A review of the clinical approach and challenges to psychogenic non-epileptic seizures

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Psychogenic non-epileptic seizures (PNES) is a relevant differential diagnosis in epilepsy clinics because of its high prevalence and impact on patient’s lives and health care services. An approach to the diagnosis and treatment of PNES is important, and many issues make the subject challenging. Video electroencephalography (VEEG) is considered the gold-standard for PNES diagnosis but there is still risk for false positive and false negative results, both with potential dire consequences. VEEG should be planned and analyzed with caution, as well as paired with other clinical variables in order to increase its predictive value. The frequent coexistence of epilepsy among PNES patients makes diagnosis and treatment even more complex. The clinician should always mind that possibility, which has important implications for diagnosis and treatment of the PNES. Patients’ understanding and acceptance of the disorder as well as health care professionals’ attitude towards the patients have impact on prognosis. Proper and coherent communication is important for patients’ acceptance of diagnosis, treatment, and prognosis.

Keywords: Epilepsy; Psychogenic non-epileptic seizures; comorbidity; diagnosis; Video-EEG; Review


Introduction

The development of long-term video-electroencephalography (VEEG) monitoring was of paramount importance for the study of psychogenic non-epileptic seizures (PNES). PNES are often clinically indistinguishable from epileptic seizures (ES) [1, 2], and VEEG made possible the accurate identification of patients with PNES. It was found that PNES accounts for up to 30% of referrals for drug-resistant seizures in epilepsy centers [3, 4]. It was also revealed that PNES presents an additional burden to both patients and health care services, since undiagnosed and untreated patients frequently search for emergency services and tend to receive unnecessary, invasive and expensive medical procedures [5, 6]. Also, individuals with longer time to diagnosis had a poor long-term prognosis [5, 7, 8]. It has been suggested that these patients’ quality of life scores are below that of patients with refractory epilepsy [9]. In order to minimize these negative consequences, it is recommended that patients with suspected PNES are promptly referred to VEEG monitoring followed by appropriate treatment [4, 10, 11].

Although PNES diagnosis approach may seem straightforward, it has many pitfalls. VEEG is a very expensive diagnostic tool, and availability is a serious issue in many clinical settings, suggesting that VEEG indications must be precise and rigorous. Also, identifying patients with suspected PNES in clinical practice remains challenging. Clinical variables and seizure semiology are often of little help to distinguish PNES from epilepsy [12, 13], and it is not often easy to identify patients who will consequently benefit from VEEG for PNES confirmation. Moreover, although VEEG is the diagnostic gold-standard, a study revealed only moderate inter-rater reliability for PNES diagnosis based on isolated VEEG recordings (videos of events...
along with EEG tracings) and a low inter-rater reliability for events other than epileptic seizures and PNES \[14\], suggesting that diagnosis cannot be based solely on recordings.

The comorbidity of PNES and epilepsy drastically increases diagnosis complexity. This is often an underestimated phenomenon, which may be explained by the misconception that a confirmed diagnosis of epilepsy means that all seizures presented by the patient are epileptic \[15\]. Such “unitarian” approach to diagnosis often discourages clinicians from considering PNES in a patient with clear evidence of an epileptic syndrome (ES) – that is, typical epileptic symptoms, EEG abnormalities and/or central nervous system lesion. This was evidenced by the fact that it took significantly longer to diagnose PNES in patients with comorbid epilepsy than in PNES-only patients \[15, 16\]. Likewise, it is not unusual to find clinicians discouraged from considering a possible comorbid epileptic syndrome in a patient with a recorded PNES. This is not based on epidemiological evidence, as studies found that 5 to 60% of patients with PNES have coexistent epileptic syndrome \[17-22\]. It should be pointed out that this variability in different studies may reflect several methodological discrepancies, such as different inclusion criteria when determining epilepsy and PNES, presence and type of ictal/interictal EEG abnormalities, referral bias, duration of VEEG monitoring and sample sizes \[20\].

Despite these obstacles, the correct diagnosis of PNES, ES or both is imperative for appropriate treatment. Omission of PNES diagnosis may be harmful, as individuals will remain at risk for unnecessary and invasive procedures, and will not receive appropriate treatment. On the other hand, failure to identify existent epilepsy may be as much, or even more damaging. Patients with a diagnosis of PNES – who may have an undiagnosed comorbid ES – are often counseled to interrupt anti-epileptic drugs (AED) use, to reduce their visits to emergency health care facilities \[23, 24\] and treatment is directed solely towards the psychogenic process \[25\]. Wyler et al \[26\] described the possible severe consequences of these procedures when reporting the case of a 15 year-old girl that perished as a result of an ES occurring after diagnosis of PNES by VEEG and medical discharge after AED withdrawal.

In this review we will briefly describe the clinical approach to PNES based on recent publications as well as on the experience of our clinical team’s collaborators. We will focus on the difficulties and pitfalls of PNES diagnosis and treatment.

**Etiology**

PNES occur in a heterogeneous patient population and no single mechanism or contributory factors have been identified as necessary or sufficient to explain it \[27\]. Hence, PNES are best understood based on a biopsychosocial, multi-factorial etiologic model, as proposed by specialists in the field \[27, 28\].

Studies proposed a set of triggering factors for PNES, such as intense emotional states, trauma, or pharmacological agent with depressant effects on CNS (such as general anesthesia and even AEDs) \[27, 29-31\]. However, trigger factors alone are insufficient to explain why some individuals present PNES, and why some individuals develop recurrent and non-triggered events thereafter.

In addition to trigger factors, the existence of predisposing factors may increase the risk for PNES. Functional and structural brain abnormalities, as well as intellectual disabilities, are significantly more prevalent in patients with PNES than in the general population \[27, 32\]. Interestingly, family history of epilepsy was found to be an independent risk factor for PNES \[33\]. Studies show that patients who have PNES are more likely to report a family history of seizures than those with epilepsy, and are more likely to have witnessed someone else have a seizure before developing their own seizure \[33, 34\]. It is hypothesized that witnessing others with seizures might shape the patient’s behavior and increase the probability of dissociation with PNES characteristics. Similarly, individuals with epilepsy might be prone to present a seizure-like behavior during dissociation, influenced by their own diagnosis of epilepsy. However, it is important to mention that the patient does not “simulate” the seizures nor copies it, but instead it is an unconscious behavior, as described in mental disorders diagnostic manuals concerning dissociative and similar disorders \[35\].

Psychological variables were also identified as possible predisposing factors. Anxiety (including health anxiety or hypochondriasis) was identified as a relevant antecedent for both PNES and other functional symptoms \[36\]. Comparative studies also showed that patients with PNES had a stronger tendency to escape or avoid dealing with problems than normal controls or even patients with epilepsy, suggesting that PNES might be involved in avoidance behavior \[29\]. It is believed that stigmatization, paired with poor coping strategies and avoidant behavior might have played a role in the PNES onset in this set of patients.

In some cases the behavior of PNES may also be reinforced by secondary gains, obtained from the patient’s role as an ill person. For some patients this “sick role” becomes an important part of their identity.
and they might perceive the cessation of seizures with great anxiety, and consequently PNES. This phenomenon was described in a group of patients with PNES and comorbid epilepsy whereby the frequency of PNES increased as the frequency of epileptic seizures decreased [21]. A similar response to epileptic seizure remission will be described in post-operative de novo PNES, in the last section of this review. Moreover, two studies suggest that patients who have PNES are more likely than those who have similarly disabling epileptic seizures to be receiving health-related benefits, which presents a financial disincentive to recovery [38, 39], and in turn reinforces the illness behavior.

Clinical Manifestations

PNES is often described as a differential diagnosis of epilepsy, and more rarely of other disorders in which there is a paroxysmal disturbance or loss of consciousness, possibly with motor symptoms (i.e. syncope, narcolepsy, other sleep disorders). Although the main clinical manifestations of PNES can be indistinguishable from epilepsy, there have been several attempts to identify patients with probable PNES among patients with neurological disorders. The identification of clinical variables that can accurately point to high probability of PNES would decrease the time for adequate diagnosis and treatment.

Patients with PNES were found to have more psychiatric comorbidities and use of psychotropic medications [19], though this was not always the case [22]. Syed et al. [40] developed an assessment that combines questions regarding seizures characteristics and also demographic, psychosocial and clinical information. This instrument was found to accurately identify 86% of patients with non-epileptic seizures or epilepsy. Hill and Gale [41] applied the “conversion subscale” of the Personality Assessment Inventory (SOM-C) combined with other variables, including the number of years since first seizure and self or witness-reported duration of seizures. This method could correctly classify as non-epileptic seizures in 84% of all cases meeting three cut-off criteria (SOM-C C >70, 8 years since first seizure, 3 min duration). A series of linguistic studies revealed that the way patients talk about their seizures may predict the nature of the patient’s event [42, 43], and may be a powerful tool to identify patients with probable PNES. Although such studies have shown positive results, it is important to mention that most of them were conducted in patients with PNES only, and their use in patients with comorbid epilepsy was not tested and it is likely to yield less encouraging results.

A more straightforward and clinical-friendly approach was suggested by a previous study, which found an 85% positive predictive value for PNES in the presence of the following criteria: 1) At least two normal EEGs, 2) at least two seizures per week, and 3) resistance to at least two AEDs [44]. However, when assessing the risk for PNES in patients with a known epileptic syndrome, a normal EEG should not be expected. Also, drug-resistant seizures may not imply PNES either, since it is not unusual to find patients with refractory epilepsy among patients with PNES. Mari et al. [15] found that 60% of patients with PNES and epilepsy have refractory epilepsy. Thus, it is important to consider other predictors of PNES when approaching patients with known epilepsy.

The presence of refractory seizures may indeed raise the suspicion for PNES when the patient presents with highly frequent, even daily events. An increase in seizure frequency after adjustment of AED dose can also suggest comorbid PNES [45]. However, it should be noted that some patients with epilepsy might respond to AED intoxication with PNES, which is a phenomenon similar to patients who present with non-epileptic seizures while under general anesthesia [30], in which the stupor induced by an exogenous substance triggers a dissociative state and the non-epileptic event. When occurring exclusively under these circumstances, such events have little to no clinical implication [45] and should not be treated as an additional disorder.

Though patients with comorbid PNES and epilepsy have at least 2 distinct seizures, it may not be easy to make a distinction on clinical grounds. Some aspects of the semiology of seizures might indicate its nature. Preserved awareness during ictus was found to be correlated with PNES [46], and possibly distinguishing PNES from epileptic seizures [47]. However, semiological signs of seizures described by the patient as well as eyewitnesses provide unreliable account of seizure semiology and do not accurately predict seizure type [2, 48-50]. Other features might indicate the possibility of PNES, such as the presence of a seizure during a medical appointment [40]. Change in seizure semiology or the presence of multiple seizure types might also point to a possible PNES [15], although these may also represent varying characteristics of the same epileptic syndrome (i.e., combination of focal seizures without loss of consciousness, seizures with loss of consciousness and secondary tonic-clonic seizures) and thus may not be helpful for distinguishing epilepsy and PNES [47].

It is imperative to remember that no single symptom or clinical sign is proven to correctly discern PNES from epilepsy [15, 50], and all markers should be taken together into account when considering the presence of comorbid
PNES in a patient with epilepsy. Also, it is recommended that diagnosis of PNES should only be stated after proper video-EEG monitoring, described below \[^{4, 10} \].

**Red flags for possible comorbid PNES in patients with epilepsy**
- Drug resistant epilepsy
- Highly frequent/daily seizures
- Increased frequency of seizures after optimization of AEDs (“paradoxical response”)
- Change in characteristics of seizures OR multiple types of seizures
- Seizures during medical appointments
- Convulsive seizures with partially preserved awareness

**Diagnosis**

Prior to referring to VEEG monitoring, patients should be assessed for risk of PNES. The assessment includes a thorough clinical history, which is invaluable for a correct diagnosis of PNES, as it increases the positive and negative predictive values of the diagnostic test. Marchetti et al. \[^{51} \] found that a suspected diagnosis raised by a neurologist had a positive predictive value for PNES of 84%, but on the other hand had a negative predictive value for epilepsy of only 50%. This demonstrates the need for improving referral of patients for VEEG, as stated before.

During VEEG monitoring, behavior and electroencephalographic activity are simultaneously registered. A spontaneous or elicited suspected event is defined as a PNES when there is no EEG evidence of epileptic discharges. However, the event must be critically investigated in the context of clinical data, as simple partial seizures and hypermotor complex partial frontal lobe seizures may occur without evident epileptic discharges \[^{10, 52, 53} \].

VEEG protocols explicitly state that a diagnosis of PNES is only made if recorded events are equivalent to those that the patient presents outside the VEEG unit setting. This assessment is done by comparing the recorded event with information obtained during clinical anamnesis (clinical validation), and mainly by presenting the recorded events to the patient and family members so they can confirm that the semiological features observed during the recorded events, both spontaneous and induced seizures, resemble the usual pattern of the patient’s seizures (observer validation) \[^{3, 10, 15, 51, 54} \]. Confirmation procedures are considered necessary to identify false positives – that is, non-epileptic seizures with no clinical relevance, as they only occurred in the context of the diagnostic testing environment \[^{55, 56} \]. It is known that a few subjects might present a single PNES episode during VEEG, but are not representative of the patient’s current seizures \[^{57} \]. Providing a false positive PNES diagnosis after VEEG, and failing to record an ES, may imply an undiagnosed and untreated epileptic syndrome.

VEEG protocols also include a provocation test, aimed to induce PNES. Provocation tests may include: hyperventilation, photic stimulation, suggestive interview, hypnosis, intravenous injection of saline, placement of a plaster with alcohol on the cervical region, among others \[^{15, 51, 54, 58} \]. Provocation tests are classically used to shorten VEEG monitoring duration. Some authors argue that the use of provocation test increases the diagnostic validity of PNES. Considering that patients who respond to provocation tests are more suggestive, it is understandable that they are more likely to have PNES; thus a positive provocation test may confirm the existence of a psychogenic mechanism \[^{59} \]. Provoked seizures should also be validated by the patients and their caregivers, since the procedure can induce isolated seizures with no clinical relevance, as with AED intoxication or general anesthesia, as mentioned before. It is relevant to add that some authors raised concerns that the procedure of seizure induction involves deception, which may be interpreted as unethical and a violation to the patient’s autonomy \[^{60} \]. Other authors argue that the beneficial implications of an accurate diagnosis outweigh possible ethical concerns \[^{59} \]. In our experience and of other authors, there has been no report of experiencing deceit or disrespect following the induction attempt \[^{58} \]. As with all medical procedures, it is recommended that induction tests should be done only after informed consent of the patient.

Studies comparing patients with PNES-only and those with PNES and comorbid epilepsy have shown important distinctions between these two populations. Patients with PNES and epilepsy usually have a mean age of onset of their paroxysmal events of 14 – 15 years (mostly epilepsy), while PNES only patients have mean age of onset of seizures around 24 – 30 \[^{22, 54} \]. Onset of seizures before the age of fifteen should alert for the possibility of comorbid epilepsy syndrome when PNES is presumed. Patients with comorbid epilepsy were found to have more AEDs prescribed and at higher doses than those with PNES only.

Patients with PNES and epilepsy are found to have PNES as their first seizure in the VEEG, within 1 to 2 days of admission \[^{54} \], while it usually takes longer for the first epileptic seizure to occur. The presence of a PNES during VEEG may lead clinicians to hastily “rule-out” epilepsy and withdraw AEDs in a patient who might have comorbid epilepsy. It is therefore important to consider features of patients with PNES-only versus PNES and comorbid epilepsy during clinical evaluation and VEEG interpretation.
Red flags for possible comorbid epilepsy in patients with suspected PNES

- Early seizures onset (<15 years old)
- EEG abnormalities OR potential epileptogenic lesions in neuroimaging (i.e. MRI)
- Other central nervous system disorders
- Intellectual disability OR other cognitive deficits
- History of sudden change in seizure characteristics
- Multiple types of seizures with one having typical epileptic semiology
- Reports of other seizures not validated through VEEG

Treatment

Several studies show that early and appropriate diagnosis of PNES followed by adequate treatment may lead to remission in 19 to 52% of cases and improvement in 75 to 95% of cases. This consequently reduced health care system costs [61-63].

The first step of the treatment is the communication of diagnosis. Patients with PNES who do not receive any communication or proper referral after diagnosis improve little or even worsen with regard to their condition [64]. Simply stating the diagnosis does not suffice. Most patients have often received previous treatment for epilepsy and some may even have developed their identity around the disease. Thus, they may not immediately accept a new diagnosis, let alone the misguided idea that “they don’t have anything” [65]. This lack of acceptance of the diagnosis may then lead to not being referred to appropriate treatment. Consequently, patients continue to experience seizures and pursue medical investigations for “drug-resistant seizures” [65].

Indeed, the proper communication of diagnosis has been found to positively impact the prognosis. Duncan et al. [66] and McKenzie et al. [67] found that 21% to 50% of patients with newly diagnosis PNES in a first seizure clinic were seizure-free after 3 months and 33% to 44% were seizure-free after 6 months. Understanding and acceptance of the diagnosis were found to be of great importance for the long-term outcome [61, 68]. Considering these as key variables for a better prognosis, Hall-Patch et al. [69] designed a communication strategy, which was found to be successful in terms of providing understanding and acceptance of the condition. The communication protocol was designed to legitimize the patients’ symptoms (“Real attacks – can be frightening and disabling”), provide a label to the disease (“Non-epileptic attacks”), reassure the patient that it is a common and recognized condition, provide an explanatory model for attacks (“nervous system becomes overloaded and shuts down”, there is no known cause, it can be triggered by stress/emotions), explain treatment (AEDs are not helpful, there is evidence that psychological treatment may be beneficial), explain the possibility of full remission and encourage the patient to commit to treatment.

The communication and understanding of the disorder can be even more complex in patients with comorbid epilepsy and/or those with learning disabilities [47]. In such cases, it is imperative that patients and their family members be thoroughly educated on both conditions. They must be assisted to understand that these patients suffer from epilepsy and therefore need to be on AEDs, and that they also present with another disorder that resembles epilepsy (PNES) which needs another kind of treatment.

It is recommended that patients with PNES-only are promptly withdrawn from AEDs once the diagnosis has been made and communicated to patients [10]. Withdrawal of inappropriately prescribed AEDs is safe for patients without comorbid epilepsy, and may lead to greater beneficial effects when done immediately after diagnosis [23]. When treating patients with PNES and comorbid epilepsy, drug adjustment may be necessary, since they may have been under inappropriately high doses of AED, and it can even decrease the frequency of PNES in some cases [45]. During drug adjustment it is important for patients, family members, and especially clinicians to be familiar with the semiological presentations of patients’ events (both epilepsy and PNES). Moreover, appropriate treatment for PNES should be delivered since decreasing PNES will also reduce the probability of the patient being placed back on higher and inappropriate doses of AEDs.

Concerning specific treatment for PNES, we found a disturbing lack of randomized clinical trials in current literature. The first clinical trial by Goldstein et al. [70] showed superiority of CBT treatment over waiting list. Other open studies of PNES treatment involve some form of psychotherapy – mostly CBT – demonstrated improvement of seizure frequency and quality of life [71-74]. It should be noted that most studies exclude subjects with suspected comorbid epilepsy. Only one study included patients with comorbid epilepsy when patients reliably distinguished both events [74].

Patients with PNES and comorbid epilepsy also pose challenges during long term follow-up. More than 50% of patients with PNES will continue to present with monthly episodes [8], and a significant proportion of patients with comorbid illness have refractory epilepsy and thus continue to have ES [15, 21]. It is important to recognize and distinguish between the two events. Failure to do so may gravely impact patient care, leading to erroneous medication of PNES or to insufficient and inadequate treatment of epilepsy. Identification of the
nature of events in patients with comorbid illness is further confounded by the fact that a significant proportion of patients after one year of diagnosis were either unable to recall being informed of a PNES diagnosis or to distinguish between PNES and epileptic events. This difficulty represents a severe limitation for clinical management of these patients assessing the outcomes of treatments.

**Surgery**

As mentioned in previous sections, a significant proportion of individuals with PNES have refractory epilepsy as comorbidity. For these patients, surgical treatment may be an option. Some neurologists are reluctant to refer patients with possible surgical indication for preoperative evaluation if they have comorbid PNES.

Reuber et al. evaluated 13 patients with PNES and comorbid refractory epilepsy who underwent epilepsy surgery. It was found that 11 of 13 patients presented improvement after epilepsy surgery, and seven became free of both epileptic and psychogenic seizures after surgery. It was concluded that comorbid PNES presented no negative impact on postoperative outcome in terms of epileptic seizures control, and suggested that patients with medically refractory epilepsy should not be denied surgery because of comorbid PNES.

Non-epileptic seizures may also be an issue for postoperative care in patients without evidence of preoperative PNES. De novo PNES has long been identified in patients undergone surgery for refractory epilepsy. In postoperative follow-up studies, de novo postoperative PNES affected 3.7% to 4.2% of individuals, and were associated with preoperative psychiatric disorder and lower IQ. Ney et al. suggested that when patients with an epileptic syndrome are confronted with psychological stresses involved in increased social demands they might try to express their learned helplessness by re-enacting their chronic disease. In fact, this concept of “burden of normality” after epilepsy surgery, as a cause of de novo PNES is consistent with previously described factors involved in the etiology of PNES.

**Conclusions**

Despite advances in the understanding of PNES, diagnosis and management remain challenging. It is important to have clinical suspicion of PNES during patient assessment based on risk factors and associated features. This will allow stratification of the probability of PNES, and further plan the correct diagnostic and treatment approach. One should also keep in mind the risk of possible comorbid epilepsy. Diagnosis communication and treatment procedures should follow protocols suggested by recent literature. However, it should also be adapted for the patient’s characteristics, including learning disabilities, comorbid epilepsy, acceptance of the disorder, and even cultural and social particularities.

It would be of interest for future studies to focus on methods to increase acceptance and understanding of the disorder among patients, and possibly their family members, given its importance to prognosis. Understanding should be evaluated both at the time of diagnosis communication and during long term follow-up. Also, patients with comorbid epilepsy should be included in studies aimed at identifying predictors of PNES and in clinical trials for PNES treatment.

**Conflict of interest**

The authors have no conflict of interest to disclose.

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