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LEVETIRACETAM-ASSOCIATED PSYCHOGENIC NON-EPILEPTIC SEIZURES: A HIDDEN PARADOX

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ABSTRACT

Objectives
To study the clinical profile and outcome in patients with epilepsy who developed psychogenic non-epileptic seizures (PNES) associated with levetiracetam (LEV) use.

Methods
In this prospective observational study, conducted over 1 year, 13 patients with epilepsy and PNES, documented by video electroencephalogram (VEEG) while on LEV, were included. Those with past history of psychiatric illnesses were excluded. VEEG, high-resolution magnetic resonance imaging, neuropsychological and psychiatric evaluation were performed. Patients in Group I (07) were treated with psychotherapy, psychiatric medications and immediate withdrawal of LEV while, those in Group II (06) received psychotherapy, anxiolytics and LEV for initial 2 months after which it was stopped. Follow-up period was six months.

Results
Mean (±SD) age of patients was 25 ± 12.28 years; there were 11 (84.62%) females. All were on antiepileptic agents which included LEV >1000 mg/day, except one. Mean dose of LEV was 1269.23 ± 483.71 mg/day.

Three patient's scores were suggestive of depression or anxiety; one had both depression and anxiety. Eight patients had mood disorders; three had a history of emotional abuse or neglect. PNES subsided in all patients within 1–3 months, only after withdrawl of LEV and did not recur in any after stopping LEV.

Conclusion

LEV can induce PNES in susceptible populations. Awareness of this association is crucial for timely withdrawal of triggering factor and appropriate management. This will reduce inadvertent additional prescription of antiepileptic agents.

Psychogenic non-epileptic seizure (PNES) is an observable abrupt paroxysmal change in behaviour or consciousness that are similar to an epileptic seizure, but not accompanied by changes in the electroencephalogram (EEG) that accompany an epileptic seizure. An epileptic seizure is a clinical diagnosis, based on the entirety of the clinical and para-clinical findings. Generally, positive evidence or strong suspicion for psychogenic factors that may have caused are noted in PNES.[1–3] Presence of an underlying personality disorder is suggested to be a significant predictor of the disease.[4] Emotional dysregulation, dissociations, abuse and cognitive disturbances are more frequently seen in patients with PNES.[5,6]

Use of levetiracetam (LEV) is increasing in the management of epilepsy. Though it has a better safety profile, physicians need to be aware of its consider-able association with behavioural changes, which may manifest as psychosis.[7,8] A paradoxical effect of LEV with exacerbation of true seizures is well documented[9]but very few case reports of emergence of non-epileptic seizures are available.[10,11] There is a high incidence of PNES in patients treated with LEV. In such patients, PNES could either be stopped, or reduced significantly after discontinuation of the drug along with supportive psychiatric treatment.

PNES is a condition where diagnosis is more challenging and delay in diagnosis may result in further addition of antiepileptic agents. Early diagnosis and withdrawal of precipitating drug is crucial in the management as under recognition may result in unwarranted investigations and treatment. In this study, we describe the occurrence of PNES in a cohort of patients with epilepsy while on LEV therapy and subsidence after the drug withdrawal.

METHODS

Patients

This prospective study was undertaken by the Department of Neurology, Nizams Institute of Medical Sciences, Hyderabad, India, a tertiary referral centre. The study group consisted of a series of patients diagnosed to have PNES causatively associated with LEV use, treated by a single neurologist between January 2015 and December 2015.

Diagnosis of PNES was as defined by LaFrance et al.[12] Patients were included if they had a definite past history of epilepsy and PNES documented by video electroencephalogram (VEEG) while receiving LEV either as a monotherapy or as an adjuvant with other antiepileptic drugs. Patients having a strong correlation between the onset of PNES during addition or recent increase in the dose of LEV and those in whom there was subsidence of PNES after discontinuation of LEV were also included. Patients with past history of psychiatric illness, PNES and those in whom detailed neuropsychological functions could not be performed were excluded.

All patients underwent VEEG, high-resolution magnetic resonance imaging (MRI), neuro-psychological and psychiatric evaluation. Details of seizure semiology of both true and PNES, including duration, type, medications, patient & family history, and clinical response to treatment (stoppage of LEV and psychiatric medications) were recorded. Detailed neuropsychological evaluation performed by clinical psychologist included Intelligence Quotient (IQ) assessment and Hamilton depression and anxiety stress scores (DASS).[13,14] Weschler adult intelligence scale was administered for adults.[15] Malin's Intelligence Scale for Indian children, which is a validated Indian

adaptation of Wechsler's Intelligence Scale for children, was used to assess the IQ of children.[16]

Seven patients (patients 1–7, Group I) were treated by a psychiatrist and prescribed psychiatric medications (a combination of escitalopram or sertraline with clonazepam). LEV was gradually withdrawn over the ensuing two weeks.

A different strategy was applied to the next 8 patients (patients 8–13, Group II). These patients received psychiatric consultation for the initial two months along with anxiolytics but LEV was continued. After two months, LEV was gradually withdrawn. All patients were followed up for six months and monitored for relapse of PNES.

Assessments

Video Electroencephalography

All recordings were carried out on a 16-channel VEEG acquisition system (NicVue, Nicolet-Viking, USA) with the scalp electrodes placed according to the International10–20 system. VEEG was recorded for 40 minutes (20 minute awake and 20 minute sleep record), included 3 minutes of hyperventilation and photic stimulation in wakefulness. A partial sleep deprivation protocol was used. All patients with referral diagnosis of PNES underwent induction for precipitation of PNES with the help of a vibrating tunic fork.[17,18]

The distribution of interictal epileptiform discharges (IEDs) was assessed by visual analysis of EEG samples. The background activity was assessed for evidence of any focal slowing defined as the presence of localized slow waves not present in the other homotopic regions. IEDs were categorized as either diphasic/triphasicsharp-wave/spike or a spike-wave complex pattern. Any activation of IEDs in sleep was noted.

The standard method of inducing a PNES was used in which patients were hypnotized using vibrating tuning fork. The EEG correlate was noted. These episodes were also confirmed with the patient family whether they were current habitual seizures. These PNES were classified using the standard classification.[19]

STATISTICAL ANALYSIS

Data was captured on Microsoft Excel 2007 worksheets and analyzed data was expressed as frequency, mean ± Standard Deviation (SD), percentage and range. Assessments and outcomes were explained using descriptive analysis.

RESULTS

We included 13 patients with LEV induced PNES. There were 11 females (86 %) and two males (14%). Mean (±SD) age of patients was 25.75 ± 12.28 years with a range of 12–54 years. Mean duration of true seizures was 10.77 ± 6.47 years, (range 1–22 years). The duration of PNES was short in all these patients with a mean of 7.66 ± 5.28 months (range 2-18 months).

PNES was classified using the Hubsch classification system.[19] Five (39%) patients each belonged to Class 3 and 4; There were one patient (7%) each in Class 1, Class 2 and Class 5 (Table1). In all these patients, PNES were frequent (daily in four patients) and manifested only when they were awake. None of these patients suffered injuries. All were subjected to 1.5 Tesla MRI brain scan and 11 (84.62%) demonstrated the respective abnormalities (Table 1).

All received antiepileptic agents along with LEV. All were prescribed ≥1000mg/day except one patient who was using 500 mg/day of LEV (Table 2). Mean dose of LEV received by our patients was 1269.23 ± 483.71mg/day.

Relationship to Levetiracetam Therapy

In group II, patients in whom LEV was continued for two months after the diagnosis of PNES, all continued to have PNES though psychiatric treatment was given. They had complete remission of PNES only after the withdrawal of LEV. Mean time taken for subsidence of PNES in group II was 1.08 (± 0.50) months, after discontinuation of LEV. In group 1, patients in whom LEV was withdrawn initially, after the diagnosis of PNES, there was resolution of PNES in 1 to 2 months, with mean of 1.57(± 0.5) months. There was no statistically significant difference ($p>0.05$) between the two groups.

Neuropsychological and Psychiatric Evaluation

All patients underwent a baseline psychiatric evaluation and a detailed neuropsychological assessment. IQ was normal in all except four patients (Table 3).

Scores were suggestive of depression or anxiety in three (23.08%) patients and there was evidence of

TABLE 1 Presenting Clinical features and VEEG Report of Study Population

Serial number	Age of patient	Gender	Final diagnosis	Duration of True seizures (in years)	Video EEG findings	Duration of PNES (in months)	Type of PNES	Frequency of PNES
1	14	F	Focal epilepsy due to bilparietooccipital gliosis	10 years	Left PHR IEDs, with PNES recorded	12 months	Class 5	2–3 per day
2	27	F	Focal epilepsy following viral encephalitis	14 years	Diffuse theta slowing in EEG with a documented PNES	18 months	Class 3	1–2 /month
3	35	F	Focal epilepsy secondary to right frontal calcified granuloma	14 years	Normal awake and sleep EEG with spontaneous PNES	3 months	Class 4	2–4 /month
4	18	F	Focal epilepsy secondary to right parietal gliosis	17 year	Normal EEG, PNES recorded	12 months	Class 1	4–6/month
5	20	F	Focal epilepsy secondary to left MTS	10 years	Left temporal IEDs, PNES recorded	6 months	Class 2	1–2 per week
6	25	F	Generalized epilepsy due to tuberous sclerosis	18 yrs	Gen polyspikes, GPFA, PNES recorded	12 months	Class 3	4–6 per month
7	14	F	Symptomatic epilepsy secondary to right parietal granuloma	1 year	Normal EEG, PNES recorded	2 months	Class 4	6–8 per month

Continued

Serial number	Age of patient	Gender	Final diagnosis	Duration of True seizures (in years)	Video EEG findings	Duration of PNES (in months)	Type of PNES	Frequency of PNES
8	34	F	Focal epilepsy secondary to left MTS	8 years	Normal EEG, Documented PNES	3 months	Class 4	4–6 / month
9	18	M	Left frontal epilepsy	6 years	Normal EEG, documented PNES	6 months	Class 3	2–3/day
10	40	F	Focal epilepsy secondary to right MTS	16 years	Normal EEG, PNES recorded	3 months	Class 3	1–2 per day
11	10	F	Focal epilepsy due to right parietooccipitalporencephalic cyst	4 yrs	Bil frontal IEDS, PNES Recorded	1 month	Class 3	Daily
12	54	M	Left frontal epilepsy with normal MRI	22 years	Normal EEG, PNES recorded	12 months	Class 4	4–6 per month
13	16	F	Epilepsy due to right parietal FCD post resection	10 years	Right frontal IEDs, PNES recorded	3 months	Class 4	10–12/day

EEG = electroencephalogram; IEDs = interictal epileptiform discharges; FCD = focal cortical dysplasia; MRI = magnetic resonance imaging; PNES = psychogenic non-epileptic seizures; VEEG = video electroencephalogram.

TABLE 2 Antiepileptic Drugs Prescribed

Pt. No	Drug	Dose (mg/day)	Time taken for resolution of PNES after withdrawal of LEV
1	Valproic acid Topiramate Levetiracetam	900 125 500	1 month
2	Oxcarbazepine Clobazam Levetiracetam	900 10 2000	2 months
3	Clobazam Levetiracetam	10 1000	2 months
4	Valproic acid Clobazam Levetiracetam	400 10 1000	2 months
5	Oxcarbazepine Clobazam Levetiracetam	900 10 1000	2 months
6	Valproic acid Clobazam Levetiracetam	1000 20 1000	1 months
7	Levetiracetam	1000	1 month
8	Oxcarbazepine Levetiracetam	600 2000	2 months
9	Valproic acid Levetiracetam	1000 1000	1 month
10	Levetiracetam	1000	1 month
11	Carbamazepine Levetiracetam	600 1500	15 days
12	Carbamazepine Clobazam Levetiracetam	800 20 2000	1 month
13	Carbamazepine Clobazam Levetiracetam	800 10 1500	1 month

LEV = levetiracetam; PNES = psychogenic non-epileptic seizures

both depression and anxiety in one patient. Psychiatric assessment revealed mood disorder in eight (61.54%); history of emotional abuse or neglect was noted in three (23.08%) patients. Psychiatric evaluations were normal in five (38.46%) patients (Table 3).

All 13 patients were followed up for 6 months after subsidence of PNES. We observed that after withdrawal of LEV, PNES subsided in all patients; none of them had reemergence of PNES after subsidence.

DISCUSSION

PNES is an under reported condition due to difficulty in differentiating from epileptic seizures and a high index of clinical suspicion supported by VEEG is essential for the confirmation of diagnosis.[20] Reported cases represent only the tip of the iceberg. Its incidence is estimated to be 0.91/100,000 per annum.[20] The proportion of patients suffering from epilepsy and PNES ranges from 5–20% in outpatient setting and 10–40% in hospitalized.[20–24] Treatment outcome depends not only on the age, early diagnosis, severity of associated psychological co-morbidites, but also on the management and longterm follow-up.[25,26] Chabolla et al[27] described the characteristic features of PNES, diagnostic features and identified the favourable factors influencing therapeutic outcome. They concluded

TABLE 3 Intelligence Quotient, Neuropsychological and Psychiatric Evaluation of Study Population

Pt. No	Intelligence Quotient	Psychiatric Evaluation (Evaluation by a Psychiatrist)	Neuropsychological Assessment (Assessment by a Psychologist)
1	73	Emotional abuse with mood disorder	Anxiety ++
2	90	Mood disorder (anxiety+)	Anxiety ++
3	102	Normal	No evidence of Depression/Anxiety
4	60	Emotional neglect, mood disorder	Depression
5	90	Mood disorder (Depression & Anxiety)	Anxiety ++
6	75	Normal	No evidence of Depression/Anxiety
7	90	Normal	No evidence of Depression/Anxiety
8	100	Emotional abuse Mood disorder (Depression, Anxiety)	Evidence of Depression/Anxiety
9	75	Normal	No evidence of Depression/Anxiety
10	90	Mood disorder	Evidence of Depression +
11	100	Mood disorder	Evidence of Anxiety
12	90	Normal	No evidence of Depression/Anxiety
13	85	Mood disorder	Evidence of Depression +

that higher IQ, VEEG without any abnormal findings contribute towards favourable outcome. Outcome can be expected to be good in female patients leading independent lifestyle, and in those who have not received any prior psychotherapy.

In our study, females (86%) outnumbered males. Mean age of our patients was 25.75 years with a range of 12–54 years. Our patients had a long duration of true seizures with a mean of 10.77years (range 1–22 years) suggesting that PNES can occur at any stage of epilepsy. Interestingly, an incidental observation was that the duration of PNES was short in all our patients with a mean of 7.66 months (range 2–18 months).

All our patients were receiving ≥1000 mg/day LEV, except one on 500 mg/day. Mean dose of LEV was 1269.23 mg/day in our patients. This observation suggests that PNES is often associated with higher doses ≥1000 mg/day of LEV. We followed Hubsch clas-sification system to classify PNES. We had all types of patients with more number of patients with Class 3 and Class 4 (n=5, 39 %). In all our patients PNES manifested only when they were awake and none of these patients suffered injuries. We suspected PNES in 69% patients from history, and confirmed the same on VEEG, while in the others remaining it was diagnosed only during recording. This supports the diagnostic role of VEEG in PNES. It predicts the occurrence of PNES more precisely in females (86% vs 61%).[28] Though studies on PNES show female predominance O'Sullivan et al observed male affliction in their study.[21] Though mean age of occurrence of PNES is 3rd decade, there have been reports wherein the higher age group between 34 and 39 years is affected.[29–31]

We grouped our patients into two, to compare the therapeutic effect after withdrawal of the drug and confirm whether any other intervention can cause a subsidence of PNES without LEV tapering. Our patients in group II had complete remission of PNES only after the withdrawal of LEV, and continuation of psychiatric medications. This observation indicates the positive role of LEV in PNES in our patients.

Neuropsychological and psychiatric evaluation revealed association of depression and/or anxiety in these patients and associated mood disorder. History of emotional abuse or neglect was also seen in these patients. These revelations indicate the importance of these tests in identifying the subset of patients who are more liable to manifest PNES.

Underlying pathophysiology of PNES still remains unclear. Many psychosocial factors and psychological mechanisms have been found to be responsible for PNES,[23,32] which indicate the significance of psychological assessment.[33] There is a strong association of multiple psychiatric conditions with PNES,[20] as seen in our patients.

There is an established positive relationship between shorter duration of consumption, number of antiepileptic drugs and the incidence of PNES[34]; all of our patients were receiving multiple antiepileptic drugs, along with LEV. In the recent past there is increasing evidence on the behavioural side effects of LEV that are dose dependent.[7,8] The onset of PNES was associated with the addition/increase in the dose of LEV as an antiepileptic agent in all our patients. This was the initial reason to suspect LEV as the offender. Subsidence of seizures after withdrawing the drug indicates the role of LEV in inducing PNES. In addition, none of these patients had recurrences and after the withdrawal of LEV, an observation that supports the positive association of PNES in these patients with LEV use.

The paradoxical ability of antiepileptic drugs to increase seizure activity has been recognized for decades. This may occur as a result of two separate mechanisms: (i) involving a nonspecific manifestation of drug intoxication; seizure worsening in this context is usually reversible by dosage reduction or elimination of unnecessary polypharmacy, (ii) a distinct adverse primary action of the drug in specific seizure types or in syndromic forms.[34,35] These have been detailed in Table 4.

Possible mechanisms underlying LEV induced behavioural disorders are idiosyncratic, dose-unrelated drug effects, dose related toxicity due to its unique mechanism of action and alternative psychoses (or behavioural disturbances) associated with the phenomenon of forced normalization.[10] Galimberti et al.[36] suggested a multifactorial role in the development of PNES LEV acts as a trigger point in those with predisposing psychiatric disorders in precipitating PNES. In our series, there were five patients in whom

TABLE 4 Worsening of Seizures due to Antiepileptic Drugs

a) As a manifestation of AED overdose or intoxication	
Phenytoin	Increase GTCS especially with ophisthotonic posturing Increase in focal myoclonic seizures Can precipitate Choreoathetosis
Carbamazepine	Increases focal atonic seizures, GTCS; Can precipitate myoclonus , status epilepticus
Tiagabine	Increases myoclonic seizures, NCSE
Valproate	Increases negative myoclonus especially when hepatotoxicity is present
Phenobarbitone	NCSE
b) Due to drug specific effect	
Phenobarbitone	In BRE increases negative myoclonus and spike load especially in atypical variants Increases tonic seizures in LGS Increases absence seizures
Benzodiazepine	Increases tonic seizures, induces status epilepticus Increase tonic seizures in LGS Absence status in generalized epilepsies
Carbamazepine	Increases typical and atypical absences, atonic, tonic, myoclonic seizures in generalized epilepsies Increases seizure frequency and myoclonic astatic status in Angelman syndrome Increases CSWS in LKS, BRE Increases epileptic negative myoclonus in atypical BRE Increases epileptic spasms. Can precipitate non-epileptic multifocal myoclonus
Gabapentin	Increases absences and myoclonus
Phenytoin	Increases typical and atypical absences atonic, myoclonic seizures in generalized epilepsies Increases CSWS in LKS
Valproate	Little or no evidence of causing deterioration of specific seizure types
Vigabatrin	Increases myoclonic seizures, may increase absences, tonic seizures and status epilepticus (partial or generalized)
Lamotrigine	Increases myoclonic seizures
Levitirecetam	Can be associated with psychogenic non-epileptic events

AED = antiepileptic drugs; BRE = benign rolandic epilepsy; CSWS = continuous spike and wave of slow wave sleep; LKS = Landau Klefner syndrome; NCSE = Non-convulsive status epilepticus; GTCS = generalized tonic clonic seizure.

psychiatric and neuropsychological evaluations were completely normal. Thus, the mechanism still remains elusive and requires more investigation.

Of the approved therapies, psychotherapy has proved to be the most effective (92.2%), while education (75%) and psychopharmacotherpay (70.3%) were next in the order.[17] LaFrance et al[29] in their multi-centric analysis observed reduction in seizure occurrence along with improvement in psychological functions, supporting the role of psychotherapy in the management. Brown et al[37] too advised psychotherapy in the management of PNES. Hence, we followed the standard treatment protocol of psychotherapy in both groups along with psychiatric medications and observed good therapeutic outcome.

Our study supports the positive association between LEV use and PNES; identifying the association, timely withdrawal of the medication, administering psychiatric treatment will result in better clinical outcome.

To the best of our knowledge this is the first case series of LEV associated PNES; there have been isolated single case reports.[10,11] A good constellation of cases with strict inclusion criteria, would provide a stronger evidence for the positive association between the drug and PNES.

CONCLUSION

LEV can induce PNES in susceptible population. Multiple antiepileptic drugs with high dosage are the risk factors. Physician should be aware of this malady; timely withdrawal of the drug followed by appropriate psychotherapy is essential for recovery. Before escalating to higher dose of antiepileptic drugs, drug-induced PNES should be considered in the differential diagnosis to avoid unnecessary pill burden.

CONFLICT OF INTEREST

None.

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