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Auditory event-related potentials (P300) in partial and generalized epileptic patients

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We evaluated the P300 components of event-related potentials (ERP) in 64 cryptogenic partial epilepsy (CPE) patients, and 52 idiopathic generalized epilepsy (IGE) patients as well as in their age-matched control groups. The P200, N200 and P300 latencies recorded from Cz were significantly longer in CPE patients compared with those of their control group ($P = 0.0371$, $P = 0.0092$ and $P = 0.0405$, respectively). The P200 and N200 latencies recorded from Fz were significantly longer than in their control group ($P = 0.0448$ and $P = 0.0107$) while the prolongation in the P300 latencies was not found to be statistically significant ($P = 0.0733$). All latencies were longer in IGE patients, and the amplitudes of the N200/P300 components of ERP were lower in both epileptic groups compared with their control groups, but these differences were not significant. The prolongation of the P300 latencies was not correlated with the type or serum level of antiepileptic drug or seizure control. Our findings suggest that the prolongation of the P300 latency of ERP is related to the type of epilepsy.

Key words: cryptogenic partial epilepsy; idiopathic generalized epilepsy; P300; event-related potentials.

INTRODUCTION

The P300 component of event-related potentials (ERPs) is generated when a subject attends and discriminates between two different stimuli, one of which is presented infrequently[1–4]. It was first described by Sutton in 1965[5–8]. Since then, many investigations have focused on P300 generators and their relationships with cognitive functions[9–12]. The hippocampus, thalamus and frontal lobe have been considered as possible locations of the P300 generators[1–3, 6, 7, 11, 13–21]. As a result, it has been emphasized that P300 might represent the sum of the activities of many different generators[7, 20].

It is also known that various neurological disorders including epilepsy are accompanied by cognitive impairment that is related to the latency of the P300 component[1–3, 7, 8, 13, 15–24]. Various degrees of cognitive impairment have been reported in different epileptic syndromes[2, 7, 8, 13, 15, 16, 18, 20, 22, 24]. We aimed to evaluate the latency and amplitude of the P300 component of auditory ERP in epileptic patients with cryptogenic partial epilepsy and idiopathic generalized seizures, and compare them with those of volunteer, age-matched, healthy controls.

MATERIALS AND METHODS

Sixty-four (35 men and 29 women) cryptogenic partial epilepsy (CPE) patients and 52 (19 men and 33 women) idiopathic generalized epilepsy (IGE) patients were studied at the epilepsy outpatient clinic of Bakırköy State Hospital for Neurological and Psychiatric Diseases. All patients were selected according to the criteria of the ILAE. The mean age was 19.56 ± 6.09 years (ranging from 12 to 43 years) for IGE, and 25.64 ± 10.75 years (ranging from 15 to 54 years) for the CPE group. There was no structural lesion in cranial CT/MRI investigations of patients with partial epilepsy. In the CPE group, 21 patients had been treated with phenytoin (PHT), 40 with carbamazepine (CBZ) and three with valproic acid (VPA); and in the IGE group four with PHT, two with CBZ, one with phenobarbital (PB) and 45 with VPA. The seizures of 10 IGE and

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26 CPE patients were not satisfactorily controlled with antiepileptic drugs. Their antiepileptic serum drug levels were in therapeutic ranges and none of the patients showed the stigma of intoxication. Since the mean age of the IGE patients was significantly lower than that of the CPE patients, we had to use two different age-matched control groups of healthy volunteers for each study group. The control groups for IGE and CPE consisted of 15 (eight men and seven women; the mean age was 22.00 $\pm$ 6.64 years, ranging from 12 to 32 years) and 20 (10 men and 10 women; the mean age was 24.85 $\pm$ 7.71 years, ranging from 12 to 35 years) individuals, respectively.

ERPs were studied by using a Medelec Sapphire 4ME device. Binaural auditory stimuli were presented by earphones. Fifteen percent of stimuli were rare (target) tones of 1000 Hz (95 dB) whereas the remainder were frequent (nontarget) tones of 8000 Hz (95 dB). The stimulus sequence was random.

ERPs were recorded at Fz and Cz using Ag/AgCl electrodes which were referred to linked mastoids, according to a 10–20 system. All the electrodes had a resistance of 2 kΩ or less and the filter bandpass was 0.1–50 Hz. Randomized, artifact free, 32 target and 168 nontarget stimuli were averaged simultaneously and separately. Data from the two trials were obtained consecutively and stored. The latency and the amplitude of the P300 component of the target averages recorded at Fz and Cz were measured.

Patients and control subjects were seated on a comfortable chair in a quiet room with their eyes lightly closed, and requested to count the number of rare tones. Prior to the recordings, experimental procedures were explained to the subjects, a short test was given to be sure that the patients understood the instructions, and then recordings were taken.

The latency of the N100, P200, N200, P300 responses and the amplitude of the N100/P200, P200/N200, N200/P300 responses to rare tone stimulation were measured with cursors, and the results of the patients were compared with those of their control groups using Student's *t*-test, the Mann Whitney *U*-test and Pearson correlation tests.

RESULTS

Table 1 shows the N100, P200, N200 and P300 latencies and Table 2 summarizes the N100/P200, P200/N200 and N200/P300 amplitudes of the P300 components of auditory ERPs recorded from Fz and Cz in the IGE/CPE patients and their control groups. In the CPE group, the P2, N2 and P3 latencies recorded from Cz were significantly longer than in their control group ($P = 0.0371$, $P = 0.0092$ and $P = 0.0405$, respectively). The P200 and N200 latencies recorded from Fz were significantly longer than their control group ($P = 0.0448$ and $P = 0.0107$); the P300 latencies were longer than in their control group as well, but this difference was not found to be significant ($P = 0.0733$). All latencies were longer in IGE patients than in their control group. However, there was no significant difference between the IGE patients and their control group. In both epileptic groups, the amplitudes of the N200/P300 components recorded from Fz and Cz were lower than their control groups; these however, were not found to be significant.

When considering the changes in the latencies and amplitudes of the P300 components among epileptic patients with controlled or uncontrolled seizures, no differences were found. Again, no specific effect resulting from the type or serum level of the antiepileptic medications was noticed.

DISCUSSION

In the literature, it has been reported that there are some abnormalities in the P300 component of ERPs in epileptic patients. However, the results are controversial. Drake *et al.*[13] reported increased P300 latencies in patients with complex partial seizures and partial seizures with secondary generalization. Fukai *et al.*[7] found that the P300 latencies were significantly longer in temporal lobe epilepsy (TLE) patients compared with those of IGE patients and their control groups. Nelson *et al.*[16] noted variability in the amplitude and latency of the P300 component during pre-surgical evaluation of temporal lobectomy patients. Puce *et al.*[2] reported that the limbic P300 potential was absent or rudimentary on the site of the focus in 48 of 59 patients (81%) having TLE. As a result, all the investigators mentioned above have hypothesized that the hippocampus might play an important role in the generation of the P300. On the other hand, Rugg *et al.*[18] reported that the P300s were symmetrical and of normal amplitude in a patient with a low grade infiltrating glioma which involved the full extent of the left medial temporal lobe. Thus, they claimed that it was difficult to support the hypothesis suggesting that the hippocampus, or any other medial temporal structure, makes a substantial contribution to the scalp P300. In another study, Sunage *et al.*[20] examined the P300 latencies in children with IGE and TLE, and found prolonged P300 latencies in IGE patients. They speculated that the dysfunction of the mesencephalic reticular formation and thalamus may play major roles in the genesis of generalized epilepsy, and thus, in the prolongation of the P300 latencies. However, the impact of the antiepileptic therapy on the P300 latencies in Sunago's study was not apparently discussed.

Table 1: The latencies of P300 components of auditory ERPs recorded from Fz and Cz in IGE epilepsy patients and CPE patients and their control groups.

Wave form	IGE	Control	*P*	CPE	Control	*P*
FzN100	138.4 ± 34.5	137.7 ± 27.3	0.9520	144.8 ± 38.7	132.9 ± 28.9	0.4947
FzP200	180.1 ± 3.2	178.4 ± 26.7	0.8390	192.0 ± 35.2	171.3 ± 29.1	0.0448
FzN200	223.3 ± 40.2	219.8 ± 27.0	0.5523	235.7 ± 38.1	211.6 ± 32.4	0.0107
FzP300	320.9 ± 33.2	317.0 ± 16.6	0.8039	337.4 ± 56.4	316.5 ± 33.0	0.0733
CzN100	137.1 ± 35.7	137.2 ± 27.2	0.9520	143.5 ± 38.7	133.0 ± 28.4	0.4980
CzP200	179.9 ± 40.0	176.7 ± 26.6	0.9940	190.5 ± 37.0	169.7 ± 29.0	0.0371
CzN200	221.4 ± 41.1	214.9 ± 26.7	0.4889	232.6 ± 39.2	207.4 ± 31.9	0.0092
CzP300	318.7 ± 33.3	314.3 ± 14.6	0.7634	336.3 ± 55.5	314.8 ± 29.2	0.0405

Table 2: The amplitudes of P300 components of auditory ERPs recorded from Fz and Cz in IGE epilepsy patients and CPE patients and their control groups.

Wave form	IGE	Control	*P*	CPE	Control	*P*
FzN100/P200	7.44 ± 5.18	7.47 ± 3.46	0.5778	7.79 ± 4.02	6.49 ± 3.55	0.1954
FzP200/N200	-7.03 ± 4.83	-6.51 ± 4.01	0.8745	-6.16 ± 3.91	-6.05 ± 3.67	0.9247
FzN200/P300	17.44 ± 8.33	19.87 ± 6.52	0.1856	18.0 ± 11.1	20.2 ± 8.09	0.1840
CzN100/P200	8.91 ± 6.54	9.15 ± 5.59	0.6736	9.17 ± 5.36	7.93 ± 5.43	0.3184
CzP200/N200	-7.07 ± 5.22	-7.29 ± 4.96	0.7924	-6.12 ± 4.19	-6.79 ± 4.56	0.6365
CzN200/P300	19.8 ± 10.14	20.8 ± 6.04	0.2924	19.8 ± 9.86	20.1 ± 6.15	0.6216

Rodin *et al*. found that chronic epilepsy patients had more prolonged P300 latencies than normal subjects, but there were significant differences on the basis of seizure type or anticonvulsant concentrations[20]. Enoki *et al*. reported that the type of epilepsy had no effect on the latency of P300 in epileptic children[20]. Our data showed that the P300 latencies of patients with CPE were longer than those of normal subjects, but was not influenced in patients with IGE. Thus, we suggest that seizure type had a significant effect on the latency of P300.

In two different studies, Van Rijckevorsel-Harmant *et al*.[15] and Naganuma *et al*.[8] reported a significant correlation between the serum concentration of antiepileptic drugs and the latencies of P300. In another two studies, however, Sunaga *et al*.[20] and Fukai *et al*.[7] did not support these findings. Our findings were similar to Sunaga's and Fukai's studies.

In conclusion, we found that the latencies of the P300 components of ERP in CPE patients were longer than those of their control group, and this prolongation is not related to the type/serum level of antiepileptic drug and seizure control, but related to the type of epilepsy. As all but three of the patients with CPE were taking sedative drugs such as CBZ, PHT and PB, whereas all but seven of those with IGE were on VPA monotherapy, it is difficult to rule out the impact of the type of antiepileptic therapy on the results in our study. Although we have not statistically found any difference in P300 latencies between the groups taking different medications, it should be taken into account that the patients were not homogeneously distributed with respect to antiepileptic medication. Therefore, further studies evaluating P300 latencies in epileptic patients before and after antiepileptic drug administration are needed to explain the controversies in recent studies.

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