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Event related potentials in patients with transient global amnesia—A prospective controlled study ☆

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ABSTRACT

Objective: The aim of this study is to evaluate changes in the latencies and amplitudes of event-related potential (ERP) components as well as cognitive habituation in patients with transient global amnesia (TGA) in order to further characterize the pathology of this syndrome.
Methods: Clinical data of 43 consecutive patients with TGA was collected at a university neurology department. Follow-up examination was performed at an average of 17 months after TGA. Results were compared to 43 age- and sex-matched healthy control subjects.
Results: All ERP latencies of patients examined within 10 days after the TGA period were significantly increased, and the P3 amplitude was significantly decreased as compared to healthy control subjects. The rate of pathological P3 latencies was significantly higher in TGA patients. A normal P3 latency habituation was detected in 84% of all healthy controls (mean habituation 10 ms) and in 33% of all TGA patients (mean habituation −6 ms). There was no significant improvement of all latencies and the other ERP parameters, including the loss of habituation, after a mean observation period of 17 months. The data of three patients who were measured during the TGA period suggest a severe impairment of ERP during this period.
Conclusions: Our findings give new insight into the pathology of TGA and put into question if TGA is an event of a simple transient character. In this first investigation of cognitive habituation in patients with TGA, we found a characteristic loss of cognitive habituation similar to observations in migraine.

1. Introduction

Transient global amnesia (TGA) is a syndrome of high scientific interest. Numerous questions concerning its origin and etiology remain unanswered to date. TGA is defined as a loss of episodic memory with sudden onset and recovery within 24 h [1]. The attack usually lasts a few hours. The patient may suffer from mild vegetative symptoms and subclinical neuropsychological deficits up to some days [2–6], but amnesia for the time of the episode is commonly acknowledged as the only sequel [1]. Nevertheless, some neuropsychological studies suggest a mild memory impairment persisting for months after acute TGA [6–8].

The diagnosis is based on clinical criteria: 1. presence of anterograde amnesia during the attack that is witnessed by a capable observer; 2. absence of clouding of consciousness or loss of personal identity, cognitive impairment other than amnesia, focal neurological signs, epileptic seizure signs, recent history of head injury or seizures; and 3. resolution of the attack within 24 h [1].

Various factors have been proposed to contribute to the etiology of TGA such as migraine, epilepsy, focal ischemia, and cerebral venous flow abnormalities [6,9–12]. However, its exact origin still remains poorly understood. Recently, hyperintense lesions in diffusion weighted imaging were detected in the mesiotemporal region of the hippocampus [5,11,13–17]. It is assumed that these structures might play a crucial part in the etiology of TGA [6].

Event-related potentials (ERP) are regarded as an objective tool to measure individual cognitive memory functions [18] and have been investigated in TGA [19]. They represent the cognitive processing of relevant stimuli as a correlate of brain electric activity. As a primary goal, our study evaluated changes in the latencies and amplitudes of ERP components in a larger cohort of patients with TGA at different time intervals. Further, cognitive habituation has never been investigated in patients with TGA. It is defined as the decrease in neural responsiveness due to repeated stimulation and is represented by changes of ERP components (i.e., latencies and amplitudes) in a two-trial analysis [20]. Examination of the P3 component has shown a loss of habituation in patients suffering from migraine [21]. This

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might be of particular interest because common elements in the pathophysiology between migraine and TGA have often been proposed yet failed to be proven [6,22].

2. Patients and methods

2.1. Patients

A total of 43 consecutive patients who suffered at least from one definite episode of TGA were included in this study. Clinical data was collected at the Department of Neurology, University of Münster.

Patients were diagnosed with TGA if they met the diagnostic criteria defined by Hodges and Warlow [1]. Their medical examination and diagnosis was performed by a physician experienced in TGA. An electroencephalogram (EEG) and magnetic resonance imaging (MRI) were performed to exclude intracranial lesions and epileptic activity. We also recorded age, sex, other disorders, in particular a history of migraine or arterial hypertension, a positive family history, height, weight, and the duration of the amnesia and TGA, respectively. In addition, 43 age- and sex-matched healthy control subjects were recruited from an internal database of healthy volunteers.

All patients gave informed consent prior to study examination. Event-related potentials were recorded at different times after TGA, depending on the time of admission. A follow up-examination was performed at an average of 17 months after TGA. We were able to record ERP during an acute TGA attack in 3 patients, within10 days (average 3.3 days) after an episode of TGA in 27 patients (early time period), and more than 10 days up to 3 years (average 17 months) after the attack in 29 patients (late time period). In 29 patients, we obtained ERP data both from the early and the late time period.

2.2. Event-related potentials

In all patients, ERP were recorded by the same procedure published previously [18,20,21]. They were seated in a dark air-conditioned room where they were asked to observe a 30×30 cm screen placed 150 cm in front of them and to press a button with the dominant hand whenever a red light occurred on the screen while to ignoring a white light.

ERP were evoked by an oddball paradigm with 15% flashes of red light (6 Candela) and 85% flashes of white light (17 Candela). Four hundred red and white flashes of 100 ms each were presented in two trials (with 200 flashes each) in a randomized order. Flashes occurred in an interval of 1800 ms.

ERP were recorded by an EEG amplifier using Ag–AgCl surface electrodes placed at centroparietal and linked to the mastoid according to the international 10–20 system. Eye movement was controlled by electrooculography in order to exclude EEG periods with eye movement artifacts from the subsequent averaging process. Curves with a maximum amplitude of more than 200% of the average were automatically rejected. A high frequency filter was set at 70 Hz, and a low one at 0.1 Hz. The EEG was digitally stored by a computer system which averaged the EEG periods of 300 ms before and 1100 ms after onset of the stimulus separately for the red and white flash.

ERP following the red (target) stimulus were evaluated. Latencies of the components P2, N2, and P3, amplitude of the P3 component (difference to average voltage before stimulus) and also the mean choice reaction time (onset of pressing the button) were measured according to international recommendations [23]. ERP were averaged separately for each of the two trials with 200 stimuli each in order to detect habituation. Typical ERP curves of our system including analysis of potentials have been published elsewhere [24].

Age-related local laboratory normal values in adults for P3 latency have been evaluated and published previously [20,25]. If latencies were longer than the age-matched arithmetic mean plus two standard deviations, they were classified as pathologically increased.

2.3. Statistical analysis

Statistical analysis was performed with SPSS software, version 18.0. The values (latencies, habituation, amplitude etc.) of ERP in TGA patients and healthy control subjects were statistically compared by Mann–Whitney–*U*-test or by χ^2-test. Comparison between the ERP data at different time points after the period of amnesia was performed by Wilcoxon-test. For comparison of mean values, $p<0.05$ was considered significant as well as $p<0.01$ for analysis of correlation.

3. Results

In total, we enrolled 43 patients with TGA and 43 age- and sex-matched healthy control subjects. In Table 1, the clinical and demographic data of the TGA patients is presented. Of note, there were a very high prevalence of arterial hypertension and a higher prevalence of migraine than could be expected from the general population. TGA was recurrent in 15%. The duration of the remaining amnesia was longer in average than the duration of the TGA period as described by the relatives and observed in the hospital.

The ERP data of the patients examined within 10 days after the TGA period and of the healthy control subjects are presented in Table 2. All latencies were significantly increased in the TGA patients, and the P3 amplitude was significantly decreased as compared to the healthy control subjects. The rate of pathological P3 latencies was significantly higher in the TGA patients. In healthy controls, a normal P3 latency habituation was detected in 84% of all cases with a mean habituation of 10 ms. In contrast, a normal habituation was seen in 33% of all TGA patients, the mean habituation was −6 ms.

In Table 3, the ERP data of the TGA patients at different time points are presented. We could measure three patients during the TGA period. The data show no significant improvement of all latencies and other ERP parameters after a mean observation period of 17 months. Even the loss of habituation remained stable during this observation period.

The correlation between the duration after the TGA event (in days) and the amount of P3 habituation (in ms) was $r=-0.337$ ($p=0.099$; Spearman correlation coefficient). Although this correlation was not significant, it showed the trend that the loss of habituation increased with the duration of the interval from the TGA event.

The data of the three patients who were measured during the TGA period suggest a severe impairment of ERP during this period. In these patients, the habituation was normal, although they later showed a loss of habituation. However, the number of these patients is too low to allow any statistical comparison.

4. Discussion

TGA is a syndrome of distinct clinical definition, but little knowledge about its origin and neurophysiologic processes exists. We measured ERP and cognitive habituation in patients with TGA to elucidate abnormal cognitive functions after the event. We found that both P3 latencies and amplitudes are pathologically altered in comparison to

Table 1
Clinical and demographic data of the patients with TGA.

Age (years)	63 +/− 11
Sex (female)	54%
History of arterial hypertension	71%
History of migraine	29%
Height (cm)	171 +/− 8
Weight (kg)	78 +/− 10
TGA	
Positive family history	6%
Duration of TGA (hours)	5.1 +/− 3.8
Recurrent TGA	15%
Duration of amnesia (hours)	7.2 +/− 6.5