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Brief Communication

Use of noninvasive induction techniques in the diagnosis of PNES

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ABSTRACT

The diagnosis of psychogenic nonepileptic seizures (PNES) remains challenging. In the correct clinical setting with prolonged electroencephalography (EEG) monitoring, the specificity of provocative techniques to distinguish induced epileptic event from a nonepileptic event approaches 90%. We report our epilepsy monitoring unit (EMU) experience with the use of noninvasive verbal suggestion (VS) during hyperventilation (HV), photic stimulation (PS) as induction technique in making the diagnosis of PNES. In total, 189/423 patients were diagnosed with PNES during the EMU evaluation. Of the 189, 20 had mixed disorder and 169 patients had only PNES, 80 patients (47.3%) had a PNES with induction, and the remaining 89 of 169 patients (52.7%) had a spontaneous PNES episode that did not require induction. Verbal suggestion during HV and PS confirmed the diagnosis of PNES in 47% of the patients who otherwise did not have spontaneous events. Within the group who was diagnosed with PNES following induction, antiepileptic drugs (AEDs) were stopped in 53% of the patients. We believe that this is a large proportion of patients that would possibly remain undiagnosed if no induction were performed.

1. Background

Patients are frequently referred to the epilepsy monitoring unit (EMU) for the evaluation and classification of seizures or seizure-like events. The EMU is considered the gold standard for diagnosing epileptic seizures and psychogenic nonepileptic seizures (PNES).

Psychogenic nonepileptic seizures are a physical manifestation of psychological disturbances that resemble an epileptic seizure without any abnormal neuronal electrical discharges. Approximately 10–20% of the new presentations seen in epilepsy clinic that includes 20–30% of patients with intractable epilepsy and about 2–33 per 100,000 in general population are diagnosed with PNES [1]. Up to 40% of the patients are maintained on antiepileptic drugs (AEDs) after the diagnosis of PNES has been established because of placebo response [2]. An individual with PNES can incur an estimated lifetime cost of up to $100,000 in diagnostic tests, procedures, and medications [3,4]. In the United States, $900 million is spent annually in diagnosis, laboratory studies, medications, and hospital management of patients with PNES [4]. Therefore, accurate diagnosis in patients with possible PNES is of utmost importance. For this reason, patients are monitored in EMU on prolonged electroencephalography (EEG), and if an event is not captured by the second or third day, provocative techniques are used to induce an event. Hypnosis is one of the techniques employed by Schwarz et al. in 1955 [5] to distinguish epilepsy and nonepileptic seizures. Since then, several published studies in the literature have reported the effectiveness of suggestive seizure induction (SSI) techniques such as hyperventilation (HV) and photic stimulation (PS) and placebo induction techniques such as compression of temple region (CTR), verbal suggestion (VS), tuning fork application (TFA), moist swab application (MSA), torch light stimulation (TLS), saline injections (SI), and tilt testing [6–10]. Suggestive seizure induction, including PS and HV, can provoke epileptic seizures in addition to PNES. Therefore, in the correct clinical setting with simultaneous prolonged EEG monitoring, the specificity of provocative techniques to distinguish an epileptic event from a nonepileptic event is over 90% [11]. However, only 39–73% of epilepsy centers employ provocative techniques to assist in the diagnosis of PNES because of lack of established protocol, universal consensus on the ethical framework, and only a limited number of studies on diagnostic yield [12,13]. There are several potential risks and benefits of using provocative techniques in the diagnosis of PNES. Ethical concerns must be considered as induction practitioners risk fostering deception as well as violation of physician–patient trust, especially when explicitly deceptive methods are used [12,13]. The risks must be weighed against

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the increased likelihood of an accurate and timely diagnosis as most of these patients with PNES, typically experience a diagnostic delay of 7–10 years where in that time, they are treated with Anti Epileptic Drugs [14].

Of all the placebo induction techniques, the utility of simple VS without the use of placebo injections involves the least ethical and technical limitations [10,11]. To the authors' knowledge, there are only limited reports worldwide where only VS without induction injections was used for the diagnosis of PNES [10,15]. Therefore, the purpose of this study was to report our EMU experience with the use of VS during PS and HV in making the diagnosis of PNES.

2. Methodology

2.1. EMU induction techniques and practice at our institution

At our institution, once patients are admitted to the EMU, they are monitored on prolonged EEG for five days to capture an event and to determine whether or not the event is epileptic or a PNES. The patients who had spontaneous PNES within the first few days of admission, similar to their typical event, did not undergo placebo induction and were continued to be monitored for a possible mixed disorder. However, if no typical event was captured, then on the 3rd day of monitoring, induction techniques were used. Sleep deprivation was performed the night before the induction to increase the likelihood of capturing epileptiform activity. We followed the procedure described by Benbadis et al. [10]. Firstly, patients were prepared and asked to reiterate their seizure description along with the stressors that trigger their events. The second step was verbal reinforcement that HV and PS are expected to cause a seizure episode, and patients should not hold back if that happens. During the second step, if abnormal movements were noted, the patients were encouraged further to lead them into a full-blown episode. At the end of EMU, we determined whether or not the diagnosis of PNES was made after induction or independent of induction.

2.2. Data collection

After obtaining the Institutional Review Board (IRB) approval, we proceeded with this retrospective study. We reviewed the chart of the patients admitted to our EMU between 3/4/2013 and 2/23/2018. The data included demographic details such as age, sex, final diagnosis with induction or independent of induction, number of AEDs before the admission to EMU, and AEDs on discharge with their indication. The patients with a known diagnosis of epilepsy and those who had electrographic seizures regardless of the use of induction for their events were excluded from the study. We compiled the data into Microsoft excel sheet. The calculations were done using simple excel formulas.

3. Results

A total of 423 patients were admitted to our institution from 3/4/2013 to 2/23/2018. Based on the type of events, patients were grouped into the following: 1. Electrographic seizures, 2. PNES, and 3. Undiagnosed as shown in Table 1. Later, during monitoring, 20 from group 2 had another type of event with electrographic seizures and were excluded after being diagnosed with a mixed disorder. Table 2 shows group 2 patients (n = 169) with confirmed PNES ranging between 16 and 93 (mean age: 44 years). In this group, there was female (79.2%) predominance over males. Eighty patients (47.3%) were diagnosed with PNES after induction on the third day of EMU, and the remaining 89 of 169 patients (52.6%) had a spontaneous PNES that did not require induction. Such patients who needed induction (n = 80) for PNES diagnosis, 58/80 (72%) were on AEDs prior to induction. Following induction and PNES diagnosis, the number of patients who were stopped on AEDs were 31/58 (53.4%).

Table 1
Total number of EMU admission during 03/2013–02/2018 (n = 423).

1.	
● Number of patients who had electrographic seizures or interictal epileptiform discharges (excluded)	66
● Mixed disorder	20
2.	
● Total number of patients with confirmed PNES diagnosis with spontaneous or with induction	169
3.	
● Patients who remained undiagnosed	168

4. Discussion

Long-term EEG is referred to as the gold standard in terms of diagnostic accuracy. Placebo induction in the EMU under video-EEG monitoring has a high specificity (>90%) for the diagnosis of PNES [11]. There is an increasing role for ambulatory video-EEG monitoring, and induction techniques are one of the advantages of inpatient video-EEG monitoring. The use of SSI and placebo induction techniques has been controversial for decades because of ethical concerns [11,12]. More recently, International League Against Epilepsy (ILAE) proposed a multidisciplinary approach towards PNES management and included seizure induction as a standard diagnostic technique for PNES diagnosis with preference to least invasive methods [15]. As discussed in Section 1, there are numerous provocative techniques routinely utilized to induce seizures and PNES in the EMU. At our institution, VS during HV and PS is the routinely employed method. Hyperventilation and PS are known to induce epileptic seizures. However, an event triggered by VS during HV and PS favors more for PNES than epileptic seizures. There are a handful of articles in the literature that suggested that the use of short-term EEG and VS was useful in effectively confirming the diagnosis of PNES and ruling out epilepsy [16], and provocative induction without placebo was noninferior when compared with placebo induction techniques [17]. To the authors' knowledge, there is paucity of reports on induction using VS only in EMU setting [18]. In concordance to previous reports [9,10,19], our findings suggest that in patients who experience PNES occasionally, prolonged EEG supports the diagnosis only when spontaneous events occur during the monitoring as 53% (89/169) whereas, without induction technique, the diagnosis would have been missed in 47% (80/169) of the patients with suspected PNES. There are no prospective studies to compare the yield of VS + PS + HV versus PS + HV alone, however, based on the available literature, our data indicate an increased rate (47%) of PNES diagnosis compared with 30% reported in prior studies that used HV only [20,21].

As a consequence of inconclusive EMU stay or missed diagnosis, often, patients are started on AEDs or asked to continue the same AEDs as prior. Therefore, inappropriate treatment of PNES with AEDs puts patients at risk for the adverse events associated with these medications and increases costs to the patient and medical system. In this cohort, approximately 75% (127/169) of the patients were on one or more AEDs for months. Following the diagnosis of PNES, regardless of induction, this number was reduced to 43% (74/169). Within the group who was diagnosed with PNES following induction, AEDs were stopped in 53% of the patients. In many patients, AEDs such as valproic acid, lamotrigine, gabapentin, and topiramate were continued because of

Table 2
Patients with confirmed PNES diagnosis (n = 169).

● Females	134
● Males	35
● Spontaneous	89
● With induction	80
Number of patients with PNES on one or more AEDs prior to EMU	127
Number of patients with PNES on AEDs after EMU	74

other reasons such as migraine headaches, mood disorders, and neuropathy. Therefore, it is evident from our data that without induction techniques, there would likely be an increased risk of further delays in diagnosis and prolonged erroneous treatment with AEDs. There is no definite treatment approach for PNES and is usually followed by psychiatry for Cognitive Behavioral Therapy (CBT) and other psychological interventions. There is a high percentage of patients who do not follow up with recommended therapy and continue to have PNES after the diagnosis. A study reported that long-term outcomes in patients with the mixed disorder (PNES and epilepsy) have better outcomes than patients with only PNES [22]. This was beyond the scope of this study and warrants more longitudinal studies in collaboration with psychiatry to understand the long-term outcome in these patients.

5. Limitations

This communication is a retrospective study, and we do not have a control arm to compare the yield of VS + PS + HV versus PS + HV alone, a future prospective study is needed. Perhaps it may be valuable to dissect out how many patients of the diagnosed PNES had any recent or remote psychiatric history or trauma. Additionally, there is still a large proportion of people who remained undiagnosed despite one round of induction. Therefore, it will be interesting to see how many attempts of VS are needed to provoke an event.

6. Conclusion

The use of VS during HV and PS confirmed the diagnosis of PNES in 47% of the patients who otherwise did not have spontaneous events. Within the group who was diagnosed with PNES following induction, AEDs were stopped in 53% of the patients. We believe that this is a large proportion of patients that would possibly remain undiagnosed if no induction was performed. Compared with the existing literature, our data suggest that VS + HV + PS may be more sensitive than HV alone in the diagnosis of PNES, however, further study is required to compare the two.

Declaration of Competing Interest

None of the authors have any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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