Coexistence of Epilepsy and Psychogenic Nonepileptic Seizures; a Faceless Menace Underlying Pseudointractability

Epilepsi ve Psikojenik Nonepileptik Nöbet Birlikteliği; Psödodirencin Altında Yatan Görünmeyen Tehlike

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Abstract

Psychogenic nonepileptic seizures (PNES) may be evaluated as epileptic seizures (ES). Moreover, PNES may be accompanied by ES and might be the cause of resistance to antiepileptic drug (AED) in patients with ES which can be defined as pseudoresistance. We aimed to evaluate the rate of PNES and comorbidity of PNES and ES in our database as well as evaluating the prognosis in these patients. We retrospectively evaluated the records of all patients who were admitted to the epilepsy center between January 1, 2007, and March 31, 2015. Medical record review included outpatient clinic notes, neurological findings, video-EEG monitorization reports, home videos of patients, routine EEG reports, brain images, and follow-up of patients. A total of 4247 patients were evaluated and 114 of these patients had PNES. There were 65 patients with PNES only and 49 patients with PNES/ES. Patients with PNES/ES had a longer duration of diagnosis than patients with PNES ($p<0.001$). Psychiatric treatment was recommended to all, 105 (92.1%) of them had accepted to go under treatment but only 16 (18%) of them took benefit from treatment. Once the patient had epilepsy, all spells were usually considered as epileptic seizures and dosage and number of AED treatment was increased because it was considered as drug resistant epilepsy. We found that suspicion about PNES in patients with intractable epilepsy is helpful to make the right diagnosis and treatment. The clinician who is interested in patients with epilepsy should always keep PNES in mind.

Keywords: Diagnostic Delay, Non-Epileptic Seizures, Outcome, Seizure

Öz

Psikojenik nonepileptik nöbetler (PNEN), epileptik nöbetler (EN) olarak değerlendirilebilir. Bundan da fazla olarak PNEN, EN'ye eşlik edebilir ve epilepsi hastalarında psödodirenç olarak tanımlayabileceğimiz antiepileptik ilaca (AEİ) direncin nedeni olabilir. Bu çalışmada PNEN ve PNEN ile EN birlikteliğini ve bu hastalarda prognozu değerlendirmeyi amaçladık. 1 Ocak 2007 ve 1 Mart 2016 tarihleri arasında epilepsi merkezine gelen hastaların dosyalarını retrospektif olarak inceledik. Hastaların poliklinik notlarını, nörolojik bulguları, video-EEG monitörizasyonu raporlarını, hastaların ev videolarını, rutin EEG kayıtlarını ve takiplerini değerlendirdik. Toplamda 4247 hasta incelendi ve 114 hastada PNEN saptandı. Sadece PNEN olan 65 hasta, PNEN/EN birlikteliği olan 49 hasta vardı. PNEN/EN birlikteliği olan hastalarda tanı koyma süresi, sadece PNEN olanlara göre daha uzundu ($p<0.001$). Psikiyatrik tedavi bütün hastalara önerildi, 105 (%92.1) hasta tedaviyi kabul etti, ancak sadece 16 (%15.2) hasta tedaviden fayda gördü. Eğer hasta epilepsi hastası ise genellikle bütün ataklar EN olarak kabul ediliyor ve AEİ dozu ve sayısı, hasta ilaca dirençli kabul edilerek artırılıyor. Biz dirençli epilepsili hastalarda PNEN'den şüphe edilmesinin doğru tanı koymada ve doğru tedavide yardımcı olacağını bulduk. Epilepsi ile ilgilenen klinisyenlerin PNEN'i hep akıllarının bir köşesinde tutması önemlidir.

Anahtar Kelimeler: Nonepileptik Nöbetler, Nöbet, Prognoz, Tanıda Gecikme

Introduction

Psychogenic nonepileptic seizures (PNES) are involuntary experiential and behavioral spells which resemble epileptic seizures (ES) (1). About one in five patients first presenting to an epilepsy clinic is diagnosed with PNES and is one of the three most common diagnoses in patients presenting with temporary loss of consciousness (1, 2). On the other hand, coexistence of ES in patients with PNES was found 5.3% (3, 4). Also, 12.3% of all patients with epilepsy had PNES and 14.8% of all patients with PNES had epilepsy (3). In this coexistence, PNES may be evaluated as ES and patients were misdiagnosed as refractory to antiepileptic drug (AED) treatment. PNES generally looks behaviorally similar to ES, especially to the patient's caregiver, for that reason commonly was a mistaken diagnosis of ES because the prevalence is much higher than that of PNES (5). Recording of seizures with home video rather than video-EEG monitorization is very helpful to distinguish the two diseases, but these cannot be obtained easily especially in daily clinical practice. Patients with PNES may be treated as having epilepsy and the correct diagnosis delay more than seven years (5, 6). One of the reasons for the diagnostic delay in patients is that providers are not familiar with PNES (7). To make the earlier diagnosis is very important as the longer the duration of diagnosis of PNES the poorer outcome of patients (8).

Treatment for ES involves AEDs, and if resistance occurs ketogenic diet, neurostimulation and surgery may be applied, whereas standard treatment for solely PNES should be addressed

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underlying psychological distress with cognitive behavioral-inspired therapy and sometimes psychoactive medications, but not AEDs (6, 9). So to differentiate these two conditions is very important that the treatment and dealing with these patients differs. Also if the patient had both PNES and ES, treatment of both should be applied.

We aimed to evaluate the rate of PNES and comorbidity of PNES and ES in our database as well as evaluating the prognosis in these patients.

Material and Method

We retrospectively evaluated the records of all patients admitted to the epilepsy center between January 1, 2007, and March 31, 2015. Medical record review included outpatient clinic notes, neurological findings, video-EEG monitorization (VEM) reports with a detailed description of clinical events if applicable, home videos of patients if applicable, routine EEG reports, brain images, and follow-up of patients.

All patients had known either epilepsy or spells of unknown nature and need to be classified. We systematically evaluated the clinical characteristics of patients with epilepsy/PNES, in comparison with those with pure PNES to identify and respond to treatment.

A diagnosis of PNES was made when seizure semiology is consistent with PNES and/or without ictal EEG changes. A diagnosis of epilepsy was made when seizure semiology is consistent with epilepsy and/or with ictal EEG changes. Coexistence of PNES and ES was made once the patients had both type of seizures. If all type of events were obtained, the patients were classified PNES alone, ES alone or PNES/ES coexistence. When the suspected seizures were not obtained, patients were excluded from the study. Seizure types were obtained either video-EEG monitorization or camera recording of patients. If the patient's history includes more than one seizure type, we try to obtained all seizure types due to the coexistence of ES and PNES.

Gender, age, marital status, family history for both epilepsy and psychiatric disorders, diagnosis, AED treatment, psychological treatment, brain MRI findings, EEG results of the patients were evaluated. Epilepsy and PNES risk factors were evaluated (Table 1) (3). The initial diagnosis was determined according to the referring physicians' impressions and it was compared to our final decision (3). Our retrospective study was approved by the Etimesgut Hospital ethical committee (8000-19-16–03.31.2016). As, this is retrospective study written consent of patients was not required.

The variables were investigated using visual (histograms) and analytical methods (Kolmogorov–Smirnov) to determine normal distribution. The data were represented as a median (minimum–maximum) and mean±SD for continuous parameters. Chi-square analysis was used to compare the proportions. For independent groups, the nonnormal distributed data were compared by using the Mann-Whitney U test. Statistical analyses were performed with Statistical Package for the Social Sciences (SPSS) 23.0 (IBM, Chicago, Illinois, USA). A p value of <0.05 was accepted to be statistically significant.

Table 1. Epilepsy and PNES risk factors

Epilepsy risk factors	PNES risk factors
Perinatal injury	Abuse (physical or sexual)
Febrile seizures	Unemployed or disability
Head injury with loss of consciousness	Psychiatric disorders
Stroke, tumor, focal cortical dysplasia etc.	Specific identified triggers, (death in the family, etc)

Results

A total of 4247 patients were evaluated and 114 of these patients had PNES. There were 65 (57%) patients with PNES only and 49 (43%) patients with PNES/ES. There were 86 (75.4%) women and 28 men (%24.6) all over. The median age of patients was 28.5 (range of 18-66) years. 56 (49.1%) of patients were married and 58 (50.9%) were single. The diagnosis of patients was made with VEM in 36 (31.6%) and with a videorecording of spells in 78 (68.4%) patients. The median duration of making the diagnosis was 5.5 (range of 1-37) years. Brain MRI was normal in 91 (79.8%) and neurological examination was normal in 102 (89.5%) patients. While 29 (25.4%) patients had epilepsy risk factors, 19 patients had (16.7%) PNES risk factors. In 17 (14.9%) patients out of all had a family history of epilepsy whereas only one (0.87%) patient had a family history of PNES. EEG results revealed normal EEG activity in 76 (66.7%) patients, nonspecific EEG abnormality in 19 (16.7%) patients, and specific epileptiform activity in 19 (16.7%) patients. Prediagnosis and diagnostic accuracy were 69 (60.5%) in our study. Psychiatric treatment was recommended to all patients and 105 (92.1%) of them had accepted to go under treatment but only 16 (15.2%) of them took benefit from treatment.

When patients were classified according to PNES only and PNES/ES comorbidity group there was a statistically significant difference in duration of diagnosis, AED treatment, brain MRI, EEG, neurological examination, epilepsy risk factors, psychiatric treatment between the groups. Patients with PNES/ES had a longer duration time to diagnosis than patients with PNES only ($p<0.001$, Mann-Whitney U test) (Figure 1). Patients with PNES/ES had more abnormal brain MRI, EEG, epilepsy risk factors (all $p<0.001$, chi-square test) and neurological examination ($p=0.003$, chi-square test) than patients with PNES only. Treatment with AED is higher in patients with PNES/ES when compared with the patients with PNES only. 38 (58.4

%) patients with PNES only had AED treatment. Also, the accuracy between diagnosis and prediagnosis are higher in patients with PNES compared than patients with PNES/ES ($p<0.001$, chi-square test). Patients data according to groups were shown in Table 2.

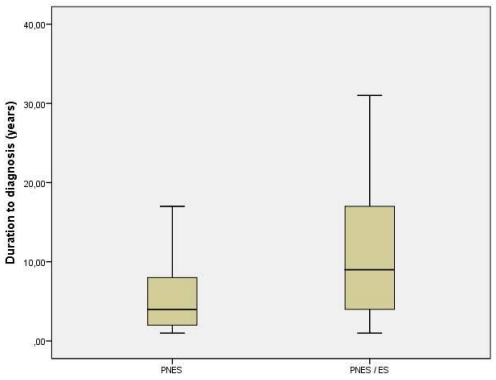

Figure 1. Duration to diagnosis PNES in patients with PNES only and patients with PNES/ES.

Discussion

The major finding of this study was the difference in the duration of diagnosis between the patients with PNES/ES and PNES only. Once the patient had epilepsy usually all spells were considered as epileptic seizures and AED treatment was increased because it was considered as drug resistant epilepsy. But, in reality they have coexistent PNES which explains the resistance. Also, patients with PNES/ES did not accept psychiatric treatment as much as patients with PNES only. On the other hand, both groups did not take benefit from psychiatric treatment. One of the interesting findings of this study is the accuracy of prediagnosis-diagnosis; it is different between the groups which suggest that to make the diagnosis of PNES in patients with epilepsy is very difficult.

Asadi-Pooya et al. investigated patients with PNES only and found that the mean time to diagnosis 5.6±8.2 years and median time to diagnosis 3 years (range of less than one week – 40 years). They did not evaluate patients with PNES/ES (10). We also found that the mean duration to diagnosis was 6.15±6.50 years in patients with PNES only, but in patients with PNES/ES, the mean duration to diagnosis increased to 11.95±8.98 years. In previous studies, the mean time to obtain the diagnosis generally found 5-7 years but even prolonged to 11 years (11). Physician factors played a role in delay to diagnosis (12). We found that physicians thought more of PNES in patients with PNES only group and less of PNES in patients with PNES/ES group which had a longer duration time to diagnosis. Kerr et al. revealed that the response to AED treatment is not associated with diagnostic delay instead a number of AEDs tried was associated with a delay in the diagnosis (6). This finding may be helpful to understand why we found the duration to diagnosis in PNES/ES group longer.

Table 2. Comparison of patients with PNES only and patients with PNES/ES

	PNES only	**PNES/ES**	**P value**
Gender (F/M)	53/12	33/16	0.081
Age (years)	29 (18-66) 33.03±13.44	30(18-48) 29.46±7.18	0.643
Maritial status (Married /Single)	36/29	20/29	0.123
Duration of diagnosis (years)	4 (1-30) 6.15±6.50	9 (1-31) 11.95±8.98	<0.001
AED treatment	27 No AED 24 monotherapy 14 polytherapy	0 No AED 15 monotherapy 34 polytherapy	<0.001
Brain MRI (Normal/Abnormal)	63/2	28/21	<0.001
Neurological examination (Normal/Abnormal)	63/2	39/10	0.003
EEG	59 Normal 4 nonspecific abnormal 2 epileptiform discharges	17 normal 15 nonspesific abnormal 17 epileptiform discharges	<0.001
Epilepsy risk factors (Y/N)	6/59	23/26	<0.001
PNES risk factors (Y/N)	12/53	7/42	0.554
Diagnosis/ Prediagnosis	55/10	14/35	<0.001
Accurate/Inaccurate Treatment (Y/N)	63/2	42/7	0.028
Benefit of treatment (Y/N)	8/42	8/31	0.582

Long-term outcome of patients with PNES had controversial results. Asadi-Pooya et al. found that 86% of patients with PNES did not take appropriate psychotherapy but 54.7% of patients with PNES were seizure free for one year (13). Tolchin et al. investigated long-term adherence with psychiatric treatment among patients with PNES and found that only 14% remained adherent through the fourth visit (14). Duncan et al found that only 34.4% of patients with PNES were seizure free at the 3-4 years follow up (15). We found that only 18% of patients with PNES take benefit from psychiatric treatment in our series. These results suggest that the treatment of patients with PNES is very long and challenging. One of the interesting findings in this study was patients with PNES only had accepted psychiatric treatment more than patients with PNES/ES.

Our study had female dominance in both groups consistent with the literature (16). Brain MRI, EEG, neurological examination was much more abnormal as well as epilepsy risk factors in patients with PNES/ES compared to PNES only as expected.

The limitations of our study were that this was a retrospective study, and patients data came from a single institution. The risk factors, response to treatment and prognostic factors can be evaluated with prospective studies. Also, not all of our patients had VEM which was a gold standard diagnostic tool for paroxysmal events. However, our study involved a large number of patients who evaluated for

epilepsy and gave us clue to suspect about PNES especially patients with intractable epilepsy.

As a result, we found that especially in patients with intractable epilepsy to suspect about PNES is very helpful to make the right diagnosis and right treatment of PNES. The first step to make the diagnosis of PNES is to consider it. The physician who is interested in patients with epilepsy should always keep PNES in mind.

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