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Treatment and Diagnosis of Psychogenic Nonepileptic Seizures

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Abstract

Psychogenic nonepileptic seizure (PNES) is one of the most common clinical conditions in which the diagnostic complexity is experienced. Misdiagnosis leads to many years of wrong treatment regimens, side effects of drugs, additional financial burdens and adverse effects on social life. Differential diagnosis with epileptic seizures (ES) is one of the most common problems in neurology clinics as well as other health centers. A careful history from the patient and his relatives, detailed neurological and psychiatric examination are very important in reaching the correct diagnosis and treatment. Although imaging advances such as video electroencephalography (vEEG) have improved the ability of physicians to accurately identify these disorders, the diagnosis and treatment of PNES is still a challenging issue. Early diagnosis, young age, less psychiatric comorbidity have a positive effect on prognosis. Psychiatric evaluation of patients with PNES may be particularly helpful in elucidating the etiology and detecting comorbid diseases and may be helpful in the long-term treatment of these patients.

Keywords: psychogenic nonepileptic seizures, diagnosis, treatment

1. Introduction

Psychogenic nonepileptic seizures (PNESs) are neuropsychiatric disorders caused by the combination of neurological findings and basic psychological conflicts [1–3]. Over a period of a century, medical community collects data and information about the phenomenology, epidemiology, risks, comorbidities and prognosis of PNES [4–9]. However, information about PNES is insufficient. Video electroencephalography (vEEG) has become a gold standard in diagnostic examination to distinguish neurological seizures from PNES [10–15]. For this reason, video electroencephalography is preferred for diagnosis. In this section, we

systematically reviewed our current knowledge about diagnosis, differential diagnosis and treatment of PNES.

2. What is a psychogenic nonepileptic seizure?

PNESs, also referred to as hysterioepilepsy, pseudoseizure, hysterical seizures, psychogenic seizures, dissociative disorders, are sensory, motor or behavioral episodes similar to epileptic seizures (ES) without accompanying abnormal neuronal discharges [15–18]. PNESs do not have neurological roots, on the contrary, they are concrete manifestations of psychological distress. The prevalence in the society ranges from 1/3000 to 1/5000 [6]. Although the prevalence is lower than the epilepsy, it causes serious workload in the emergency departments and neurology clinics due to the tendency to frequent repetition. About 10–30% of patients admitted to epilepsy centers with the history of treatment-resistant seizure are created by patients with PNES [19, 20]. ES have also been reported in 5–40% of patients with PNES at the same time. In other words, both types of seizures can be seen together in the same patient [5, 6, 9, 20–22]. Although ESs and PNESs are seen in both sexes and ages, PNESs often affect young adult women. Lesser reviewed 21 studies investigating gender differences (734 women and 250 men diagnosed with PNES) [23]. It has been reported that 75–85% of the diagnosed PNES patients are female, it is 10 times more likely to be seen than men, and the majority of patients are 30–40 years old [24–25]. There are also cases of PNES diagnosed in childhood and adolescence [2]. Two studies have reported sexual abuse in female patients and work-related problems in males more frequently [26, 27]. However, traumatic experiences such as warfare and captivity are higher in male patients [28]. About 5–10% of patients followed up with a diagnosis of epilepsy and 20–40% of patients with epileptic patients receiving inpatient treatment experienced PNES [24, 29]. These patients often have accompanying psychiatric illnesses (mostly depression, posttraumatic stress disorder, other dissociative and somatoform disorders and personality pathology), especially borderline personality types [30]. In most cases, it is reported that there is a story of childhood trauma (story of sexual or physical abuse) [31–35]. In one study, it was suggested that childhood traumatic experience may be a predisposing factor for PNES [36]. Patients with PNES followed up with the diagnosis of ES are diagnosed at an average of 7.2 years [2]. This situation led those patients with PNES to be exposed to incorrect treatment regimens for many years with the diagnosis of epilepsy, additional financial burdens, drug side effects and adverse social life [29, 36]. Considering that the cases were exposed to aggressive interventions such as intubation, considering status epilepticus by the emergency department, the importance of early differential diagnosis with epilepsy is once again emerging [37].

3. Diagnosis

3.1. Epileptic seizure? Psychogenic nonepileptic seizure?

The main question to be answered in patients with seizure history is whether there is an epileptic seizure. When the patient is brought to the clinic, the seizure is usually terminated

and the most important information is obtained in order to distinguish from the patient and the relatives who witnessed it during the seizure. Although any other diagnostic methods are available for diagnosis of epilepsy such as electroencephalogram (EEG), vEEG, cerebral magnetic resonance imaging (MRI), cerebral perfusion scintigraphy and, the most important first step in diagnosis is accurate history from patients and their relatives, and careful neurological examination, as well as semiologic recording of the seizure [38]. In cases where anamnesis is not sufficient, the differential diagnosis of the patient becomes difficult. With good history, information can be obtained to suggest whether there is a nonepileptic seizure. For example, many reasons may be useful for differential diagnosis such as the onset and the duration of seizure, the appearance pattern, motor movements and reflex changes, the induction property of seizure [16, 39, 40]. If the seizures happen very often and repeat several times a day, this is a more common finding for PNES. Furthermore, while patients are normal in the period between the seizures due to the absence of postictal confusion in PNES, there may be consciousness disorders during the period between seizures in patients with ES due to prolonged confusion and sleepiness in frequent seizures. While epileptic seizures generally last a few minutes, PNESs tend to last much longer [41, 42]. Patients with epilepsy generally respond to treatment with one antiepileptic drug at around 50%, while patients with PNES do not respond to treatment with antiepileptic drugs [41]. During examination, it is often learned that patients with PNESs received prior antiepileptic treatment and no response obtained to treatment. If the seizures are in a specific place, time and crowded environment, it is favorable for PNES. In ES, such a place and time difference is generally absent. While ES is seen in sleep and awake state, PNESs are seen awake state [17, 18]. A careful history can be used to determine that the patient is not asleep, although the patients report that they are asleep. vEEG can be used as an assistant method in cases where sleep and awake state cannot be distinguished [40]. The type of seizure is generally the same with the reason that the discharge is in the same region in the brain in ES. In PNES, seizure types can be seen in different forms in the same patient [43]. While seizures are usually sudden onset in epileptic patients, it starts gradually in patients with PNES. While there are complaints such as screaming, palpitations, hyperventilation, numbness in the hands and feet before the seizure in PNES, epigastric sensations, *deja vu*, swallowing, swallowing and automatisms in the hands may occur in ES [17, 18]. A complete loss of consciousness is observed according to type of seizure in ES, no loss of consciousness is seen in PNES, the patient hears around, and cannot respond. There may be physical injuries in ES due to fall. Even the patients with PNES fall, they usually have controlled falls and injuries are not often experienced [23, 42, 44]. In ES, contractions occurring in the extremities are tonic, clonic or tonic-clonic and rhythmic, whereas PNES is more tonic in contraction and not rhythmic. When the eyelids are attempted to open, patients with PNES show resistance, but this is not observed with ES. At ES, abnormal alignment of the eyes and unilateral clonic contractions in the eyelid can be seen [43]. In patients with epilepsy, pupil dilatation and reflex changes are observed, however, these neurological findings are not seen in patients with PNES. In patients with PNES, pelvic pushing is a frequent finding, while it may be seen much less and lighter in epileptic patients [16]. Urinary incontinence is a more common finding in ES, although it is rarely reported in patients with PNES [42]. In the differential diagnosis, sudden onset of seizures, pupillary dilation during seizure and postictal confusion are semiologic findings in favor of ES, awareness of the environment, influencing the severity of seizures by the presence of people around and blinking of the eyes are

semiologic findings in favor of PNES [45]. At ES, there may be epileptic cries at the onset of the seizure and tonic-clonic contractions continue with wheezing. In patients with PNES, longer moaning during seizures, speech, which can be understood, can be observed with challenging hyperventilation, and generally last longer than ES [43]. While postictal confusion is a frequent finding in ES, postictal confusion is not seen after PNES. EEG is the most important diagnostic method besides clinical information. Because it is a noninvasive and inexpensive method, it still maintains its importance as the most commonly used method in the orientation of diagnosis and treatment today. However, the normal EEG of the patient with seizure does not exclude the diagnosis of epilepsy, and many epileptic patients may have continuous normal EEG findings during the interictal period. Again, especially in cases where seizures with low frequency are difficult to get caught in the ictal period and take EEG recording, it often cannot help the diagnosis. In PNES cases, EEG taken during interictal and ictal period is normal. However, it should not be forgotten that EEG cannot be sufficient for the differential diagnosis of ES and PNES. Comparisons of clinical characteristics of ES and PNES are given in **Table 1**.

3.2. Video EEG imaging in psychogenic nonepileptic seizures

For the differentiation of PNES and epileptic seizures, when the decision cannot be taken with anamnesis, clinical examination and EEG, 'gold standard' method is video EEG imaging. Despite the use of antiepileptic drug, it is recommended for all patients with no change in seizure frequency [46]. However, its use is limited due to the difficulties in its implementation, not being in every center, extending the length of hospital stay and having a high cost.

Features	PNES	ES
Antiepileptic treatment response	No response	Usually present
Psychiatric changes	Common	Rare
Seizure duration	May be prolonged (10–15 min)	Short (1–2 min)
Onset of the seizure	Gradually	Sudden
Urinary incontinence	Rare	Present
Biting tongue, physical injury	Rare (tongue tip)	Common
Cyanosis	No cyanosis	Common
Pupil dilatation, reflex changes	Absent	Present
Motor movements	Extended, uncoordinated	Automatism, coordinated, short
Postictal confusion	Rare	Common
Seizure type	Variable	Usually the same
Interictal EEG	Normal	Frequently changed
Ictal EEG	Normal	Changed

Table 1. Comparison of clinical characteristics of ES and PNES.

This system works by taking the patient's long-term EEG recording and simultaneous video recording [16]. In this way, it enables the observation of the ictal semiology of the seizures clearly, it is possible to evaluate both the clinical features of the seizure and the EEG records in the ictal period together [16]. The absence of a change in the EEG record during the clinical event and not being compatible with some partial epileptic seizures which is not accompanied by EEG changes are diagnostic in favor of PNES. In addition, some impressions such as gradual starting and ending of the seizure acquired during the monitoring of the video recording, noncontinuous (stopping and starting) irregular and asynchronous activity, head movements to the side, pelvic push movements, opisthotonic posture, stuttering, groaning, crying, yelling and abusive speech, conscious self-protection during motor activity and insistently keeping the eyes closed support the diagnosis of PNES. However, it should be noted that none of these behaviors are diagnostic for the PNES alone [46]. Al-Quadah and colleagues have evaluated an average of eight patients with seizure classification with an average of 3.2 h of vEEG in the study and could record episodes in five patients. In this study, it was determined that three epilepsy episodes were nonepileptic [47]. In another study, epileptic seizures were seen in eight patients (22%) and epileptic seizures were not seen in two patients (67%). This means EN/PNES can be distinguished in 32 patients (89%) [48]. McGonical and colleagues have examined cases with seizure story with short-term vEEG and the diagnosis of PNES was detected in 50% of cases [49]. It can be said that the vEEG technique is a successful method for imaging the ictal period in patients and the differential diagnosis of ES/PNES. In this way, the wrong diagnosis, treatment, health expenditure burden will also be reduced by preventing misdiagnosis and wrong treatment. However, it should be known that vEEG cannot be sufficient in differential diagnosis of all patients.

3.3. Is there a biomarker and a test for a psychogenic nonepileptic seizure?

The search for biomarkers for the differentiation of ES and PNES has been a subject of interest to many authors. In the first studies in this area, changes in prolactin level after epileptic seizures and whether these changes were different in ES and PNES were examined. Ohman and colleagues found that plasma levels of prolactin increased after electroconvulsive therapy and it has been emphasized that an increase in prolactin level after epileptic seizures may be an important predictor of PNES differentiation [50]. It has been revealed in eight of these studies that the postictal increase in serum prolactin level had a positive diagnostic value in terms of epilepsy but no increase did not exclude epilepsy and no significant increase was seen in PNES, whereas it has been revealed in the other two studies that there was a statistically significant increase in serum prolactin level in PNES, but this increase was significantly lower than in epilepsy [51]. Shah et al. have indicated that there was an average increase of 17% in serum prolactin levels after PNES, therefore at least a two-fold increase may be considered significant for epilepsy [52]. In one study, 69% sensitivity and 93% specificity were found for the prolactin level at the distinction of epileptic seizure and psychogenic nonepileptic seizure, in another study, 100% positive predictive value was reported for ES [53]. However, the use of postictal prolactin level as a biomarker in EN/PNES differentiation was not supported in two studies [54, 55]. In addition, while a higher increase in prolactin was expected in generalized tonic-clonic seizures affecting the entire or most part of the brain, increase may not be seen

after simple partial and frontal lobe seizures. Postictal serum prolactin level measurement is recommended to distinguish between epileptic and nonepileptic seizures, but it should be remembered that after half an hour following the seizure, it returns to normal level rapidly and is affected by stress, hypoglycemia, exercise, drug intake. Sundararajan et al. have evaluated 49 studies conducted between 1980 and 2015 on use of biomarkers in the diagnosis of psychogenic nonepileptic seizures. It has been indicated in this review study that neuroimaging (BT, fMRI, SPECT, etc.), autonomic nervous system, prolactin, postictal cortisol, creatine kinase, neuron specific enolase, brain-derived neurotropic factor, ghrelin, leptin, leukocytosis, heart rate have been studied as a biomarker to distinguish psychogenic nonepileptic seizures and epileptic seizures. However, it was reported that none of them could obtain sufficient evidence level. In addition, the authors noted that studies have significant limitations due to small sample and methodological differences and subtypes of psychogenic nonepileptic seizures have not been investigated [56].

Although there is no standardized protocol yet, it is thought that psychological tests may also be helpful for the differential diagnosis of ES-PNES in cases where necessary. It is reported that psychiatric disorders such as anxiety and depression are more frequent in patients with psychogenic seizures than epileptic patients, these patients have a higher incidence of suicide attempts and story of psychiatric treatment. In addition, researchers have also observed that patients with psychogenic seizures have a lower quality of life, more frequent long-term health problems and more dysfunctional family relationships than epileptic patients [57]. Personality problems that occur in patients with psychogenic nonepileptic seizures have been the subject of many investigations. The Minnesota Multiphasic Personality Inventory (MMPI) is a very sensitive but nonspecific test in this area. There were statistically significant differences between the patients with epileptic seizures and psychogenic seizures with MMPI especially in hypochondriasis, depression, hysteria and schizophrenia scales, pathologic elevation (T-score ≥ 70) was detected in patients with psychogenic seizures [58]. However, no significant difference was found in cases with ES and PNES in the other two studies [59, 60]. In other words, there are conflicting results about the clinical benefits of MMPI in the differential diagnosis of ES/PNES.

Alexithymia is a Greek term which is used to describe individuals who have difficulty to define and verbalize their emotions or which means "no words for emotions", emerged in order to explain the symptoms of psychosomatic patients and gained a quick recognition among psychiatrists. It was first observed in psychosomatic patients who were also been seen on several psychiatric disorders such as depression, posttraumatic stress disorder, substance abuse and dependence [61]. Patients exposed to trauma are reported to exhibit alexithymia more frequently than control group without trauma experience [62]. A significant portion of PNES patients have a trauma history, so alexithymia is also common. On the other hand, alexithymia is not a common condition in patients with ES, so alexithymia can be helpful to distinguish ES/PNES.

Despite not being overworked, it is reported that the tendency of hypnosis is relatively increased in patients with PNES. High tendency of hypnosis has been found in a study conducted on 24 patients with ES and PNES by Kuyk et al. with Stanford Hypnotic Clinical Scale measurements in patients with PNES compared to general population and patients with ES [63].

On the other hand, it is necessary to evaluate whether the patients with psychogenic nonepileptic seizures are surely making symptoms consciously. Simulation is easier to notice as it is obviously benefit-oriented. In artificial disorder, the unconscious desire to 'become ill' is the motive that drives the patient. However, secondary gains can also be clearly identified [64].

As noted above, it is very clear that there have been many unanswered questions, even though there have been many studies to distinguish psychogenic nonepileptic seizures from epileptic seizures. It is seen that comparison was made with patients with generalized epileptic seizure, in a significant part of the studies and the heterogeneous structure of psychological nonepileptic seizures, subgroups and the effect of cultural characteristics were not addressed in studies. Moreover, although many studies point out that ictal vEEG is the 'gold standard' in diagnosis, it is still not certain. On the other hand, the place of psychogenic nonepileptic seizures in the classification diagnosis of epileptic seizures is also uncertain. At present, although there is a lot of information in the ES/PNES distinction, the diagnostic criteria of PNES disorders have not yet been established. The heterogeneous clinical appearance of the PNES causes this uncertainty. It is not clear whether it will be evaluated as multiple comorbid mental and personality disorders or neuropsychiatric syndromes in DSM classification system. Because it is not included in the diagnostic classifications, the development of appropriate treatment options and information and studies related to its prognosis are limited.

4. Treatment

Historically, the use apomorphine, saline injection as a placebo, or mouth and nose closure for 20–30 s have been seen for the treatment of PNESs, defined as 'hysterical seizures'. It is also known that Charcot tried different abdominal compressions that failed in PNES treatment [29]. A more acceptable approach is to ensure that the patient speaks about seizures and distress created by seizures in order to provide self-control rather than strengthening their dependence on others [65]. In this way, the patients experiencing seizures alerts generally learn how to control seizures using external focus and abdominal breathing techniques.

The results of treatment trials are contradictory because patients with PNES form a heterogeneous group. It has been reported in some studies that the psychogenic nonepileptic seizures of approximately one-third of the patients stopped after the diagnosis was told to them, better results were obtained for a group of patients who received psychotherapy than those who did not take, in some cases, 34–53% of patients recovered without treatment [66–69]. One of the most important issues in treatment is to report the diagnosis to the patient, because the transmission of the diagnosis can cause some problems. Some patients evaluate the current situation as 'no physical cause' or 'a mental illness'. At the same time, this can be unacceptable for them [70]. On the other hand, seizures may discontinue with a successful communication in 10% patients who were informed about diagnosis [71]. It is reported in a study that the patients were confronted first their diagnosis, then underwent psychotherapeutic approaches and early diagnosis and therapeutic interventions increased the chances of success of treatment [72]. In another study, the health expenditure of the patient, health institution applications and the vEEG costs decreased within 6 months after the diagnosis [10].

The preliminary aim of treatment is to inform and educate the patient and his/her family about the diagnosis. Thus, it will be possible for the patient to be directed to psychiatric care. In addition, unnecessary admission to emergency services, unnecessary treatments and possible adverse effects will be avoided. Antiepileptic drugs may be useful to prevent return in patients with severe abuse or posttraumatic stress disorder, and sometimes it may be appropriate to continue antiepileptic drugs as a mood stabilizer. Although it will continue to be used, the intended use of the antiepileptic drug should be clearly explained to the patient and his/her family in order not to give a double message. It is necessary to cut the antiepileptic drugs gradually when diagnosed except for these conditions [73, 74]. In a prospective study, epileptic seizures were observed in only 3 of 64 patients that antiepileptic medication was discontinued and those informed that seizures were not due to a brain disorder [26]. Especially for patients with dissociative features it is not possible to say that they will certainly not be harmed by seizures. There was no consensus on the recommendation of restrictions on certain activities (such as driving) until these patients had their seizures controlled [64]. PNES treatment has been reviewed by various authors [29, 75, 76]. Most of the studies related to the subject are in the form of small sample case reports and there are few enough powerful or reliable controlled studies. In a study involving psychopharmacological treatment approaches in this area, inpatient group treated with psychological intervention (paradoxical intention) and outpatient group treated with diazepam (5–15 mg/day) were compared. It has been reported that the anxiety is reduced and the symptoms are controlled more effectively in the group treated with paradoxical intention [77]. However, it should be noted that the control group was formed by 15 cases in the study and only 9 cases completed the study. Despite the fact that antidepressants may be effective in other medically unexplained symptoms, there is no adequate data and studies on the use of antidepressant drugs in patients with psychogenic nonepileptic episodes [29, 78, 79]. In all other studies, individual or group-specific psychological treatment methods were discussed [29]. Especially in these studies, cognitive behavioral therapy (CBT), psychodynamic approaches, interpersonal therapy, operant conditioning, eye movement desensitization and reprocessing (EMDR), biofeedback, hypnotherapy, family therapy and multidisciplinary therapies are at the forefront [80–83]. A significant decrease in seizure frequency, anxiety and depression levels, an increase in psychosocial functioning with CBT targeting fear and avoidance behavior have been reported in a 12-session prospective study which is one of the best study done up to this day [84].

Psychoanalytically, psychogenic nonepileptic seizures are an attempt to counteract/defend the traumatic experience of the patient, and at the same time to resolve conflicts related to this experience. At the same time, it is a defense that serves also in the control of the anger, instead of harming someone else, they prefer to hurt themselves. Therefore, it will be appropriate to shape treatment in the direction of these principles, especially in patients who have trauma or unresolved grievances in the past. In other words, patients diagnosed with PNES form a heterogeneous group, and psychodynamic psychotherapy may be a good treatment option for the patients with psychic trauma stories and those who could not mourn. The story of what happened to the patient needs to be formed and the meanings of it should be studied. At the outset of treatment, psychoeducation, prevention of secondary gains, raising awareness of the patient about the relation of psychic processes and seizures and developing a good therapeutic

alliance is a priority. After that the meaning of the symptoms can be focused in depth [64]. However, it should be remembered that psychotherapy may be beneficial for some patients and the same results cannot be achieved in all patients.

5. Conclusion

As a result, epileptic and psychogenic nonepileptic seizures are two pathological conditions that should be evaluated separately in terms of both etiological, formation mechanism and treatment approach. Detailed history of seizures and careful neurological, psychiatric examination, as it provides for the correct diagnosis and treatment for the patients, it will also prevent many negative consequences that the wrong treatment may bring. Since it has been named as hysterical seizure, there has been considerable progress in the diagnosis of PNES with the use of EEG and vEEG in clinical practice. However, focusing on differential diagnosis for the PNES diagnosis by comparing with cases with epileptic seizure only, and the lack of comparison of the clinical appearance of the different subtypes of PNES are the shortcoming of the work done up to this day. Also, the effects of cultural differences on PNES are unknown. For a better understanding of treatment approaches, there is a need for studies with a large sample involving the control group.

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