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Can short-term video-EEG substitute long-term video-EEG monitoring in psychogenic nonepileptic seizures? A prospective observational study

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ABSTRACT

Background: Psychogenic nonepileptic seizures (PNES), the commonest nonepileptic event, represent 20–30% of drug-resistant epilepsy. Correct identification of PNES avoids unnecessary hospitalization and exposure of antiepileptic drugs (AEDs), and helps implement appropriate psychological treatment. Long-term video-electroencephalography (LTVEEG) is the gold standard test to diagnose PNES. However, in a poor-resource country like India, hypothetically, short-term video-electroencephalography (STVEEG) may substitute it, as its usefulness is established in attack disorders.

Objective: The objective of this study was to evaluate effectiveness of STVEEG in PNES and to look into their clinical profile and outcome.

Design/Methods: Consecutive cases of PNES diagnosed with STVEEG or LTVEEG during 2015–16 (two years) were enrolled. All cases were followed for 12 months or more. Detailed clinical evaluation was done including demography, semiology, coexisting anxiety/depressive disorders, and seizure frequency at time of first diagnosis and follow-up. The PNES were classified as Type I hypermotor, type II hypomotor, and type III unclassified/mixed. Favorable outcome was defined as seizure freedom or >50% reduction in seizure frequency while unfavorable outcome was defined as <50% reduction in seizure frequency on follow-up at 6 and 12 months.

Results: Among 57 patients with PNES [median age of onset 24 years (10–69 years), F:M ratio = 7:3)], STVEEG ± induction could record event(s) in 80.7% while the rest required LTVEEG to confirm diagnosis. Among 82 events analyzed, the mean ± 2 standard deviation (SD) duration of events was 5′14″ ± 13′4″. Sixty-two (75.6%) and 10 (12.1%) events were hypermotor and hypomotor respectively, while 10 (12.1%) were unclassified/mixed. Forty-five (79%) patients had pure PNES, while 12 (21%) had coexistent epilepsy. Forty-nine (86%) and 54 (94.7%) patients had statistically significant reduction of seizure frequency (favorable outcome), at 6 and 12 months of follow-up respectively, while the rest had an unfavorable outcome.

Conclusions: The STVEEG has a remarkably good yield in diagnosing PNES, and it may be used when LTVEEG is not feasible. However, further studies are needed to show if it can substitute LTVEEG in PNES.

1. Introduction

Many physiological and nonphysiological events are often misinterpreted as epileptic seizures. Nonepileptic seizures (NES) are paroxysmal episodes that resemble an epileptic seizure, but are not because of abnormal cortical discharges [1]. Psychogenic NES (PNES) constitute nearly 35% of the NES cohort [2]. According to the Diagnostic and Statistical Manual of Mental Disorders 4th Edition (Text Revision) (DSM-IV-TR), PNES is classified as a conversion disorder with seizures or convulsions [3]; PNES resemble epileptic seizures, but without concurrent epileptiform activity and has psychological substrates [4].

Patients with PNES are relatively common with an incidence rate of about 1.4–2 per 100,000 people per year in adults [5], 0.3–0.5 per 100,000 people per year in children [6,7] and prevalence rate of 2 to 33 per 100,000 people [8]. They account 20–30% of intractable epilepsy center referrals [9]. Up to 20% of patients with PNES may present a "status", where attacks are prolonged over several minutes to hours [10] ;, and a considerable proportion may be prescribed inappropriate antiepileptic drugs (AEDs) [11]. In addition, they face the emotional, social, academic, and professional consequences with risk of development of further psychiatric illnesses [12]. Moreover, patients with PNES show

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high mortality rate [13]. Keeping in view the above reasons, correct diagnosis of PNES is highly desired.

Long-term VEEG (LTVEEG) is the gold standard investigation to confirm clinical diagnosis of PNES [14]. However, in resource poor countries, LTVEEG facility is not readily available. [15]. Effectiveness of short-term VEEG (STVEEG) has been established in diagnosing attack disorders, including PNES [2], but evidence from Indian subcontinent is sparse [15–18]. In the present study, we primarily aimed to evaluate the hypothesis that STVEEG is effective in diagnosing PNES. The secondary objective was to look in to the clinical profile and outcome of patients with PNES.

2. Material and methods

This is a prospective observational cohort study conducted at Epilepsy Unit (EU) under Neurology department at Government Medical College and New Civil Hospital, Surat, which is a tertiary care center in western India. Our standard evaluation protocol of patients with epilepsy includes a detailed clinical history and examination, ST/LTVEEG and magnetic resonance imaging (MRI). The study was approved by the Institutional Ethics Committee.

2.1. Inclusion and exclusion criteria

All patients with age >6 years who were with diagnosed PNES during study period from January 2015 to December 2016 with a minimum 12 months of follow-up and informed written consent were included in study. Patients were enrolled immediately when diagnosis of PNES was established during VEEG monitoring. Those patients with coexistent true epilepsy were also included in study. Patients with a) high clinical suspiciousness of PNES who did not have habitual events with ictal record despite having normal interictal electroencephalogram (EEG) report, b) physiological and benign movements (e.g., shuddering attacks, sleep myoclonus, breath holding spells, and stereotypes), c) nonepileptic events (e.g., syncope), d) only true epileptic events, and e) patients with a known diagnosis of cognitive impairment or intellectual disability were excluded from study.

2.2. Diagnosis of PNES

During the EU evaluation, all patients underwent STVEEG to confirm diagnosis of PNES by intended recording of the habitual events. However, if the conclusive diagnosis was not reached with STVEEG, then patients were continued with LTVEEG. We did not stop AEDs in those who were already taking it before confirming the diagnosis of PNES. Patients' habitual events were identified by the technologist (VJ) in confirmation with the attendant. The event semiology and the simultaneous EEG were independently reviewed and agreed by two coinvestigators (PZ and AS). We diagnosed PNES based on the semiology of the episode, along with the presence of a normal "ictal" EEG. Patients with concurrent epileptic events were diagnosed as having "PNES and true events related to coexistent epilepsy".

2.3. Patient evaluation at diagnosis

Detailed clinical history of all patients was noted including age, gender, marital status, socioeconomical class, birth and developmental history, antecedents, age of onset of events, duration and frequency of events as dictated by attendants, detailed semiology, coexisting epilepsy, anxiety/depressive disorders, and clinical examination. The STVEEG was done using the 10–20 international system for electrode placement with awake and sleep recording inclusive of activation procedures viz. hyperventilation and intermittent photic stimulation. Time duration in typical STVEEG was decided as 40–120 min, irrespective of sleep records. When there was clinical suspicion and if patient did not have habitual seizures in 30 min of awake record or after 20 min of sleep record, verbal and if required, tactile suggestion was given to patients (only once) by VJ, and events were marked during VEEG monitoring. Verbal suggestion was done by showing patient video camera and then instructing him/her to visualize his/her own seizure on an imaginary movie screen, allow the habitual seizure to happen, and when clinical seizure like symptoms is present, he/she is verbally reinforced by the technologist (VJ). Tactile suggestion is done by rubbing spirit swab over the right forearm to provoke habitual seizures. All ST/LTVEEG data were evaluated, including the semiology of the habitual events.

The PNES were classified based on video analysis aided semiology as Type-I hypermotor (A-limb dystonic posturing, B-bizarre limb/trunk movements, C-hyperventilation with subtle or no limb/facial movements, D-Sudden symmetric/asymmetric jerking, E-axial dystonic movements), type-II hypomotor (A-unresponsiveness with paucity of movements, B-pseudosyncope), and type-III unclassified/mixed. Comorbid epilepsy was diagnosed based on adequate clues in clinical history aided by abnormal interictal EEG. Ictal recording of true seizure was not mandatory to define associated true epilepsy.

All patients with PNES were referred to psychiatry department for assessment and diagnosis of main comorbidities, i.e., depression and anxiety disorder based on DSM-V criteria [19]. Appropriate treatment was given including counseling, 6 cycles of once per week cognitive behavioral therapy informed psychotherapy (CBT-IP), drugs, or combination as per discretion of psychiatrist.

2.4. Patient evaluation at follow-up

All patients were followed up at 6 months and at the end of one year. During each visit, we noted the frequency of events in last two blank pages of Epilepsy Information Booklet. Favorable outcome was defined by sustained seizure freedom or more than or equal to 50% reduction of seizure frequency, while unfavorable outcome meant no or less than 50% reduction seizure frequency or had recurrence of seizure after initial remission.

2.5. Statistical analysis

The patient-wise information was recorded in Microsoft excel sheets and Statistical Package for the Social Science (SPSS) software version 15.0. For analysis, all identifiers were removed. For nominal (categorical) outcome variables nonparametric statistical tests of significance like chi-square (goodness of fit) and Mann–Whitney tests were applied. If the expected number of observations was less than five in any category, then, Yates's corrected chi-square or Fisher's exact test was used. For testing clinical outcomes among patients in this study, "one-tailed" chi-square or goodness of fit tests were applied because we envisaged improvement in patients' condition on treatment. The age of patient and time duration of events were calculated as mean ± SD (standard deviation) as well as median (with range). Quantitative variables (frequency and duration of events) were tested by Student's *t*-test. A probability (p) value of less than 0.05 was considered statistically significant.

3. Results

3.1. Subject disposition and baseline characteristics

A total of 1197 patients were admitted to our EU during the study period. As depicted in Fig. 1, various forms of nonepileptic spells were seen in 92 patients, of which 73 were eventually evaluated with PNES. Follow-up data were lacking in 16 patients. Finally, total 57 patients with PNES met the study protocol. The demographic and clinical characteristics of these 57 patients are described in Table 1.

As shown in Table 1, PNES could be diagnosed by STVEEG in 46 out of 57 (80.7%), while the rest of the 11 patients required LTVEEG to confirm the diagnosis, which was statistically significant. The interobserver agreement (k) was 0.82 between investigators PZ and AS. Sleep was achieved in 35 (61%), which included 29 (63%) and 6 (54.5%) patients

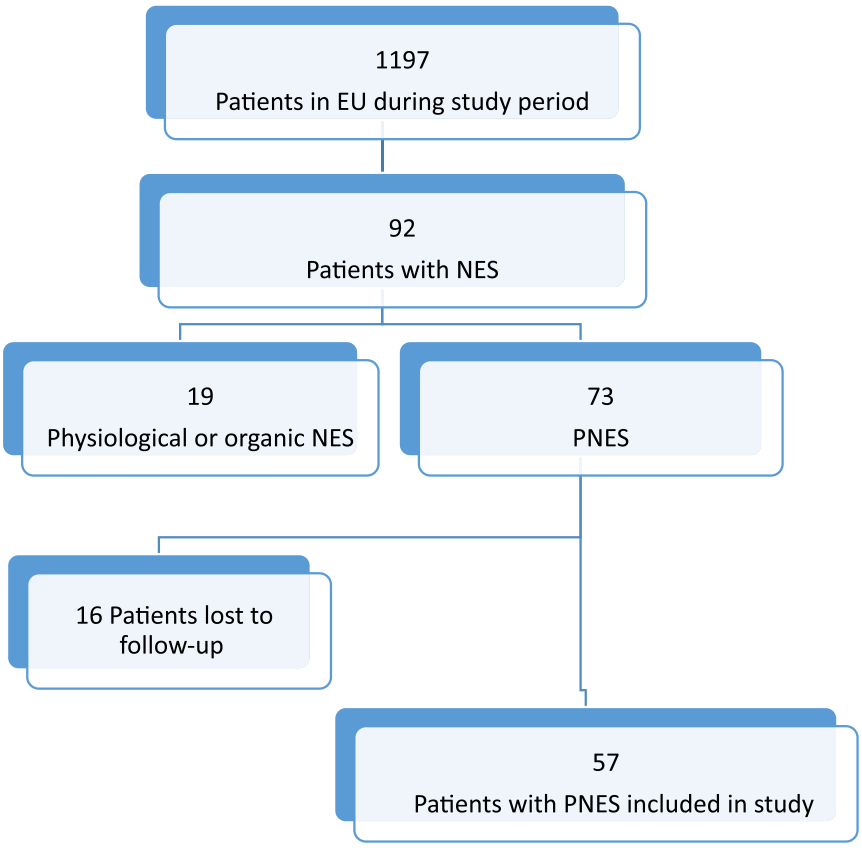

Fig. 1. Selection of patients with psychogenic nonepileptic seizures in the study.

Table 1
Patient baseline characteristics and evaluation.

Variables		Value	Statistical significance
Age (years)	Range	10–69	
	Median	24	
Sex	Female	39	
	Male	18	
Duration of events (days)	Range	2–1095	
	Mean ± SD	141 ± 248	
Coexisting diseases	Epilepsy	12 (21%)	
	Anxiety	35 (61.4%)	
	Depressive disorder	46 (80.7%)	
No. Of patients on AEDs	AEDs (one or two)	16 (28.1%)	
	None	41 (72%)	
	AEDs in pure PNES	9 (15.8%)	
	AEDs in epileptics	7 (58.3%)	
Type of monitoring required to reach to diagnosis	STVEEG	46 (80.7%)	$p = 0.04^*$
	LTVEEG	11 (19.3%)	
Induction required	No	20 (35.1%)	$p = 0.19^*$
	Yes	37 (64.9%)	
Total events recorded (excluding four patients with multiple events)	Range	1–6	
	Mean ± SD	1.5 ± 1.3	
Duration of events during VEEG monitoring	Range (min, sec)	1″–86′30″	
	Mean ± SD (min, sec)	5′14″ ± 13′4″	
Sleep achieved during VEEG	Yes	35 (61.4%)	$p = 0.12^*$
	No	22 (38.6%)	
Abnormal Interictal VEEG	Normal	45 (78.9%)	
	Abnormal	12 (21.1%)	
Patterns of Abnormal VEEG	Focal	11 (91.7%)	$p = 0.04^*$
	Generalized	1 (8.3%)	

AEDs: Antiepileptic drugs, SD: standard deviation, PNES: psychogenic nonepileptic seizures, VEEG: Video-electroencephalography, STVEEG: short-term video-electroencephalography, LEVEEG: long-term video-electroencephalography.

* Statistical test applied is chi-square test. Statistical significance is noted in type of monitoring (STVEEG vs. LTVEEG) required to reach diagnosis and patterns of abnormal EEG (focal vs. generalized) among patients with comorbid epilepsy. There was no statistical difference in whether induction required or not during monitoring, and if sleep was achieved or not during VEEG.

Table 2
Semiological classification of patients with PNES (Total events = 82).

Type I: Hypermotor	A. limb tonic/dystonic posturing	27 (32.9%)
	B. bizarre limb/trunk movements	19 (23.1%)
	C. hyperventilation with subtle or no limb/-facial movements	8 (9.7%)
	D. Sudden symmetric/asymmetric jerking	6 (7.3%)
	E. axial tonic/dystonic movements	2 (2.4%)
Type II: Hypomotor	A. unresponsiveness with paucity of movements	7 (8.5%)
	B. pseudosyncope	3 (3.6%)
Type III: Mixed or Unclassified	unclassified or mixed	10 (12.1%)

during STVEEG and LTVEEG monitoring respectively. During evaluation, 16 (28%) patients were on either one or two AEDs.

3.2. Semiological classification of PNES

Among 57 patients, 37 (64.9%) patients had spontaneous seizures while the rest required either verbal or tactile induction. The STVEEG could record event(s) in further 14 (70%) patients with induction, while the rest of the 7 (30%) patients required LTVEEG to document event(s). This difference was not statistically significant. Majority of the patients had developed one, and a few patients had developed two to three events. Four patients had developed too many events to count, described as multiple events. A total of 82 events were evaluated, excluding those patients with multiple events. Duration of events ranged from 1″ to 86′30″, with an average of 5′14″. As shown in Table 2, hypermotor semiology was observed in 62 (75.6%) of the events, followed by 10 (12.1%) events in hypomotor and mixed categories each. The detailed semiological features are shown in Table X in the supplementary data.

3.3. Comorbid illness in cohort

Coexisting epilepsy was noted in 12 (21%) patients. The EEG was abnormal (consistent with diagnosis of focal or generalized epilepsy) in 9 (75%) patients with STVEEG and 3 (25%) patients with LTVEEG monitoring, which was not statistically significant. During follow-up, AEDs were withdrawn in 9 (16%) patients who were on AEDs with misdiagnosis of epilepsy, while appropriate AEDs were prescribed in 5 (42%) patients who had coexisting epilepsy but were not on AEDs previously.

Anxiety and depression was found in 35 (61.4%) and 46 (80.7%) respectively in our cohort. A psychiastrist (ML) evaluated and counseled all patients with PNES. Drug treatment was given in 26 (45.6%) and combined (CBT-IP plus drug) treatment was given in 12 (21%) patients with depression. Drugs tried were selective serotonin reuptake inhibitors (SSRI), tricyclic antidepressants (TCAs), and serotonin and noradrenalin reuptake inhibitors (SNRI). Anxiolytic drugs were prescribed in 19 (33.3%) patients with anxiety disorder.

3.4. Follow-up and outcome of PNES

During follow-up, 39 patients (70%) had turned up personally for visit, while 17 patients were contacted on telephone. As shown in Tables 3 and 4, forty-nine (86%) patients at 6 months and 54 (94.7%) patients at 12 months follow-up had either complete seizure freedom or more than 50% seizure frequency reduction. This was statistically significant compared to baseline values and comprised of favorable outcome group. While, 8 (14%) patients at 6 months and 3 (5.3%) patients at one-year follow-up had less than 50% reduction in seizure frequency compared to baseline comprised of unfavorable outcome group. One of the patients in unfavorable outcome group had committed suicide because of depression.

4. Discussion

This study shows that in a resource constrained settings, majority PNES can be diagnosed with STVEEG as compared to the gold standard test LTVEEG. In the present communication, at least one episode of PNES could be recorded by STVEEG among 80.7% of the patients with PNES, with or without induction to reach a definite diagnosis. Also, interobserver agreement for diagnosis of PNES by STVEEG was satisfactory with high yield during present study.

The LTVEEG is not readily available in resource poor countries as it is expensive and labor- and time-intensive. On the other hand, STVEEG is done as daycare procedure, and it has advantage of video analysis for seizure semiology as compare to routine scalp EEG. Moreover, during STVEEG, patient could achieve sleep, which could help diagnose underlying epilepsy types correctly based on interictal epileptiform discharges (IEDs). Our results support utility of STVEEG with or without induction for confirming the diagnosis of PNES, and it may obviate the need for more demanding LTVEEG in vast majority of cases. Hence, we believe that in a given clinical scenario with high suspicion of PNES, although gold standard, doing a LTVEEG study may not be cost-effective compared with STVEEG.

Though few studies [20,21] reported high yield (60–75%) of PNES diagnosis using induction with saline injection during VEEG, a recent study [22] showed that a diagnostic approach without using placebo injection is noninferior to placebo saline-induced seizure provocation and is ethically more acceptable. However, other studies [23,24], which did not practice induction during recording had a very low yield (35%) of confirming diagnosis of PNES with STVEEG. Since we adopted the protocol of induction only if they did not develop spontaneous seizures during VEEG, we utilized maximum advantage of provocative methods only when necessary, in this study.

Table 3
Seizure frequency of patients on follow-up.

Seizure frequency (per month)		At baseline	6 months F/u	Statistical significance*	12 months F/u	Statistical significance*
All patients (n = 57)		29.2 ± 49.1	2 ± 8.1	p = 0.0008 (t = 4.1)	1.4 ± 5.8	p = 0.0005 (t = 4.2)
Favorable outcome	Complete seizure freedom	28.1 ± 48.5 (n = 45)	0 (n = 45)	p = 0.00002 (t = 3.8)	0 (n = 50)	p = 0.000008(t = 4.1)
	>50% reduction in seizure frequency	87 ± 58.8 (n = 4)	1.6 ± 8.3 (n = 4)	p = 0.02 (t = 2.8)	1.2 ± 5.8 (n = 4)	p = 0.03 (t = 2.9)
	Total	33.2 ± 51.5 (n = 49)	1.2 ± 7.7 (n = 49)	p = 0.0002 (t = 4.5)	0.8 ± 4.9 (n = 54)	p = 0.00002 (t = 4.6)
Unfavorable outcome		2.9 ± 2.8 (n = 8)	6.6 ± 3.6 (n = 8)	p = 0.23 (t = 1.4)	3.1 ± 5.4 (n = 3)	p = 0.9 (t = 0.06)

* Statistical test applied: Student's *t*-test for determining difference between seizure frequency at 6 and 12 months of follow-up compared with baseline seizure frequency.

Table 4
Follow-up and outcome.

Variables	Favorable			Unfavorable	Statistical significance*
	Complete seizure freedom	>50% improvement in seizure frequency	Total		
6 months	45 (79%)	4 (7%)	49 (86%)	8 (14%)	p = 0.001
12 months	50 (87.7%)	4 (7%)	54 (94.7%)	3 (5.3%)	P = 0.001

* Statistical analysis is done using chi square goodness of fit test between favorable vs. unfavorable outcomes.

We classified PNES semiology into hypermotor, hypomotor, or mixed categories based on motor and behavioral manifestation. Our classification scheme is comparable to various other studies [24], which show similar proportion of hypermotor semiology (61% vs. 75.6% in our study), although slightly higher proportion was noted for dialeptic PNES in other studies [18,25]. However, this difference could be subtle as many of the patient belonged to mixed or unclassified semiology. This raises the concern and need for a universal classification schema for PNES in the International League against Epilepsy (ILAE) classification system.

This study gives rough estimate that STVEEG can correctly identify true patients with epilepsy in a substantial number of patients as coexisting epilepsy was noted in 21% in our cohort with PNES. This is similar to other studies [12,25,26] where epilepsy ranges from 21% to 32% based on varied inclusion criteria. In our cohort, we could withdraw AEDs in 16% of patients who were on AEDs with misdiagnosis of epilepsy, while appropriate AEDs were prescribed in 42% of patients who had coexisting epilepsy but were not on AEDs before. Hence, we could opine regarding need for AEDs in 25% of our cohort. Anxiety and depressive disorders were found in 60% and 80% respectively in our cohort, which is comparable to various psychiatric comorbidity ranges from 53% to 100% in PNES as shown in recent meta-analysis [27]. In our cohort, a psychiatrist evaluated and counseled all patients with PNES, while few patients were given drugs for depression and anxiety or combined (CBT-IP and drugs) treatment for depression. Overall, STVEEG helped in holistic management patients with PNES including ones with comorbid epilepsy or psychiatry illness.

In our cohort, significant number of patients with PNES had sustained remission of seizures or substantial reduction in seizure frequency at end of 6 months (79%) and one year (87%) of diagnosis of PNES and psychiatric counseling or treatment thereafter. Different studies conducted in pediatric and adult populations found seizure remission at follow-up to be between 72 to 78% [28–31]. However, overall seizure outcome is very low (38–45%) including higher mortality rates in other studies [12,32,33] attributed mainly by small sample size, retrospective study design and selection bias. Outcome of PNES need to be assessed not only in terms of seizure outcome but also with regard to psychiatric comorbidity and productive life thereafter.

Better (early and sustained) remission of seizures in majority of our patients is probably due to prospective study design, early referrals to psychiatrist and psychologists, and stringent follow-up by neurologist and psychiatrist. Also, our protocol of sharing good news with the patient about not having true epileptic seizures may have helped better coping. Proper explanation and discussion of diagnosis and stressors with family in the presence of the patient could further ameliorate outcomes. Counseling by psychiatrist and psychologist, taking vows about not letting it happen, maintaining healthy relationship with friends and family, and occupational therapy may have resulted better outcomes in our cohort.

The limitations of our study were the mixed age cohort and the short duration of follow-up. Also, we did not assess predisposing, precipitating and perpetuating factors, prognostic outcome variables, and outcomes depending on PNES semiology. However, all the patients in study were assessed by single team of neurologists and a technologist using a standardized method of evaluation. The prospective observation study design represents unique and factual observation in terms of results and outcome.

5. Conclusion

The STVEEG has a remarkably good yield in PNES, and it may be used when LTVEEG is not feasible However, further studies are needed to show if it can substitute LTVEEG in PNES.

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Conflict of interest

The authors report no actual or potential conflicts of interest related to the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2019.03.034.

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