, the aim of the present study was to evaluate the association between cerebral blood flow velocities and ERP parameters in MS patients.

Methods

The study protocol was in accordance with the Helsinki declaration of human rights, and was approved by the local Ethics Committee and all volunteers gave written informed consent to participate to the study. 30 patients (8 male, 22 female) with a mean age of 37 ± 8 years (range: 21-56) with a diagnosis of relapsing remitting MS according to Mc Donald's criteria [17] were included. All patients were assessed with the Kurtzke Scale and their degree of disability was measured by Kurtzke EDSS [18]. Their mean EDSS score was 1.8 ± 1.7 (range: 0-5.5) and mean duration of disease was 70 ± 64 (range: 3-228) months. This is indicating that this group of patients had mild to moderate disability. All of the patients were receiving immunomodulatory treatment. None of the patients were receiving immunosuppressant in the prior 6 months, or corticosteroids in prior 3 months because of an acute relapse. Patients with history of head injury, alcohol or drug abuse, psychiatric illness, or central nervous system (CNS) disease other than MS, those receiving ant cholinergic or psychoactive drugs, and those having hearing impairment were excluded. Control group consisted from 30 sex matched healthy controls with a mean age of 39 ± 11 .

ERP

First subjects were screened using Mini-Mental State Examination (MMSE) [19]. Recordings were performed using Nihon Kohden-Neuropack (MEB-5504 K) equipment. Evoked potentials were recorded from the scalp by collodion mounted Ag/Ag Cl cup scalp electrodes (type: NE-132B) placed at FZ, CZ and PZ and were linked to the referred ears. Skin impedance was below 5 k Ω . The subjects were sitting comfortably with their eyes closed. They were instructed to mentally count the target tones but not the frequent tones and then asked to report the number of target tones counted at the end of each run. Rest periods were provided between test conditions as appropriate. ERP were elicited with an auditory discrimination task paradigm by presenting a series of binaural 1000 Hz (standard) versus 2000 Hz (target) tones at 70 dB with a 10 ms rise/fall and 40 ms plateau times using DR-531-B10 ear phones. Tones were presented at a rate of 1.1/s with target tones occurring randomly with a 0.2 probability. Filter settings were between 0.1 and 50 Hz, analysis time 1 s, sensitivity 50 μ v and duration of stimulus 0.1 ms. To assess the performance accuracy at the end of each session the patients count was compared with the actual number of target tones presented. Two or 3 trials were performed in order to demonstrate the consistency of the waveform.

Responses to target tone consisted of a prominent negative peak between 65 and 150 milliseconds, identified as N1, followed by a frontocentral positive wave (between 100 and 250 milliseconds) identified as P2. Responses to infrequent tone showed similar N1 and P2 followed by an additional through N2 and the paired, variably separated P300 peaks. P200 and P300 latencies were measured from the stimulus artifact to the first and second major positive peaks with a range 250 to 500 ms respectively [6,13].

TCD

Middle cerebral arteries were insolated through the temporal windows using standardized protocol. Mean (V_m) velocities of right and left middle cerebral artery (MCAM) flow was recorded at depths of 55-65 mm, with a 2-MHz probe by the technique described elsewhere by Aaslid [15]. Only measurements with the best signal-to noise ratio were used and the highest values for cerebral blood flow velocities were selected for analysis. Sample volume was 8-10 mm in the axial and 5 mm in the lateral direction at the depth of 50 mm. All TCD studies were performed with the use of commercially available TCD apparatus Viasons/Sonara (Cardinal Health-Madison-WI/USA).

Statistical analysis

The SPSS 11.0 package was used to perform the statistical evaluation. Continuous data are tested for normality by histograms, p-p plots & Kolmogorov Smirnov test. Independent samples t-test was used to assess the differences between MS patients and controls. Since the variables are normally distributed, the continuous variables are compared by using analysis of variance (ANOVA)-PostHoc Tukey HSD between three groups. Pearson's correlation of coefficient was used when appropriate. A level of $p < 0.05$ was accepted as statistically significant. Data are expressed as the mean \pm SD.

Results

Cerebral blood flow velocities

There were no significant differences between the measurements of the right and left arms of the arteries, so the data were pooled for further analysis ($p > 0.05$) (Table 1). The mean MCA blood flow velocities did not differ from those of normal controls ($p > 0.05$).

The patients were subdivided according to their mean disease duration and reanalyzed. The group with the shorter disease duration comprised 15 MS patients who had been diagnosed with MS for less than 5 years (MS-short), and the group with the longer duration comprised 15 patients with disease durations exceeding 5 years (MS-long). Mean blood flow velocity in the MCA (63 ± 14 cm/s) was higher

	Control(30)	MS(30)	p
Age	39 \pm 11	37 \pm 8	0.7
Dur. of Disease (Months)		70 \pm 64	
EDSS		1.8 \pm 1.7	
MMSE		27 \pm 3	
Frontal Latency(ms)			
N100	105 \pm 18	107 \pm 11	0.6
P200	173 \pm 18	183 \pm 25	0.1
N200	225 \pm 23	249 \pm 40	0.006***
P300	342 \pm 42	347 \pm 66	0.7
Central Latency(ms)			
N100	105 \pm 18	112 \pm 17	0.1
P200	173 \pm 18	184 \pm 24	0.7
N200	225 \pm 23	246 \pm 42	0.024***
P300	345 \pm 37	346 \pm 66	0.97
Parietal Latency(ms)			
N100	106 \pm 18	114 \pm 19	0.1
P200	173 \pm 18	186 \pm 28	0.42
P200	226 \pm 23	251 \pm 37	0.003***
N200	342 \pm 32	346 \pm 83	0.8
P300			
MCA Velocity (cm/s) Mean:	56 \pm 13	60 \pm 14	0.08

Table 1: MCA blood flow velocities and ERP of MS patients and controls.

relative to controls in the short duration group ($p < 0.05$) but not the long duration (59 ± 14 cm/s) group ($p > 0.05$).

Event-related potentials

The latencies of the N100, P200, N200, and P300 potentials recorded from the frontal, central, and parietal areas in the MS patients and controls are presented in Table 1. In the MS patients, the N200 potentials recorded from all three regions were prolonged relative to the controls and the differences were significant ($p = 0.006$, $p = 0.024$, and $p = 0.003$, respectively).

Post Hoc analysis of ANOVA comparisons in between 3 groups (controls vs short vs long) revealed significant differences (increases) in latencies of both the N200 and P300 potentials recorded from frontal ($p = 0.038$, $p = 0.014$), central P300 ($p = 0.010$) and parietal ($p = 0.016$, $p = 0.000$) regions in the group with longer disease duration when compared to controls (Table 2).

Correlations

Cerebral Blood Flow Velocity vs. Event-related Potentials: There was a negative correlation between the latency of the frontal and parietal N100 and mean MCA velocity ($r = -0.442$, $p = 0.021$).

Mini Mental State Examination: There was a positive correlation between Mini Mental State Examination (MMSE) scores and MCA blood flow velocity ($r = +0.374$, $p = 0.046$).

Expanded Disability Status Scale (EDSS): There was a negative correlation between EDSS and MMSE scores ($r = -0.419$, $p = 0.024$) and a positive correlation between EDSS scores and disease duration ($r = +0.557$, $p = 0.002$). EDSS was also positively correlated ($r = +0.426$, $p = 0.027$) with the parietal P300 latency.

Discussion

The P300 latency is increased in patients with dementia, regardless

	Control (30)	MS(15) (Short)	MS(15) (Long)	Z	P
Age	39 ± 11	36 ± 8	39 ± 9		
Dur of Disease (Months)		16 ± 10	124 ± 48		
EDSS		1.2 ± 1	2.6 ± 2		
MMSE		27 ± 2	26 ± 3		
Frontal Latency (ms)					
N100	105 ± 18	106 ± 8	109 ± 13	0.254	0.77
P200	173 ± 18	182 ± 29	183 ± 22	1.364	0.26
N200	225 ± 23	244 ± 45	250 ± 30	3.460	0.038***
P300	342 ± 42	335 ± 43	376 ± 42	4.653	0.014***
Central Latency(ms)					
N100	105 ± 18	107 ± 9	111 ± 18	0.744	0.48
P200	173 ± 18	184 ± 27	181 ± 19	1.343	0.27
N200	225 ± 23	236 ± 45	250 ± 33	2.688	0.07
P300	345 ± 37	332 ± 43	378 ± 38	5.041	0.010***
Parietal Latency(ms)					
N100	106 ± 18	108 ± 14	115 ± 16	1.21	0.30
P200	173 ± 18	183 ± 29	186 ± 24	1.748	0.18
N200	226 ± 23	243 ± 35	253 ± 31	4.432	0.016***
P300	342 ± 32	337 ± 42	390 ± 39	9.121	0.000***

***PostHoc analysis of ANOVA comparisons revealed that the significant differences (increases) in ERP latencies was present in between controls and in patients with longer disease duration

Table 2: ERPs of MS patients with a disease duration of less (short) and more than (long) 5 years.

of the etiology of their mental dysfunction. P300 abnormalities are particularly connected to certain cognitive deficits such as defective short term memory, perceptual processing speed, and decreased alertness and attention in patients with dementia and in older age population. The decreased P300 latency is believed to reflect maturation as well as the speed of the cognitive processes [8].

Cortical and subcortical gray matter injury is increasingly recognized as a prominent pathological substrate of irreversible neurological dysfunction in MS [20]. A number of studies using single photon emission computed tomography revealed reduced cerebral blood flow (CBF) as well as hypometabolism in gray and white matter areas that have been examined. Studies with functional magnetic resonance imaging have shown adaptive changes in cortex as well as increased activation in certain regions that were remote from the lesions and were considered to be due to cortical plasticity [21]. Hypo perfusion of gray matter in MS is believed to be the result of the disconnection between cerebral cortex and subcortical structures because of white matter damage [22].

MS patients with disease duration of less than five years had increased middle cerebral artery (MCA) velocities, whereas those with duration of greater than five years had MCA blood flow velocities similar to control levels. The increased MCA blood flow velocities observed in the early stages of MS may be a consequence of inflammation mediated hyperemia. It is obvious that inflammation can cause increases in blood flow velocities due to increased perfusion caused by the secretion of vasoactive amines, and amines causes the vasodilatation of the arteries which leads to increases in cerebral blood flow [23]. In MS, as in other inflammatory diseases, vasodilatation occurs as a result of perivascular inflammation which theoretically, would increase cerebral blood volume [24].

Our results are consistent with the reported results of ERP abnormalities [5,12-14]. As a whole, MS patients showed latency prolongation of the N200 component, as compared to controls. However, when the patients were subdivided according to their mean duration of disease, those with disease durations of less than five years did not show any ERP abnormalities, while those with the disease for more than five years had prolongation in the frontal, central, and parietal N200 and P300 latencies. The positive correlation between P300 latency and disease duration has been reported previously [3,7,12,13]. Even though ERP latencies do not necessarily correlate with a cognitive dysfunction relevant to daily life, they are believed to express an organic impairment of specific aspects of cognitive processing that can become pertinent in the advanced stages of disease [3].

The significant negative correlation between P300 latency and cerebral blood flow has been reported in patients with multiple cerebral infarctions using the Xe133 inhalation method [25,26]. Sakai et al., investigated P300 and PET in various neurological diseases and believed that the blood flow in the right parietal lobe, bilateral thalamus, and bilateral temporal lobes have an effect on the increases of P300 latency [27]. Kawata et al. investigated P300 and cold xenon computed tomography in a group of neurosurgical patients and reported that the right cerebral hemisphere and thalamus have an effect on the prolongation of P300 latencies [28].

Although there was a negative correlation between MCA velocity and the frontal and parietal N100 latencies, there was no definite correlation between MCA blood flow velocity and ERP parameters. One important finding is the positive correlation between MCA blood flow velocity and Mini-Mental State Examination (MMSE) score,

which has previously been reported [29] Cerebral hypoperfusion has been considered and accepted as an important risk factor for cognitive dysfunction and dementia [30].

Cognitive dysfunction can be evaluated by neurophysiological testing, a procedure that takes 3 to 5 hours to complete and heavily depends on subject's cooperation. On the other hand, brief assessment tools for screening, like MMSE, have been shown to be fairly insensitive as well as unreliable to detect mild cognitive dysfunction [3]. We believe ERPs may be a potentially useful technique for demonstrating electrophysiological abnormalities in the absence of clinically demonstrable deficits.

Conclusion

We believe that this is one of the first transcranial Doppler ultrasound studies to evaluate the relationship between ERP and cerebral blood flow velocities. Although no definite relationship was shown, there was a positive correlation between MMSE scores and MCA blood flow velocity.

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