

To study the Clinical Psychological and Neurological Profile and Assessing the Outcome Predictors of Patients with Psychogenic Non Epileptic Seizures (PNES): A Study of 74 Cases

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Abstract: *Objective:* To Study the Clinical, Psychological and Neurological Profile and Assessing the Outcome Predictors of Patients with Psychogenic Non Epileptic Seizures in North Indian adult population. *Design of study:* A prospective observational study, conducted at tertiary teaching institute at Jaipur. *Materials and Methods:* Seventy-four patients with PNES were enrolled. The diagnosis was based on mobile recordings of episodes, and video-electroencephalography (video-EEG) monitoring. A detailed clinical evaluation was done including evaluation for coexistent anxiety, depression or other psychiatric disorder. Patients were followed-up to 2 months. *Statistical Analysis:* Appropriate statistical tests were used. *Results:* The mean age at onset was 22 years; with female to male ratio were 17.5:1. Coexisting epilepsy was present in 6 (8.10%). 40 patients (54.05%) had received one or multiple antiepileptic drugs. Out of 74 patients of PNES 48 (64.86%) had predominant motor phenomenon, whereas 26 patients (35.13%) had other manifestations. The common features observed were jaw clenching, ictal eye closure, pre-ictal headache, ictal weeping, resistant behavior, ictal vocalization, and unresponsiveness during episodes. Comorbid anxiety and depressive disorders were seen in 43 (58.10%) and 62 (83.78%) patients respectively. Short-term (2 months) outcome of 62 patients was good (seizure freedom in 49 {66.21%} and >50% improvement in 21 {28.37%}). *Conclusion:* PNES is common, but frequently misdiagnosed and treated as epileptic seizures. A high index of suspicion is required for an early diagnosis. Proper disclosure of diagnosis and management of the psychiatric comorbidities can improve their outcome. *Limitation:* Limited sample size, change in seizures frequency, socio-occupational functioning, quality of life was not assessed.

Keywords: Psychogenic non-epileptic seizures, video-electroencephalography, Coexistent epilepsy

1. Introduction

Non-epileptic seizures (NES) are episodes of altered movement, sensation, or experience resembling epileptic seizures, without ictal electrical discharges in the brain.^[1] The physiological causes of NES include convulsive syncope, paroxysmal vertigo, sleep disorders, panic attacks, movement disorders, transient ischemic attacks, complicated migraine, metabolic disorders, and drug intoxication or withdrawal.^{[2],[3]} Psychogenic non-epileptic seizures (PNES) are the commonest non-epileptic events; represents 20-30% of patients being referred for epilepsy surgery evaluation.^[4] The incidence of PNES is estimated to be 1.5-3/lakh/year^{[5],[6]} and the prevalence ranges from 2-33 cases/lakh persons in the general population.^{[7],[8]} PNES occur more frequently in women (75-85%); with onset in young adulthood.^{[1],[9]} The prevalence data of coexistent epilepsy and PNES is variably estimated between 5% and 40%.^{[10],[11],[12]}

PNES are categorized as Dissociative (International Classification of Diseases; ICD-10) or Conversion disorder [Functional Neurological Symptom Disorder] in Diagnostic and Statistical Manual of Mental Disorders; DSM-V. The major psychiatric comorbidities are somatoform, depressive, anxiety, post-traumatic stress, and personality disorders.^{[13],[14]} There are various pre-disposing (sexual or physical abuse, childhood trauma, head injury, intellectual disability, dysfunctional family, borderline-like personality, other psychopathology, defective illness perceptions and coping styles etc.), precipitating (emotional

or physical stress, onset of new illnesses, life events, relationship conflicts etc.) and perpetuating factors (frequent health-care contacts, social or financial gain) have been associated with PNES.^{[15],[16],[17],[18],[19]}

PNES can imitate any type of seizure event and sometimes may be confused with frontal lobe seizures.^{[20],[21],[22],[23]} Owing to clinical variability there is no well-established diagnostic criteria and clinical classification. The historical facts, ability to be induced by suggestion, psychological tests, serum prolactin, and ambulatory EEG are insufficient for the diagnosis of PNES.^{[24],[25],[26],[27]} The demonstration of clinical event without concomitant EEG changes during video-EEG is the diagnostic gold standard.^{[23],[28]}

PNES requires a very different approach for management and misdiagnosis places the patient at risk of increased morbidity and mortality. The indirect effect through loss of quality of life is much more than direct costs of drugs and investigations. Early diagnosis, proper disclosure of diagnosis, and comprehensive management by psychotherapy and pharmacotherapy can improve the outcome. The outcome of PNES in a given patient is variable, with good short-term outcome.^{[29],[30],[31],[32],[33],[34]} However, on long-term follow-up, most patients had recurrences of events.^{[35],[36],[37],[38],[39]} The mean latency between manifestation and the diagnosis is about 7-16 years; indicating lack of awareness among patients, their family members as well as among treating doctor.^{[11],[40],[41]}

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Among adults there are very few studies from India. [42],[43],[44] Aim of our study was to diagnose PNES, study their clinical and video-EEG profile, and psychiatric comorbidity and short term outcome in adult population.

2. Materials and Methods

A total of 96 patients, age >14 years with clinical suspicion of PNES with or without any coexisting epilepsy attending neurology outpatient in a tertiary care hospital in North India were enrolled over a period of 2 years (August 2016-July 2018). Clinical suspicion was based on the following criteria:

- Refractory epilepsy or change in symptomatology
- Episodes of variably prolonged unresponsiveness and lying motionless
- Multiple or non-stereotypical seizure patterns
- Occurrence in situations as in front of audience, doctor or in waiting room
- Seizure provoked by emotional stress
- Associated psychiatric disorders.

After a thorough clinical history and detailed neurological examination, all the cases were subjected to video-EEG monitoring. Of 96 patients, 78 (81.25%) had confirmed diagnosis of PNES. Four patients lost in follow-up. The diagnosis of PNES was based on witnessing the event, that occurred either spontaneously or on induction by hyperventilation and verbal suggestion during video-EEG. Based on the clinical semiology, the patients were divided into two groups; type A characterized by excessive motor phenomenon or type B with non-motor or limp attack phenomenon. All patients were further evaluated for any coexisting anxiety or depressive disorders using DSM-V criteria and their severities were assessed using Hamilton Depression/Anxiety rating scales and Dissociation Questionnaire. After confirming the diagnosis of PNES, all the patients and the family members were properly explained about the diagnosis; that these episodic events were not due to epilepsy and such phenomenon may occur due to various kinds of stress, lack of coping skills or existent psychological disturbances. All the patients were thoroughly interrogated to identify the possible precipitating factors if any; counseled to increase their self-confidence and coping skills and encouraged to remain socially and occupationally active. Along with counseling, patients were started on antidepressants with/without anxiolytics; according to the psychiatric comorbidity. Antiepileptic drugs were slowly withdrawn in patients with only PNES. All patients were followed-up at 2 months either by hospital visits or telephonically regarding frequency of PNES. A good outcome was defined as achieving seizure freedom state or >50% improvement.

3. Statistical Methods

Data were entered into Microsoft Excel spreadsheet and statistically analyzed. Means and standard deviations were calculated for all continuous variables. Chi-square test was used to compare categorical variables, and Students *t*-test for continuous variables. *P* < 0.05 was considered the level of statistical significance.

4. Results

A total of 74 patients were included in the study. Majority of patients were women (94.59%), with the mean age at onset being 22.44 ± 10.22 years. Most of our patients were literate (84.12%), resident of urban areas (55.55%), from nuclear families (58.73%), and were belonging to either upper lower or lower middle class (93.65%) (Modified Kuppaswamy scale 2007). Of the 70 female patients; 33 were house wives, 10 students, and the rest 14 were widows and unmarried females. Of the six male patients, four were gainfully employed, one was unemployed, and one was a student [Table 1].

Table 1: Clinical characteristics of psychogenic non-epileptic seizures patients

Clinical characteristics(n=74)	
Females	70/74(94.59%)
Age of onset(years)	22.44+/-10.22
Age of diagnosis	27.72+/-11.02
Disease duration	42.64+/-37.22
PNES frequency(per month)	21.23+/-32.6
Emotional stress	62/74(83.78%)
Physical abuse	19/74(25.67%)
Sexual abuse	28/74(37.83%)
Stereotyped events	67/74(90.54%)
Utilized emergency services	41/74(55.40%)
Coexistent epilepsy (n=16)	
Partial	11/16(68.75%)
Generalized	5/16(31.25%)
Only PNES patients(n=68)	
On AEDs	41/68(60.29%)
Duration of AEDs use(months)	18.66+/-37.08
Abnormal EEG	
Nonspecific	8/66(12.12%)
Epileptiform	nil
Abnormal imaging	
Single/multiple calcifications	11/68(16.17%)
PNES type(74)	
Motor features	48/74(64.86%)
Other features	26/74(35.14%)

The main reason for evaluation was the confirmation of primarily suspected PNES in 68/74(91.89%) patients; of which 41/68 (60.29%) were initially diagnosed and treated as epilepsy. In the remaining 16/74 (21.62%) patients with coexisting epilepsy; the reasons were; recurrence of seizures in previously controlled epilepsy in nine patients and uncontrolled epilepsy in seven patients. Neuroimaging and EEG data of patients with epilepsy coexisting PNES were not been analyzed. Among the patients with only PNES (n = 68), we were able to perform inter-ictal EEG in 66 patients, and neuroimaging computed tomography/magnetic resonance imaging (CT/MRI) in 68 patients. Of them, we found 12.12% patients with non-specific EEG abnormalities and none with epileptiform discharges. Single or multiple calcifications were observed in 16.17% patients with only PNES who underwent neuroimaging.

Fourteen patients (18.91%) had spontaneous PNES events, whereas in rest 60 patients the diagnosis was confirmed by inducing the clinical event during video-EEG monitoring. The most common PNES type was motor attacks seen in 48 patients (64.86%); followed by non-motor attacks in 26

patients (35.14%). The common semiological characteristics observed (in either type) are listed below [Table 2]. Historically, six patients had significant injuries (forehead or occipital bruises) whereas four patients had urinary incontinence and bite on tip of the tongue during the episodes, but not observed during the witnessed episodes.

Table 2: Semiological characteristics

Features	Motor attacks (n=48) %	Non-motor attacks(n=26) %
Pre-ictal headache	75	93.78
Ictal eye closure	54.18	84.67
Resistant behavior	65.87	71.65
Jaw clenching	67	54.42
Vocalization	48.95	21.76
Unresponsiveness	26.73	28.67
Ictal weeping	27.16	26.24

The comorbid anxiety and depressive disorders were seen in 58.10% and 83.78% cases, respectively. On the assessment of severity, majority of these patients had moderate-severe scores on Hamilton depression scales (65.56%), and mild-moderate scores on Hamilton anxiety scales (81.76%) respectively [Table 3]. Neurological comorbidities were seen in 38 (60.31%) patients (six had coexistent epilepsy), commonest being chronic tension type headache in 27 patients, migraine in 2, mild mental retardation in 2, alcohol dependence in 2, tubercular meningitis in 1, drug addiction in 1, operated brain tumor in 1, history of significant head injury in 1, and neuromyelitis optica in 1 patient respectively

Table 3: Comorbidities: Psychiatric comorbidities(n=74)

Depressive disorders	62/74(83.78%)
Hamilton depression rating scale HAM-D score	17.97+/-3.36
Anxiety disorders	43/74(58.10%)
Hamilton anxiety rating scale HAM-A score	15.12+/-3.75
Somatoform disorder	23/74(31.08%)
Dissociative disorder	6/74(8.10%)
Neurological comorbidities(n=74)	
Chronic tension type headache	36/74(48.64%)
Others	14/74(18.91%)

We were able to follow-up 74 patients (94.87%) for 2 months, Four patients (5.13%) were lost to follow-up. Of these, 51 patients (68.91%) had good outcome (46.66% seizure free and 24.44% had >50% improvement). Among the 23 patients, (31.08%) with poor outcome; ten patients (13.51%) had <50% improvement, another six (8.11%) had persistent PNES with same frequency whereas the remaining seven (9.46%) patients had increase in PNES frequency from baseline. In our study, good outcome predictors were younger age ($P = 0.54$), short duration of illness ($P = 0.44$), less frequent episodes ($P = 0.66$), patients with non-motor attacks ($P = 0.27$). However, effect of gender, coexistent epilepsy, and psychiatric comorbidity could not be assessed because of incomparable data.

5. Discussion

Similar to the previous studies majority of our patients were women (94.59%) in late 2nd-3rd decade (72%) of their life; with a mean age of onset and presentation of PNES 22.44 years and 27.72 years respectively. In one previous Indian study of 71 adult patients with PNES (Lazarus 2003),

compared to our study there was a younger population group (mean age at onset 19.68 years) and a lower proportion of women (78.9%).^[42] The likely reason is the fact that majority of patients in their study were students whereas married females constituted majority of our patients.

Most of our patients came from nuclear families with poor emotional and peer support. Emotional stress was the precipitating factor in 83.78% of our patients, but only 25.67% of our patients had reported physical abuse. The higher reporting of sexual abuse (37.83%) by our patients as compared to previous studies (11-37%) was likely due to changing our social structure, literacy and use of social media.^{[14],[19],[32],[45],[46]} The data about comorbid psychiatric illnesses is highly variable because of the use of different nomenclature, criteria, and classifications.

The majority (91.89%) of our patients were having only PNES. Whereas 21.62% of our patients had coexistent PNES and epileptic seizures, of them the commonest being partial seizures (68.75%). The available data of coexistence of PNES and epilepsy is highly variable (5-40%); because of the differences in study population, study type, and reasons for video-EEG monitoring.^{[10],[11],[12]} 60.29% of our patients with only PNES ($n = 68$) were misdiagnosed and treated as epileptic seizures; which is not an uncommon observation (31-75.5%) in older studies.^{[32],[42],[47],[48],[49]} Utilization of emergency services for management of PNES is common; seen in 55.40% of our patients, similar to observations by McKenzie (49.7%).^[32] Historically, 20.63% of our patients had presentation as pseudostatus; similar to that reported by Reuber (20.1%).^[36]

In our study, the mean delay in diagnosis of PNES was nearly 5 years ; whereas most studies have reported a mean delay of 1.5-9 years.^{[14],[31],[32],[41],[42],[43]} The possible reasons for the delay in diagnosis was lack of awareness both among patients and treating doctor, use of alternative system of medicine, and belief that these events were due to supernatural causes. Shorter duration of video-EEG monitoring and early use of induction protocol, are the reasons for lower rates of spontaneous PNES events (18.91%) in our patients. As expected, more spontaneous events were seen with prolonged monitoring; as reported in 71-96.2% cases within 48 h of video-EEG monitoring in previous studies.^{[48],[50],[51]}

In contrast to older belief that a PNES patient had multiple or changing semiology; recent studies have shown that majority of PNES attacks are similar in a patient.^{[42],[52]} Historically, 90.54% of our patients were having stereotyped events that were confirmed by eye witness of previous event and event during V-EEG monitoring. There is no uniform clinical semiological classification of PNES; and in most of the studies patients were classified on the basis of either excessive or paucity of motor phenomenon. In most of the studies, the commonest PNES subtypes were attacks with excessive motor phenomenon (52-77%).^{[48],[51],[52],[53],[54],[55]} Similar results in our study-motor attacks were the most common PNES type (64.86%) seen in our patients; whereas other Indian studie showed non-motor presentation was commonest, (Lazarus 2003: 59.2%; Dhanraj 2005: 53.3%).^{[42],[43],[44]} The reason

behind this is not clear; but probably it is the cultural difference and poor emotional support in our patients, especially among the females.

Apart from classical ictal features of a typical motor or limb attack; a significant number of our patients had pre-ictal headache (75% in motor v/s 93.78 in nonmotor attacks), ictal eye closure (54.18% in motor v/s 84.67% in non-motor attacks), resistant behavior (65.87% in motor v/s 71.65% in non-motor attacks), jaw clenching (67% in motor v/s 54.42% in non-motor), ictal weeping (27.16% in motor v/s 26.24% in nonmotor), ictal vocalization (48.95% in motor v/s 21.76% in non-motor), and unresponsiveness (26.73% in motor v/s 26.24% in non-motor attacks) during episodes. A few studies had reported significant injuries, urinary incontinence and tongue bite with PNES episodes.^{[40],[53],[56]} Historically, six of our patients had significant injuries over forehead or occipital areas; whereas four each had urinary incontinence and bite over tip of the tongue.

Abnormal non-epileptiform inter-ictal EEG (46-54%),^{[41],[52],[53],[57]} and abnormal neuroimaging (30-43%)^{[30],[53]} are not uncommon in PNES patients without coexisting epilepsy. None of our patients with only PNES had epileptiform discharges; although 12.12% had non-specific inter-ictal EEG abnormality. Similarly, 16.17% our patients with only PNES had single or multiple calcified lesions on CT brain. It should be kept in mind that neurocysticercosis is endemic in India, and asymptomatic calcified lesions in brain are not uncommon in our population. Our main focus was to identify comorbid depressive and anxiety disorders. We found a high incidence of depressive (83.78%) and anxiety disorders (58.10%) in our patients. Most of them had moderate-severe depression and mild-moderate anxiety scores respectively. Chronic tension type headache (48.64%) was the commonest neurological comorbidity.

At short term follow-up (2 months), about 19-67% patients were seizure free and additional 21-56% had significant reduction in seizure frequency.^{[29],[30],[31],[32],[33],[34]} However, many patients with good initial outcome had recurrence of events on long term follow-up. The long term (1-14 years) follow-up studies variably reported seizure freedom rates from 16-40%.^{[11],[35],[36],[37],[38],[39]} In the recently published largest series (260 patients) of short term (6-12 months) outcome of PNES patients by McKenzie (2010); 66.21% of patients had been free of spells and additional 28.37% patients had at least 50% reduction in spell frequency.^[32] To the best of our knowledge, there are no studies addressing prognosis of PNES and their factors in adult population from India. Similar to older studies, the short term outcome was good in our study; which included cessation of seizures in 46.66% and >50% reduction in seizure frequency in 24.44% patients. The most important prognostic factor probably is the acceptance of the diagnosis of PNES by patients and their family members. The other favorable prognostic factors reported are young age at onset,^{[36],[47]} male^[32] or female,^[37] better education,^{[47],[55]} good social, family, and security support system,^{[31],[32],[34],[37]} employment, and independent lifestyle,^{[34],[35],[37]} low intelligence quotient^{[32],[58]} shorter duration of condition,^{[39],[47]} less

frequent episodes,^[43] accepting the diagnosis,^{[31],[34]} motionless spells,^{[39],[47],[55]} lack of comorbid epilepsy,^{[37],[47],[59]} continued antiepileptic drugs (AEDs) use,^[35] lack of physical or sexual abuse,^[30] and lack of psychiatric comorbidities.^{[30],[32],[47]} The possible good prognostic factors in our study were young age at onset ($P = 0.54$), shorter duration of illness ($P = 0.44$), less frequent episodes ($P = 0.66$), and limb attacks ($P = 0.27$); although none was statistically significant. The effect of gender, literacy status, socioeconomic status, coexisting epilepsy and comorbid psychiatric illnesses on the outcome could not be analyzed because of inadequate sample size.

Apart from small sample size and incomparable data, the other potential limitation of our study was that the outcome assessment was based only upon reduction in frequency of seizures, and other parameters as use of AEDs, employment, quality of life, etc., were not studied. So, larger studies with longer follow-up and addressing these issues are required to find out the outcome factors in Indian population.

PNES is common among young women. PNES is frequently misdiagnosed and wrongly treated as epileptic seizures. A high index of suspicion is required for an early diagnosis. Proper disclosure of diagnosis and management of the psychiatric comorbidities can improve the outcome and overall quality of life of patients with PNES.

6. Limitation

There are two major limitation of our study, first is limited sample size. Secondly, follow-up is only in terms of change in seizures frequency; while other parameters as use of AEDs, socio-occupational functioning, psychiatric comorbidity outcome, and quality of life was not assessed.

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Tables

[Table 1], [Table 2], [Table 3]

At short term follow-up (<1 year), about 19-67% patients were seizure free and additional 21-56% had significant reduction in seizure frequency. [29],[30],[31],[32],[33],[34] However, many patients with good initial outcome had recurrence of events on long term follow-up. The long term (1-14 years) follow-up studies variably reported seizure freedom rates from 16-40%. [11],[35],[36],[37],[38],[39] In the recently published largest series (260 patients) of short term (6-12 months) outcome of PNES patients by McKenzie (2010); 38% of patients had been free of spells and additional 23% patients had at least 50% reduction in spell frequency. [32] To the best of our knowledge, there are no studies addressing prognosis of PNES and their factors in adult population from India. Similar to older studies, the short term (6-12 month) outcome was good in our study; which included cessation of seizures in 46.66% and >50% reduction in seizure frequency in 24.44% patients. The most important prognostic factor probably is the acceptance of the diagnosis of PNES by patients and their family members. The other favorable prognostic factors reported are young age at onset, [36],[47] male [32] or female, [37] better education, [47],[55] good social, family, and security support system, [31],[32],[34],[37] employment, and independent lifestyle, [34],[35],[37] low intelligence quotient [32],[58] shorter duration of condition, [39],[47] less frequent episodes, [43] accepting the diagnosis, [31],[34] motionless spells, [39],[47],[55] lack of comorbid epilepsy, [37],[47],[59] continued antiepileptic drugs (AEDs) use, [35] lack of physical or sexual abuse, [30] and lack of psychiatric comorbidities. [30],[32],[47] The possible good prognostic factors in our study were young age at onset ($P = 0.54$), shorter duration of illness ($P = 0.44$), less frequent episodes ($P = 0.66$), and limb attacks ($P = 0.27$); although none was statistically significant. The effect of gender, literacy status, socioeconomic status, coexisting epilepsy and comorbid psychiatric illnesses on the outcome could not be analyzed because of inadequate sample size.

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