


REVIEW

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Clinical differentiation of psychogenic non-epileptic seizure: a practical diagnostic approach

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Abstract

Background: Psychogenic non-epileptic seizure (PNES) has long been the counterpart of epileptic seizure (ES). Despite ample of evidence differentiating the two, PNES mistakenly diagnosed as ES was still common, resulting in unnecessary exposure to long-term antiepileptic medications and reduced patient's and caregiver's quality of life, not to mention the burgeoning financial costs.

Objectives: In this review, we aimed to elucidate various differences between PNES and epileptic seizure with respect to baseline characteristics, seizure semiology, EEG pattern, and other key hallmark features.

Methods: An unstructured search was carried out in PubMed, MEDLINE, and EMBASE using keywords pertinent to PNES and ES differentiation. Relevant information was subsequently summarized herein.

Results: PNES differs significantly with ES in terms of baseline characteristics, prodromal symptoms, seizure semiology, presence of pseudosleep, and other hallmark features (for instance provoking seizure with suggestion). The combined approach, if applied appropriately, can yield high diagnostic yield.

Conclusions: PNES can be clearly differentiated from ES via careful adherence to a set of valid clinical cues. The summarized clinical hallmarks is highly useful to prevent unnecessary ES diagnosis and treatment with AEDs.

Keywords: Psychogenic non-epileptic seizure, Epileptic seizure, Semiology

Introduction

Psychogenic non-epileptic seizures (PNES) is defined as paroxysmal changes of behavior, motor, sensory, autonomic, cognitive, and/or emotion which are not an epileptic seizure (ES) [1, 2]. Despite its relatively simplistic definition, PNES continues to be a problem in which there is no clear-cut diagnostic criteria to differentiate it with ES. Moreover, the incidence of PNES is relatively high, accounting for approximately 5% of epilepsy incidence at 3–4 per 100,000 with prevalence of 2 to 33 per 100,000 persons [3, 4]. In fact, it accounted for roughly 10–40% of patients with refractory seizures referred to

tertiary epilepsy centers [4–6]. Such numbers indicate that PNES is relatively common among patients with epilepsy. Given the inherent difficulty of distinguishing it with ES and the high prevalence of PNES among ES, a cavalier practice, particularly pertaining to establishing a diagnosis, may lead to high numbers of PNES patients being treated for epilepsy. Administration of unnecessary antiepileptic medications, particularly in the long-term as in the case of epilepsy treatment, poses them to serious adverse effects, not to mention the consequential financial burden of up to USD 4 billion [7]. Numerous studies had attempted to discern PNES from ES through various aspects. This include their basic demographic characteristics, risk factors, clinical and semiological profiles of the seizure, and other significantly related parameters. These efforts, supported by long-term video-EEG

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monitoring, had been successful in increasing the diagnostic sensitivity and specificity of PNES. Herein, we would like to discuss the relevant features of PNES as opposed to ES from various aspects and how can this information be optimized, in conjunction with the video-EEG monitoring, to increase the rate of PNES detection.

Methods

This was a non-systematic literature review to discuss the clinical differentiation between PNES and ES. We performed an unstructured search in PubMed, MEDLINE, and EMBASE between February to April 2020 (with additional references included during the revision process of this manuscript) using keywords either stand alone or in combination related to clinical aspects and hallmarks of PNES and ES, including “PNES,” “pseudoseizure,” “epilepsy,” “epileptic seizure,” “ictal characteristics,” “seizure differentiation,” “motor phenomena,” “non-motor phenomena,” “seizure semiology,” “prodromal symptoms,” “post-ictal manifestation,” “EEG,” “video EEG,” “risk factors,” and “comorbidities.” We did not apply any restrictions towards date and language of publication, publisher, types of manuscript (review article, case report/series, observational studies, randomized controlled trial (RCT), or systematic review), or manuscript status (pre-print, online first, full-text) except for the sole abstract. Relevance of references to be included in the study was decided manually.

Results

There were 59 relevant references included in this study, comprising 53 observational studies (comprising diagnostic tests, prospective and retrospective observational studies) and 6 unsystematic literature reviews. As many as 48 references discussed the clinical spectrum and characteristics of PNES compared to ES, 6 described PNES association with psychiatric disorders, 3 described patient’s demographics, incidence, and prevalence, and 2 studies described cost analysis. Relevant information pertinent to the study objective was extracted and discussed as followed and summarised in Table 1.

Demographics and baseline characteristics

The majority of PNES patients had been consistently female, ranging from 50 to 87% [2, 16–19]. The reason for gender discrepancy towards PNES was unknown. However, it was presumed that personality disorders played a significant role in the development of PNES. Female patients with PNES was shown to have a significantly higher proportion of childhood abuse and anxiety [20]. PNES occurred at a later age when compared with frontal lobe seizure (FLS) [21].

The mean age of onset for PNES was 25.44 years, although late onset cases involving people with 60 years of

age or above also occurred, albeit to a smaller proportion [8, 17].

Video-EEG characteristics

Prodromal symptoms

Prodromal symptoms in PNES varied and were reported in 39% of patients. Although it is generally difficult to distinguish an aura preceding a seizure episode with prodromal phenomena of PNES, some clinical caveats do exist. The most frequent manifestations were behavioral, cognitive, and emotional changes [12]. In fact, more than half of PNES patients experienced dizziness, visual, auditory, or other complex sensations [9]. In addition, another study found that among 22 patients with PNES reportedly to have a preceding prodrome, two reported olfactory hallucination by having smelled a flower fragrance, one reported a micropsia, and the other eighteen reported non-specific symptoms, including funny feeling, dizziness, and non-lateralized numbness [18]. Meanwhile, the most commonly reported auras among ES patients were of motor symptoms such as forced head or eye deviation to one particular side (75%), bilateral shaking and/or body stiffness (45%), receptive or expressive aphasia (90%), and aberrant emotional states (for instance fear, panic, anxiety) [59%] [22]. There were only 23, 28, and 26% of ES patients reported auditory, somatosensory, and visual symptoms, respectively. Moreover, none complained of having an olfactory hallucination.

The general consensus of ES with aura is mostly perceived to be due to focal aware seizure with or without secondary generalization (primarily tonic clonic seizure) [23]. In contrast, it was reported that more than one third of PNES patients exhibited prodromal phenomena prior to atonic, absence, and persistent tonic behaviors, which if it had been a seizure, would have otherwise been highly unorthodox to be associated with an aura [18].

The onset of prodromes were also different between PNES and ES. The prodromal phenomena can either occur at the beginning or in the middle of the motor phenomena among PNES, while an aura will exclusively precedes ES [1]. Furthermore, PNES patients tended to have a more prolonged and wider duration of prodromal interval (ranging from hours to days). Prodromal symptoms with EEG alterations can also be found in patients with nonconvulsive status epilepticus [24].

Onset

PNES usually had a gradual onset, in contrast to ES which usually began abruptly. However, this was not always the case. Since some PNES were reported to have an abrupt onset as well [25].

PNES usually occurred during wakefulness, but there were also cases of PNES which occurred during apparent sleep [26]. The gradual onset was also accompanied by

Table 1 Summary of “yellow” clinical characteristics (yellow flag checklist) of PNES patients

Characteristics	Remarks
Initial evaluation (ictal and interictal period) in the emergency room (ER) or outpatient settings	
Female	Prevalence ranging from 50 to 87% [2, 8–10]
Age 25–35 years old ≥ 60 years old	44% with PNES only; 15% had both ES and PNES [11]
Seizure characterized by one or more of the followings: <ul style="list-style-type: none"> ▪ Gradual onset ▪ Ictal duration > 2 min ▪ Refractory to multiple AEDs ▪ Inconsistent semiology ▪ Does not occur during sleep ▪ Immediately provoked by identifiable emotionally stressful events (domestic violence, public speaking or in front of audience, queueing for a medical procedure) ▪ Afterward memory recollection of the event, despite having a generalized onset seizure 	10–40% of refractory seizures referred to tertiary epilepsy centers [4, 6] Emotional stress: 74.6%; physical abuse: 17.5%; sexual abuse: 7.9% [8]
Seizure semiology characterized by one or more of the followings: <ul style="list-style-type: none"> ▪ Preceded by sensory prodromes (olfactory hallucination, micropsia, and other bizarre sensory experiences) ▪ Unusual motor phenomena: <ul style="list-style-type: none"> > Out-of-phase limb movement > Side-to-side head movement > Forward pelvic thrusting > Directed rage ▪ Atypical vocalization: <ul style="list-style-type: none"> > Does not occur ictally > Non-laryngeal origin > Comprehensible word > Memory recall of vocalization ▪ Eye closure characteristics: <ul style="list-style-type: none"> > Eye closure during the episode > Closed eyes forcefully, resisted passive opening > Inhibited response of oculocephalic reflex as a hallmark ocular sign of PNES 	Occurred among 39–56% of PNES patients [7, 9, 12] 56% of motor phenomena [10] 36% of motor phenomena [10] 50% of motor phenomena 20% of PNES patients 17–26% had non-verbal vocalization [8, 9, 13] 63% (vs. 4% of ES) [10] 8.5% [13] > 56% of PNES patients
Post seizure motor manifestations comprising one or more of the followings: <ul style="list-style-type: none"> ▪ Retention of some movements (avoidance of falling arm, resistance to passive eye movements, occasional eye blink, positive Henry and Woodruff sign, convergent gaze and eye fixation upon mirror test) ▪ Absence of tongue-biting, urinary and/or fecal incontinence, fall-related trauma, or accidental burn after an episode ▪ Normal corneal reflexes after an episode ▪ Absence of bilateral extensor plantar reflexes ▪ Rapid, shallow, quiet, irregular breathing pattern (resembling an exercise) ▪ Increased sympathetic activity before seizure and parasympathetic activity after seizure ▪ Weeping after event 	Occurred among 41% of PNES patients
Laboratory parameters: <ul style="list-style-type: none"> ▪ Absence of metabolic acidosis on blood gas analysis ▪ Serum prolactin levels ≥ 500 IU/mL 	Found in 28.8% of PNES patients and 84.4% of GTCS or partial seizure [14]
Inpatient setting	
Association with psychiatric disorders Tend to have cluster A or B personality disorder (primarily borderline personality disorder) <ul style="list-style-type: none"> • Factitious disorder associated with litigation • Previous history of sexual and physical abuse (including domestic violence) 	Cluster A 4 to 31.5%; cluster B 21 to 33% [15]

Abbreviations: AED Anti-epileptic drugs, CI Confidence interval, ES Epileptic seizure, ER Emergency room, FLS Frontal lobe seizure, PNES Psychogenic non-epileptic seizure, TLS Temporal lobe seizure

fluctuating motor phenomena throughout the period (discussed later).

In all subjects, posterior alpha rhythm was present before the onset of seizure with no associated ictal or post-ictal EEG changes [26]. This were subsequently termed as pseudosleep by some authors [1, 27]. Pseudosleep occurred exclusively in PNES, and none were observed among ES patients, yielding a sensitivity and specificity of 56 and 100%, respectively [1]. In fact, this correlated

with the finding that some PNES patients were able to recall what was happening during the period of acknowledged unresponsiveness [28].

Ictal duration

PNES tended to have a longer and wider range of ictal duration than those of ES. The mean ictal duration of PNES was 148.7 s (95% CI 115.2–191.8), significantly longer than that of ES patients (47.7 s; 95% CI 37.6–

60.6) [29]. In fact, PNES usually had an ictal episode of longer than 2 min, as opposed to those with generalized tonic clonic seizure (GTCS) and FLS which usually lasted less than 2 min.

Motor phenomena

Motor phenomena were predominant in PNES, constantly reported in more than half of the patients in many studies. Out-of-phase limb movement (clonic) was prevalent, and it refers to an asynchronous jerk between left and right extremities and/or the movements being in an opposite direction between one and another [10]. In one study, it accounted for 56% of motor phenomenon for both upper and lower extremities movements, whereas none was observed in the control group [10]. In contrast, in-phase clonic movements, that is rhythmic jerking of both sides of upper and/or lower extremities, were observed significantly higher among those with ES than that of PNES patients (upper and lower extremity of 96 and 88% vs. 20 and 16%, respectively). Another study found that motor phenomena comprised 81% of ictal manifestation among PNES patients, in which bilateral and unilateral motor phenomena were observed in 68 and 13% of the patients, respectively [9]. Interestingly, 90% of the patients with multiple episodes had a stereotypical pattern which make it difficult to distinguish it with ES. In fact, one study categorized the stereotypical PNES semiology into six categories, comprising rhythmic motor, hypermotor, complex motor, dialeptic, nonepileptic auras, and mixed PNES [19].

Side-to-side head movement was observed in 36% of PNES as opposed to 8% in ES [10]. However, side-to-side head movement was significantly more common in FLS than among any other types of seizure, comprising 11 seizures among 4 out of 11 patients with frontal lobe seizure (36%) vs. 6 motor phenomena among 4 of 12 patients (33%) with PNES [21]. Indeed, FLS is often mistaken as PNES, due to its confusing clinical manifestation. The difference may lie in the quality of the movement, in which PNES tended to have a violent and high amplitude movement, whereas ES demonstrated a less aggressive movement with slower frequency [10].

Pelvic thrusting was common among PNES patients. However, it was also prevalent in ES. Geyer and colleagues [30] demonstrated that pelvic thrusting can be seen in 24 and 12% of patients with FLS and temporal lobe seizure (TLS), respectively, while the same study also found pelvic thrusting in 17% of PNES patients. Another study also found a comparable proportion of pelvic thrusting in FLS and PNES patients (55 vs. 50%, respectively) [21]. Again, a discernable difference may lie in the quality of the thrust. As many as 44% PNES patients showed forward thrust, while 12% of GTCS patients had

backward thrust [10]. Although the backward thrust was also reported among PNES cases, none of GTCS patients had forward thrust [10, 31]. The forward pelvic thrust among PNES was also described as having a higher amplitude [30].

Other motor manifestations such as kicking, thrashing, and punching were less common. These are called as directed rage and belong to the hypermotor PNES on Seneviratne and colleagues's classification and composed of only 3.3% of all PNES. All of these violent movements were invariably bilateral and unprecedented [18, 19, 32]. Furthermore, semipurposive movements were documented in several studies. Movements resembling epileptic automatisms were found in 20% of PNES [9]. In contrast, automatism was observed in ES and ES with PNES cases, but not in stand-alone PNES [33]. In PNES, however, the movement was described as more erratic and violent, with a tendency of goal direction [1, 9].

Vocalization

Vocalization during ictal episode was also common in both PNES and ES cases. Seventeen percent to 26% of PNES cases had non-verbal vocalization as their clinical manifestation [8, 9, 13]. Meanwhile, ictal vocalization was highly prevalent among mixed and complex motor PNES (64.7 and 57.6%, respectively) [19]. Vocalization in ES can be described as an ictal cry and tended to appear in the middle, rather than the beginning of the seizure [1]. In one study, the cry was described as of originating from the larynx (hence termed laryngeal sound) which was highly sensitive and specific (85% and 100%, respectively) for GTCS [34]. On the other hand, none of the vocalization in PNES occurred during seizure [10], and the manifestations varied, including moaning, coughing, with screaming or yelling being one of the commonest findings, and none expressed laryngeal sound as those observed in GTCS cases [12, 18, 34].

In addition, verbal responsiveness was found in a small proportion of PNES [1]. In fact, some patients with PNES had an understandable utterance [10]. While this can also be a perplexive sign to distinguish it with complex partial seizure (CPS), patients with PNES significantly had better memory recall than that of CPS patients (63% vs. 4%, respectively) [35]. Ictal stuttering was also identified among PNES cases, but none in ES. Although uncommon (reported in 8.5% patients with PNES), its presence was highly specific [36].

Eye condition

The majority of patients with PNES (more than 56%) closed their eyes during seizure episode. A study employed video-recorded eye closure reported 92% specificity of eye closure for PNES cases [37]. In another study, eye closure had a higher sensitivity and specificity for

PNES (96.2 and 98.1%, respectively) [38]. On the other hand, most ES patients (92–100%) had their eyes opened during the beginning or in the middle of the episode [1, 38–40]. PNES patients also tended to forcefully close their eyes and resisted passive opening, whereas in ES patients, the eye closure was non-forceful [1]. In addition, one author had suggested the use of oculocephalic reflex to differentiate between PNES and other conditions [41]. Inhibited response accompanied by random saccadic eye movements may point the diagnosis more toward PNES than any organic neurological diseases.

Post seizure manifestations

Both patients with PNES and CPS had an impaired of consciousness after an episode. However, one study reported that as many as 41% of those with PNES with total unresponsiveness still retain some forms of conscious response, such as avoidance of falling arm or resistance to passive eye movements and 70% of these patients still had motor responses. This was in accordance with other studies which reported occasional eye blink, swallowing, or mouth movements post ictally [9].

One can also apply other non-invasive tests to prove that the patients still retain some or all of their consciousness after an episode, such as to drop patients' hand to their nasopharyngeal leads and to drop their heel on the contralateral shin and see if they would avoid hitting on it. Additional tests can be performed if the patients open their eyes after an episode, comprising when rolled on to the lateral side, the patients' gaze will deviate toward the ground and when rolled to the contralateral side, the gaze would still be fixated to the ground (so-called Henry and Woodruff sign), or when the patients were still in an episode, one can applied a small mirror in front of their faces and see if there is a convergent gaze and eye fixation. A termination of the motor phenomena can also be seen by using this technique [28]. Avoidance test was particularly helpful during an episode that mimicked absence or atonic seizure, as well as during post ictal episode of GTCS.

The natural behavior of PNES patients to protect themselves from harms and injuries may as well be reflected by the absence of any tongue-bite, urinary and/or fecal incontinence, fall-related trauma, or accidental burn after an episode. In addition, all patients with GTCS reported post ictal confusion as opposed to 13% of PNES [39]. Other post ictal symptoms, including headache and fatigue were also less commonly reported in PNES cases, and the absence of such strongly indicate PNES [12, 42].

A significant proportion of PNES patients demonstrated a rapid (mean respiratory rate: PNES vs. GTCS 45.1 vs. 30.1 s, $p < 0.0001$, respectively), shallow (PNES vs. GTCS 87% vs. 0%, $p < 0.0001$, respectively), quiet

(PNES vs. GTCS 79% vs. 7%, $p < 0.0001$, respectively, and irregular breathing pattern (PNES vs. GTCS 79% vs. 4%, respectively) as opposed to that of ES patients comprising deep, regular, and loud (usually accompanied with snoring) [1, 12, 39]. Breathing pattern in PNES had a short inspiratory and expiratory phases, resembling an exercise. In addition, altered breathing pattern also lasted shorter than that of GTCS (94 vs. 357 s) [39].

There were also different patterns of autonomic nervous system (ANS) activation among patients with PNES and ES, with the latter had a greater activation. ES patients demonstrated a higher heart rate variability post ictally, indicating high sympathetic activity and reduced vagal tone [43]. Another study also found that heart rate increased significantly among PNES at 5 min before the seizure, while standard deviation of average beat-to-beat intervals and heart rate in low frequency domain decreased. The opposite findings were observed 5 min after the seizure subsided. This finding indicated an anticipated increased sympathetic followed by parasympathetic functionings during and after PNES, reflecting an increased arousal [44]. The relationship with emotion has yet to be studied. Thus, the heart rate variability can be used as another measure to differentiate between PNES and ES [45].

From an objective standpoint, ES patients usually presented with a sluggish corneal reflex or demonstrating bilateral extensor plantar reflexes (Babinski reflex) post ictally. These phenomena, particularly occur with prolonged seizure duration (including status epilepticus) by which it induced brain hypoxia and later on, brain edema. The prolonged hypoxic state can also be reflected in the systemic circulation by which a metabolic acidosis due to excessive lactate production by the contracting muscles can be observed on blood gas analysis [46].

Another useful biomarker to differentiate between PNES and ES would be to measure serum prolactin levels post ictally (the blood should be withdrawn between 10 and 20 min after a seizure). Serum prolactin levels rise to more than 500 IU/mL among 90% patients with GTCS and 60% patients with focal onset impaired awareness seizure, sparing normal values among focal onset aware seizure or a prolonged status epilepticus. Serum prolactin levels can sufficiently assist in differentiating GTCS from PNES (sensitivity 100%, specificity 73%). The result, however, should be interpreted with caution since prolactin levels were also elevated in PNES and syncope [14, 47]. A recent systematic review had documented that capillary prolactin levels had a sensitivity of 67.3%, 33.9%, and 11.1% in diagnosing GTCS, focal impaired awareness seizures (FIAS), and focal aware seizures (FAS), respectively, with a very high median specificity of 99.1%, suggesting that it could be quite useful in differentiating GTCS with PNES, but of limited

usefulness in distinguishing between FIAS or FAS with PNES [48].

Provoking seizure with suggestion

In PNES, seizure can be induced by various strategies, including compression of the temple region, verbal suggestion, by applying tuning fork, moist swab, and torch, to saline injection [49]. The patient should receive a suggestion that these maneuvers could provoke a seizure prior to the test. All of these tests had been reported to have a 100% specificity for PNES diagnosis, with compression of the temporal region had the highest diagnostic yield (65.7%). Another study involving patients with refractory epilepsy induced by intravenous saline injection also achieved 100% specificity among 91% of patients with PNES, as opposed to none in ES [50].

One can also use a more ethical approach, that is to modify the already performed routine procedure of EEG, such as applying photic stimulation and hyperventilation with accompanied suggestion to the patient that the purpose of this test was to provoke the seizure [51]. As many as 66% of PNES patients who received the stimuli with additional suggestion experienced an episode as opposed to only 33% who received identical stimuli but without an suggestion (Table 2).

Association with psychiatric disorders

Patients with PNES had been commonly associated with several psychiatric disorders. One study reported that as many as 47% of patients with PNES had some forms of psychiatric disorders and the other reported 100% prevalence of psychiatric diagnosis among PNES patients [2, 16]. Patients with PNES tended to have cluster A or B of personality type disorder, as opposed to cluster C in ES patients [2, 15]. Furthermore, the authors had pointed that cluster A and B were considered highly dysfunctional likely to become the underlying pathology of PNES [52]. Another study found no significant difference in the proportion of depression, anxiety, post traumatic stress disorder, and malingering between patients

with PNES and control [53]. However, PNES patients with ictal motor phenomena had a history of sexual and physical abuse. Similarly, Lancman and colleagues [54]. reported that history of sexual abuse was found in 10% of cases, and hysteroid traits, coping mechanism, and depression to be the most common underlying factors of PNES. Several studies had investigated the possibility of using MMPI-2 as an adjunct to video-EEG to diagnose PNES with relatively good yields (sensitivity and specificity ranging from 70 to 80% and 73–80%, respectively) [55, 56].

Discussion

PNES, if diagnosed properly, is highly prevalent among patients with epilepsy with an estimated prevalence of 2 to 33 per 100,000 general population. Undiagnosed PNES lead to inappropriate patient treatment with unnecessary chronic administration of AEDs. Oftentimes, PNES patients underwent multidrug treatments because their seizure were apparently refractory to current medications. In fact, roughly one in five patients with apparent intractable seizure turned out to be having a non-epileptic seizure. This condition, consequently, predisposes patients to unnecessary harmful effects of AEDs, not to mention the significant financial burden resulting from a prolonged and burdensome diagnostic investigation, hospitalization, and ICU stay, as well as outpatient and emergency room visits [57]. The main problem of PNES lies in the diagnosis and its separation from ES. PNES often has multiple overlapping clinical features with that of ES to a certain extent that confidently differentiating between the two may be proven to be a daunting task. However, this does not mean that discerning them is impossible. PNES and ES possess many distinguishing clinical caveats as presented in this study. In fact, the ILAE Nonepileptic Seizures Task Force had already attempted to concept a staged approach to distinguish the two, emphasizing primarily according to patient's clinical history and physical examination, instead of vEEG [58]. The latter was considered a luxury that not every center may have the facility. Patients with

Table 2 EEG characteristics of PNES patients

Characteristics	Remarks
EEG confirmation comprising one or more of the followings: <ul style="list-style-type: none"> ▪ Prodromal symptoms without EEG changes, sensory predominance (olfactory hallucination, micropsia, other bizarre phenomena) ▪ Pseudosleep ▪ Provoking seizure with suggestion: <ul style="list-style-type: none"> ➢ Standard provocation (photic stimulation and hyperventilation) ➢ Compression of the temple region ➢ Applying tuning fork ➢ Intravenous saline injection ➢ Verbal suggestion ➢ Torch light stimulation 	Occurred among 39–56% of PNES patients [7, 9, 12] Successful induction in 65 to 84% of PNES (64) Successful induction of 65.7% and 0% of PNES and ES, respectively [49] Successful induction of 61.4% and 0% of PNES and ES, respectively [49] Successful induction of 55.6% and 0% of PNES and ES, respectively [49] Successful induction of 54.3% and 0% of PNES and ES, respectively [49] Successful induction of 40.7% and 0% of PNES and ES, respectively [49]

suspected PNES should be thoroughly screened with emphasis on consideration of patients' demographics, detailed history taking, neuropsychological evaluation, and deliberate observation to delineate the semiology of the seizure along with its associated symptoms.

Clinicians are supposed to approach a case of seizure in a deliberate and systematic fashion. As an initial screening, there are several clinical "yellow flags" which raises the suspicion towards PNES, including atypical seizure semiology (discussed later), seizure that lasts more than 2 min, did not occur during sleep or if apparently sleeping can be demonstrated as a pseudosleep (confirmation with EEG later on), tends to occur among female, with onset of the first episode after the age of 10 in the absence of any secondary causes or risk factors of seizure, and previous history of any psychiatric disorders (particularly cluster A and B personality disorders [esp. borderline personality disorder], history of sexual abuse, and/or traumatic childhood experience) Table 1. An atypical seizure characteristics that could be categorized as "yellow flags" were as follows: preceded by predominantly sensory prodromes (olfactory hallucination, micropsia, and other bizarre sensory experiences), gradual onset, unusual motor phenomena (out-of-phase limb movement, side-to-side head movement, forward pelvic thrusting, and directed rage), atypical vocalization (does not occur ictally, non-laryngeal origin, comprehensible words, memory recollection of the event).

When most of these "yellow flags" appear, one would ideally proceed with EEG monitoring. Long-term video-EEG monitoring (LTM) is regarded as the gold standard [12, 59]. However, given that video-EEG monitoring is time- and resource-consuming, it should only be conducted on difficult cases wherein clinical evaluation with routine EEG failed to confirm the diagnosis.

We therefore proposed that patients with yellow flags should first undergo a standard EEG monitoring. During this period, an examiner can provoke a seizure by suggestion. If an episode turns out to occur, one should re-evaluate the yellow flags checklist and see whether or not it match the previous descriptions. Any discrepancies should be documented and reviewed. EEG recordings should also be evaluated if it has any yellow flags. For instance, the patient was in a pseudosleep state (reflected by posterior awake alpha rhythm) either during prodromal symptoms or post episode. EEG recording is particularly helpful if one is still in doubt whether the patient has an FLS or PNES, in that FLS commonly arise during sleeping, tend to be brief (less than 30 s) and ictal EEG can be observed during this period.

If a standard recording does not show any episodes or abnormalities, one can directly proceed to a 2-h video EEG observation bearing the same goals and objectives,

with yellow flag checklist in hand. During this state, it is rational to consider giving suggestion to a patient highly suspected with PNES. If a 2-h video EEG recording is still not confirmatory to provoke the occurrence of any seizure, one can proceed to a longer 4-h video EEG procedure. It is usually done consecutively as a continuation of the 2-h video EEG procedure.

One study reported that with extensive pre-LTM work-up, diagnostic uncertainty of PNES cases can be reduced to only 7% of patients [60]. Although LTM is considered as the gold standard for PNES diagnosis, some patients who underwent LTM were still having unclear diagnosis. In fact, about one in four patients had a non-diagnostic LTM [61]. Alving and colleagues [60] found that as many as 42% of recordings either had uncertain significant events (25%) or no clinical events during LTM (17%). The existing uncertain or absence of any clinical events can at least partially be backed by evidence gathered from periodic yellow flags checklist information. The corresponding information may act as a "blackbox" that record patient's activities and any significant events that appear as described in patient's history, during patient stay in the hospital ward, and during video EEG monitoring. Any discrepancies that appear in the process can further increase the index of suspicion for a PNES diagnosis.

Given the imperfect gold standard, the cost effectiveness of LTM should then be revisited, at least by comparing its diagnostic effectiveness with shorter duration of video-EEG monitoring. Indeed, one study found that 66% of PNES diagnosis can be confirmed with 1- to 2-h video-EEG monitoring, while the remainder 34% were inconclusive, a number comparable to those of LTM [62]. However, 4-h video EEG had a significantly better ability to record clinical events (50.3 vs. 6.2%) and higher sensitivity for both PNES (61.3 vs. 15.4%) and ES (69.3 vs. 49.3%) when compared to 1-h video EEG [63].

It is also important to investigate any underlying psychiatric disorders among patients with PNES. In our opinion, the involvement of any psychiatric disorders is necessary to be addressed at the earliest possible, just as important as defining whether or not it is an epileptic seizure. The corresponding physician should take a look at the previous medical record and to consult a psychiatrist as a routine evaluation whenever multiple yellow flags appear on examination. In our experience, immediate interdisciplinary management of patients suspected with PNES diagnosis can potentially lead to a better patient's cooperation and voluntary acknowledgement that they do not have a seizure, followed by efforts to not "get relapse" again. This approach can dramatically cut short the lengthy and burdensome diagnostic investigation that would otherwise be performed. In addition, by an immediate consult with a psychiatrist, one can also

better discern if a PNES patient has any underlying factitious disorder for secondary gain purpose, particularly those related to legal issues (avoidance of litigation and imprisonment, financial fraud such as falsified insurance claim, and others).

Evidence regarding the difference between PNES and ES contains many subtle, but if carefully delineated, can be proven useful clinical clues. All of this information should further be sorted and prioritized according to its predictive value. Parameters with the highest diagnostic power would then be integrated into a scoring system, which in turn tested against LTM for its sensitivity and specificity. This concept has been documented before with high satisfactory results. For instance, Gates and colleagues applied multivariate discriminant analyses involving upper and lower extremities out-of-phase movement, pelvic thrust, and rigidity to diagnose a PNES. The resulting combination resulted in 96% of diagnostic accuracy [10]. The starting point would be to use this yellow flag checklist in a prospective diagnostic study and the following validation thereafter.

In the future, a combined approach of clinical scoring system and 4-h video EEG monitoring, with or without seizure induction strategies, and routine collaborative treatment with a psychiatrist as the earliest point possible is expected to be non-inferior or perhaps exceed the diagnostic yield when compared with LTM alone. When this occurs, a set of diagnostic criteria for PNES could then be established.

Conclusion

PNES is highly prevalent, resembling ES on many levels and poses significant problems for physicians. PNES can be carefully differentiated from ES with respect to its demographics, prodromal symptoms, onset, ictal duration, semiology of the seizure and its associated symptoms, and associated psychiatric disorders. Efforts to integrate the current wealth of evidence and using a more structured and combined diagnostic approach should be done in order to increase the accuracy of PNES diagnosis.

Abbreviations

AED: Anti-epileptic drugs; ANS: Autonomic nervous system; CI: Confidence interval; CPS: Complex partial seizure; EEG: Electroencephalogram; ES: Epileptic seizure; ER: Emergency room; FLS: Frontal lobe seizure; GTCS: Generalized tonic clonic seizure; ILAE: International League Against Epilepsy; LTM: Long-term video EEG monitoring; MMPI-2: Minnesota Multiphasic Personality Inventory-2; PNES: Psychogenic non-epileptic seizure; TLS: Temporal lobe seizure

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IPEW and AS found and sorted the references, drafted, proofread, and wrote the manuscript. DPGPS and AMGS advised on the content, wrote, and final proofread of the manuscript. The authors have read and approved the manuscript.

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