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Short communication

Impairment of neuromuscular transmission in transient global amnesia – Does it really exist?

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ABSTRACT

Background: The main hypotheses regarding mechanisms of transient global amnesia (TGA) are ischemia in hippocampal structures, epileptic genesis, and migraine. In accordance with the hypothesis of a shared, common pathophysiological mechanism in both TGA and migraine, neuromuscular transmission (NMT) abnormalities previously found in migraine were also suspected in TGA.

Objective: The aim of our study was to analyze NMT in TGA patients to reveal a subclinical impairment of neuromuscular transmission as a possible indicator of underlying channelopathy, which would point to a shared etiology with migraine.

Materials and methods: The study group consisted of 15 patients (6 males) with TGA (mean age 69.5 ± 7.4 yrs). The duration of amnesia ranged from 1 to 6 h (mean 4.4 h). Single fiber electromyography (SFEMG), the most sensitive tool for NMT assessment, of the voluntarily activated frontal muscle was performed 1–5 days after a TGA incident.

Results: Abnormal SFEMG was found in 1 patient (6.6%). In all other patients, SFEMG was in the normal range.

Conclusion: Our neurophysiological study does not confirm NMT defects in TGA. The role of channelopathy with NMT dysfunction in the pathogenesis of TGA is rather unlikely, whereas subclinical NMT abnormalities were certainly proven in migraine.

1. Introduction

Transient global amnesia (TGA) is an acute episode of memory disturbance occurring in middle-aged or older patients, clinically manifesting by transient inability to lay down new memories (anterograde amnesia) with associated mild to moderate problems with access to memories of events that occurred in the past (retrograde amnesia) but without other neurological signs. According to the diagnostic criteria: (1)

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attacks must be witnessed and information should be available from a capable observer who was present for the most of the attack; (2) clear-cut anterograde amnesia must be present during the attack; (3) clouding of consciousness and loss of personal identity are absent; (4) no focal neurological signs should be present; and (5) attacks must resolve within 24 h [1].

Although the clinical criteria are clear, previous research has failed to identify the etiology of TGA, and several mechanisms have been proposed. The presumption that TGA is caused by transient dysfunction of the hippocampi which are involved in creating episodic memory is not controversial but the cause of this dysfunction remains unclear. The main hypotheses regarding TGA mechanisms are ischemia in hippocampal structures, epileptic genesis, and migraine [2–15].

A migrainous origin of TGA has been proposed due to transient dysfunction of brain structures caused by spreading depression of cerebral activity. According to this hypothesis, intensive sensory stimuli lead to glutamate release in the hippocampi and cause spreading depression and transient hippocampal dysfunction [14], with memory disturbances. Hypothetically, neurotransmitter alterations could be the reason for a functional disability of transmission in the hippocampal structures. Subclinical neuromuscular transmission (NMT) dysfunction was found in migraine and cluster headache [16–18]. Although patients with migraine do not show clinical symptoms of a neuromuscular transmission defect, single fiber electromyography (SFEMG) as the most sensitive tool for detecting NMT abnormalities may suggest P/Q Ca^{2+} channel dysfunction [17]. Voltage-dependent P/Q Ca^{2+} channels are localized in the presynaptic motor axons at the neuromuscular junctions but are also widely distributed in the central nervous system. The role of these channels is due to neurotransmitter release including glutamate, which is the main excitatory transmitter of major importance for memory functions. Glutamate-mediated depolarization with suppression of neuronal activity and spreading cortical depression could play a role in both migraine and TGA. Because of the hypothesis of a shared, common pathophysiological mechanism of TGA and migraine, NMT was also studied in TGA.

Ertas et al. investigated 6 patients diagnosed with TGA and 5 healthy volunteers at a similar age. SFEMG during voluntary contraction of the extensor digitorum communis (EDC) muscle was performed. The results suggested that TGA shares the same type of subclinical NMT abnormality as observed in migraine patients in a previous study [19]. Gursoy et al. reported one patient with TGA in whom 11/15 pairs of the jitter values exceeded the upper limit of normal range.

The aim of our study was to analyze NMT in TGA patients to reveal a subclinical impairment of neuromuscular transmission as a possible indicator of underlying channelopathy which would point to a shared etiology with migraine.

2. Materials and methods

The study group consisted of 15 patients with TGA diagnosed according to the criteria by Hodges et al. [1] (mean age 69.5 ± 7.4 yrs), including 6 males (40%). In all patients, attacks were witnessed and information was available from a capable observer, clear-cut anterograde amnesia was present during the attack, clouding of consciousness and loss of personal identity were absent, no focal neurological signs were present and all attacks resolved within 24 h [1].

All patients gave a written informed consent to participate in EMG examinations and the study protocol was approved by the Ethics Committee at the Medical University of Warsaw (approval No. KB 162/2011). Neurological examinations did not reveal any abnormalities, and the medical history was unremarkable except for well-controlled arterial hypertension in 7 cases (46.6%) and hypercholesterolemia in 4 cases (26.7%). The duration of amnesia ranged from 1 to 6 h (mean 4.4 h). Routine blood tests, electroencephalography, transcranial Doppler ultrasonography, and Doppler ultrasonography of carotid and vertebral arteries did not reveal any abnormalities. CT or MRI with diffusion-weighted imagine showed small lacunar ischemic lesions in both hemispheres in 12 patients (80%) (Table 1).

The SFEMG examination was conducted by an experienced, blinded electromyographist in the EMG Laboratory at the Department of Neurology, Medical University of Warsaw. SFEMG of the voluntarily activated frontal muscle was conducted as described by Stalberg et al. using a Keypoint electromyograph (Medtronic, Skovlunde, Denmark) [22,23]. For NMT investigation, the frontal muscle was chosen due to our experience with SFEMG of this muscle Special single fiber needle electrodes with a 25 mm recording diameter were used. In all tested subjects, 20 potential pairs were collected, and the mean consecutive difference (MCD), or jitter value was subsequently calculated for each pair. MCD is the mean of the differences between the intervals between consecutive potential pairs, calculated using dedicated software, and is a standard parameter for the assessment of neuromuscular transmission, reflecting the safety factor of the neuromuscular junction [21,22]. Filters were set between 500 Hz (high pass filter) and 30 kHz (low pass filter). Sweep velocity was set at 1 ms/division. At least 20 jitter recordings from the frontal muscle were made during voluntary activation in each subject.

The results were compared with age-specific normal values for the frontal muscle and considered abnormal when the mean MCD value exceeded the mean normal value, or more than two pairs had an MCD value above the upper limit with or without blocking [24]. The SFEMG was performed 1–5 days after the TGA incident.

Statistical analysis of the data was performed using Statistica 10 software. The chi-square test, Student's t test and multiple comparison test were used to evaluate differences between patients. Statistical significance was set at $p < 0.05$.

3. Results

Abnormal SFEMG in the frontal muscle was found only in 1 patient (6.6%) (patient no. 9). In another patient, only one jitter exceeded the upper normal limit of MCD but the mean MCD value was within the normal range (patient no. 12) (Table 2). SFEMG in all other patients showed the mean MCD value within the normal range and no abnormal single jitter