The Effect of Major Depression on Event-Related Potentials in Epileptic Patients

Epilepsili Hastalarda Majör Depresyonun Olaya Bağlı Potansiyeller Üzerine Etkisi

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Objectives: To evaluate the effect of major depression on auditory event-related potentials (P300) in epileptic patients.

Patients and Methods: The study included epileptic patients with (n=23) or without (n=37) major depression. Twenty-five healthy volunteers were also included as controls. All the patients and controls were administered the Mini-Mental State Examination and the Hamilton Depression Rating Scale. Neurologic and psychiatric examinations were made and auditory event-related potentials were recorded with the conventional technique.

Results: The mean P300 latency at Pz in patients with epilepsy and depression (401.35±48.61 ms) was significantly prolonged compared with that of patients without depression (382.51±30.95 ms) (p=0.04). Similarly, compared with the control group (353.52±40.25 ms), P300 latencies at Pz were significantly prolonged in both epileptic groups (p=0.001). P300 amplitudes did not differ significantly between the epileptic groups and the controls. P300 latencies were not different in patients taking valproate or carbamazepine.

Conclusion: Our results suggest that major depression may exert a significant effect, independent of other factors, on the prolongation of P300 latency in epileptic patients.

Key Words: Acoustic stimulation; audiometry, evoked response; depression/physiopathology/complications; electroencephalography; epilepsy/physiopathology; event-related potentials, P300/physiology; evoked potentials, auditory/physiology.

Amaç: Epilepsili hastalarda majör depresyonun işitsel olaya bağlı potansiyeller (P300) üzerine etkisini değerlendirmek.

Hastalar ve Yöntemler: Çalışmaya depresyonu olmayan epilepsili 37 hasta ve majör depresyonu olan epilepsili 23 hasta alındı. Yirmi beş sağlıklı kişiden kontrol grubu oluşturuldu. Hasta ve kontrollerin tümünde Mini-Mental Test ve Hamilton Depresyon Değerlendirme Ölçeği uygulandı; nörolojik ve psikiyatrik muayeneleri yapıldı ve işitsel olaya bağlı potansiyeller klasik yöntem ile kaydedildi.

Bulgular: Depresyonlu epilepsili hastalarda Pz'den kaydedilen P300 latansları ortalaması (401.35±48.61 ms) depresyonsuz hastaların ortalamasından (382.51±30.95 ms) anlamlı derecede uzun bulundu (p=0.04). Benzer şekilde, iki epilepsili grupta Pz'den kaydedilen P300 latansları, kontrol grubuna göre (353.52±40.25 ms) anlamlı derecede uzundu (p=0.001). Epilepsili gruplar ve kontrol grubunun P300 amplitüdleri arasında anlamlı fark yoktu. Valproat veya karbamazepin kullanan epilepsili hastaların P300 latansları birbirlerinden farklı değildi.

Sonuç: Bulgularımız majör depresyonun epileptik hastalarda P300 latans uzaması üzerinde, diğer faktörlerden ayrı olarak önemli bir rol oynadığını göstermektedir.

Anahtar Sözcükler: Akustik stimülasyon; odyometri, uyarılmış cevap; depresyon/fizyopatoloji/komplikasyon; elektroensefalografi; epilepsi/fizyopatoloji; olaya bağlı potansiyeller, P300/fizyoloji; uyarılmış potansiyeller, işitsel/fizyoloji.

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The P300 component of auditory event-related potentials (ERPs) is generated when a subject discriminates between diverse stimuli. Event-related potentials associated with cognitive activity were first reported by Sutton *et al.*[1] in 1965. In particular, the major positive component, P300, has been reported to be related to cognitive function. Some abnormalities in ERPs have been described in patients with epilepsy,[2,3] dementia,[4,5] schizophrenia,[6,7] mental retardation,[8] depression,[9-11] and various neurological disorders.[12,13] The cause of these abnormalities in patients with epilepsy is unknown. Antiepileptic medications[3,14,15] and epileptogenesis itself[3,16] may play an etiologic role in some cases.

Psychiatric morbidity occurs more frequently in patients with epilepsy than in general population.[17-20] Compared with normal controls, a history of depression was elicited 17 times more frequently in patients with partial epilepsy.[21] In a study carried out in Sweden, patients with newly diagnosed epilepsy had a history of depression that was seven times more than the controls.[22]

The present study was designed to evaluate the effect of major depression on the prolongation of P300 latency in epileptic patients.

PATIENTS AND METHODS

Sixty patients (32 males, 28 females) were diagnosed as having epilepsy according to the criteria of Commission on Classification and Terminology of the International League Against Epilepsy.[23] Computed tomography (CT) examination of the brain performed in all patients did not show any lesions. Seizure types included generalized (n=27), complex partial (n=15), simple partial (n=1), and mixed (generalized and complex partial) (n=17) seizures. All patients were normal by medical, neurologic, and psychiatric examinations except for epilepsy and depression. All patients were seizure-free or a satisfactory control of seizures was achieved using antiepileptic drugs, with the last seizure occurrence three to 11 months (mean 6.23±2.41 months) before the study. Patients were either administered monotherapy with valproate (VPA) (n=20), carbamazepine (CBZ) (n=18), and phenytoin (PHT) (n=10), or polytherapy (n=10) with the above-mentioned and other drugs. Serum concentrations of antiepileptic drugs were within or below the therapeutic range in all patients.

A control group of 25 healthy adult volunteers (13 males, 12 females) was included, with an age range of 20 to 60 years (mean age 37.16±10.80 years). They were all normal on medical, neurologic and psychiatric examinations, as assessed by the Mini-Mental State Examination (MMSE) and Hamilton Depression Rating Scale (HDRS).[24]

Prior to inclusion in the study, informed consent was obtained from all the patients and controls. All patients were assessed by MMSE and HDRS. Scores of MMSE exceeded 26 in all patients. Psychiatric examinations and HDRS demonstrated depression in 23 epileptic patients (mean age 37.54±8.96 years). All patients in this group met DSM-IV[25] criteria for major depression without any psychotic features and had not used any antidepressive agents for the last two months. No evidence of depression was documented in the remaining 37 patients (mean age 35.05±10.17 years). Data on patients are summarized in Table 1.

Event-related potentials were obtained using a conventional technique with an acoustic oddball paradigm. Recordings were made with Dantec silver chloride surface electrodes placed on the scalp (Dantec Keypoint Electrodiagnostic system). P300 responses were recorded at the Cz and Pz electrodes of the international 10/20 sys-

TABLE 1

Patients' Profiles

Type	No
Seizure types	
Generalized tonic-clonic	27
Complex partial	15
Simple partial	1
Mixed	17
Antiepileptic drugs	
Valproate	20
Carbamazepine	18
Phenytoin	10
Politheraphy	12
Age (n=60) (yrs)	36.09±9.63
Duration of epilepsy (n=60) (yrs)	11.63±5.74
Hamilton Depression Rating Scale (n=23)	19.42±6.82

tem and referred to linked earlobe with an Fpz ground. Only the recordings obtained from the Pz electrodes were used for calculations, because they were bigger and more significant. Bandwidth filters were 0.2 to 30 Hz. Standard signals were given at 1 kHz, and target sounds at 2 kHz with 15% oddball; random stimulation frequencies ranged between 0.3 Hz and 1.0 Hz. Stimulus intensity was 70 dB above the hearing level. Subjects were required to press the button held in their dominant hands upon hearing each target sound. P300 wave was accepted as the widest positive point after negative-positive-negative (N1-P2-N2) resultant values.

Comparison of the two groups was made using the Student's t-test. The correlation coefficient was calculated to analyze the relationship between the P300 component and the duration of epilepsy. All values were drawn as means and standard deviations.

RESULTS

P300 latencies of the epileptic patients with major depression were more prolonged than both patients without depression and the controls (p=0.04, p=0.001, respectively). Similarly, latencies recorded from epileptic patients without depression were more prolonged than those of the control group (p=0.002) (Table 1 and Fig. 1).

No significant difference was found between the mean P300 latencies of patients receiving VPA (n=20) and CBZ (n=18) (393.27±34.18 ms *vs* 392.88±33.76 ms; p>0.05). Patients receiving other antiepileptic drugs were excluded from statistical analysis due to small sample size.

P300 amplitudes showed no significant differences among epileptic patients with or without depression and the controls.

The mean duration of epilepsy was 11.63±5.74 years (range 1 to 25 years). Bivariate correlations showed that neither the latency nor the amplitude correlated with the duration of epilepsy (p<0.05).

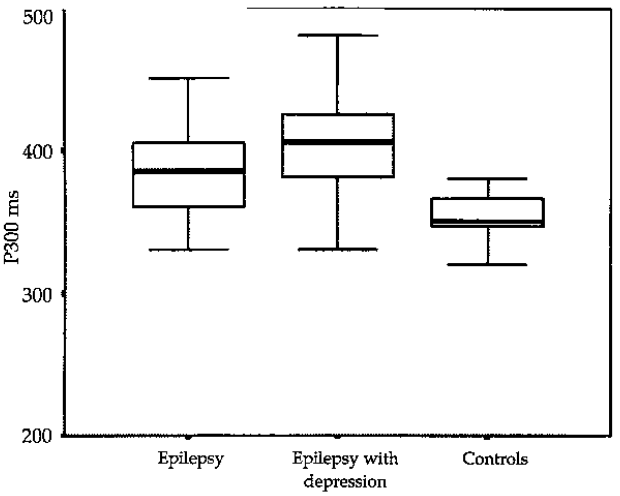

FIGURE 1

Means of P300 latencies in patients with epilepsy, epilepsy with depression, and controls.

DISCUSSION

P300 latency prolongation in epileptic patients has been the subject of controversy. The relationship between epilepsy and the P300 component has been attributed to the type of epileptic syndromes, the duration of epilepsy, ictal symptoms, and drug therapy. A relationship between seizure type and intellectual function has been proposed.[26] Age corrected P300 latencies were shown to be significantly longer in temporal lobe epilepsy than those in generalized epilepsy.[3] On the other hand, Wu *et al.*[27] found no relationship between seizure type and P300 latency.

The effects of antiepileptic drugs on P300 latency prolongation have been intensively studied and controversial results have been reported. Fukai *et al.*[3] found no significant differences in P300 latencies between patients receiving PHT, VPA, or CBZ. Triantafyllou *et al.*[28] showed significant differences in mean

TABLE 2

Means of P300 Latencies and Amplitudes

Groups	No	P300 latency (ms)	P300 amplitude (ms)	Male/female
Epilepsy	37	382.51±30.95	13.94±3.55	20/17
Epilepsy with depression	23	401.35±48.61	13.72±3.81	12/11
Controls	25	353.52±40.26	15.28±3.47	13/12

P300 latencies between patients on monotherapy and those on a combination of antiepileptic drugs. Panagopoulos *et al.*[14] found that, of patients receiving VPA, CBZ, and healthy controls, only those on VPA therapy exhibited a significant prolongation in mean P300 latencies.

Controversial results have been reported as to whether there is a relationship between the course of epilepsy and P300 latencies.[3,27] We found no correlation between P300 latencies, the course of epilepsy, and the use of antiepileptic drugs.

Depression is a very common mood disturbance encountered in epileptic patients. As with anxiety disorders, it may temporally be associated with seizures as a prodrome, an ictal or postictal effect, or as a chronic interictal mood disturbance. Interictal depression may be evoked by a reaction of the patient to having a chronic illness always associated with serious life problems, or may arise from an endogenous mood disturbance caused directly by epilepsy through its neurophysiologic mechanisms.[29] Interictal depression may be a response to the diagnosis of epilepsy representing a heavy burden in the life of patients, including driving restrictions or other independence limitations, overprotection or rejection by others, social stigmatization and ostracism, difficulty in making or maintaining romantic relations, job discriminations with unemployment or underemployment, difficulties in cognitive functions, adverse effects of medication, and uncertainty and fear of having seizures.[17,19,30]

Prolongation in P300 latency has been described in epileptic patients with depression.[9-11] However, for various reasons, depression-related symptoms are often ignored[14,27,31] or studied inadequately.[3,32,33] Firstly, patients often tend to minimize their psychiatric symptoms because of fear of being further stigmatized. Secondly, the clinical manifestations of depression in patients with epilepsy differ from those of depressed nonepileptic patients. Finally, clinicians usually fail to inquire into psychiatric symptoms, or tend to minimize their significance because of considering such symptoms a reflection of normal adaptation to this chronic disease.[21]

The results of our study suggest that depression is one of the causes of prolongation in P300 latencies in epileptic patients.

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