Suggestive seizure induction for inpatients with suspected psychogenic nonepileptic seizures

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Abstract

Objective: To determine the utility of suggestive seizure induction for inpatient work-up of suspected psychogenic nonepileptic seizures (PNES).

Methods: Prospective study of epilepsy center inpatient admissions with suspected PNES. Patients were randomized to undergo suggestive induction first (group A) and then, if necessary, long-term video–electroencephalography (EEG) monitoring, or vice versa (group B). Diagnostic pathways were compared. Potential clinical predictors for diagnostic success were evaluated.

Results: Length of in-hospital stay did not significantly differ between groups. Suspicion of PNES was confirmed in 43 of 77 (56%) patients, evenly distributed between group A (22 of 39) and group B (21 of 38). In nine patients, recorded habitual seizures were epileptic and in 25 cases, no diagnostic event could be recorded. Diagnosis of PNES was ascertained primarily by recording a typical seizure through suggestive induction in 24 patients and through long-term monitoring in 19 patients. In group A (induction first), monitoring was not deemed necessary in 21% of cases. In group B (monitoring first), 13% would have remained inconclusive without suggestive induction. Patients who reported triggers to their habitual seizures were not more likely to have spontaneous or provoked PNES during monitoring or suggestive induction, respectively. Patients with subjective seizure prodromes (auras) were significantly more likely to have a PNES during suggestive induction than those without (odds ratio [OR] 3.4, 95% confidence interval [CI] 1.1-10.4). There was no significant difference in seizure frequency between patients with spontaneous PNES during long-term monitoring and those with non-diagnostic monitoring sessions.

Significance: Our results support the notion that suggestive seizure induction can reduce the number of inconclusive inpatient workups, and can obviate resource-intensive long-term monitoring in one fifth of cases. Patients who are aware of prodromes might have a higher chance of having seizures induced through suggestion.
INTRODUCTION

The diagnosis of psychogenic nonepileptic seizures (PNES), also known as dissociative or functional seizures, remains a central challenge in epileptology. About one third of patients admitted to epilepsy monitoring units (EMUs) with seizures of unknown etiology will be diagnosed with PNES,1,2 often after many years of unnecessary, costly, and potentially harmful treatments due to diagnostic uncertainty or misdiagnosis.3 Ascertaining a PNES diagnosis is based primarily on specific seizure characteristics from history and semiology, complemented by the exclusion of epileptiform discharges through ictal video-EEG when appropriate and possible.4 Because eyewitness accounts and self-reports regarding seizure experience and appearance can be insufficient, ambiguous, or misleading,5 recording a habitual seizure on video and EEG for offline analysis and exclusion of epileptic etiology is considered the diagnostic gold standard.4 This is usually achieved through long-term video-EEG monitoring over several days in specialized epilepsy units,6 or through suggestive seizure induction during video-EEG recording.7,8 Suggestive induction has been used in epileptology for many decades, with newer protocols minimizing deception and favoring noninvasive suggestion techniques.9,10 However, there is currently no single standard of care regarding seizure induction, and practices vary widely internationally.

Both monitoring and induction have good diagnostic yields regarding the recording of a habitual event, but neither is perfect. Inconclusive diagnostic workup (19%-40% of EMU admissions in two large cohorts11,12) remains a problem, so a staged diagnostic approach of long-term monitoring first and then suggestive induction if needed is usually recommended.13,14 In two retrospective studies, 26%-32% of patients with PNES had no spontaneous seizures during monitoring (2.4 and 4.6 days of monitoring on average) but had an induced diagnostic event during induction.14,15 In a prospective study on 78 patients with suspected PNES admitted to an EMU, only 8 (10%) had a spontaneous event during the first 48 hours of monitoring, whereas 42 of 51 (82%) went on to have a habitual event during induction.16 These observations suggest that despite outstanding questions about the optimal ethical and practical implementation, the unique diagnostic utility of suggestive induction—in the face of widespread diagnostic delays and misdiagnoses—supports its continued use and efforts for improvement.8

Suggestive induction can be performed during short-term ambulatory EEG when PNES are part of the differential diagnosis, and elicits habitual diagnostic events in 33%-66% of preselected cases.17–19 This approach obviates the need for inpatient monitoring for about half of all patients referred for suspected PNES.18,20 However, outpatient services cannot always accommodate additional testing during ambulatory EEG. It is unknown whether this resource-saving acceleration of diagnosis can be translated to the inpatient setting. Furthermore, it is unclear whether clinical features can be used to identify patients who are more likely to experience PNES during suggestive induction.

Using a pragmatic prospective study design that randomized the order of monitoring and induction for PNES workup, we explored the following open questions regarding the utility of suggestive induction for inpatient workup of suspected PNES:

- Can the length of in-hospital stay be reduced by performing suggestive induction at the start of inpatient diagnostic workup?
- Can suggestive induction reduce the rate of inconclusive workup?
- Does the report of seizure triggers or prodromal symptoms (aura) predict the success of suggestive induction?
- Is a lower seizure frequency a negative predictor for having a spontaneous seizure during long-term monitoring?

METHODS

A prospective clinical study was conducted at the Ruhr-Epileptology, a tertiary epilepsy center nested within the Neurology Department of the University Hospital Knappschaftskrankenhaus in Bochum, Germany. Patients
who were admitted for seizure diagnostics in whom PNES were suspected based on initial history by the consultant epileptologists were offered participation in the study. Criteria for suspicion of PNES were not formalized, but included typical semiological elements in self-report or witness accounts (eg, eye closure or ictal crying) and suggestive history (eg, seizures occur only during interpersonal confrontations). Patients with established epilepsy were also included if a new seizure type was suspected to be nonepileptic. Exclusion criteria were the following: previous PNES diagnosis regarding the seizure type leading to the current admission, either clinically established (seizure witnessed by medical expert) or documented (through ictal video-EEG recording); less than two events in the last 6 months; and age younger than 16 years at time of admission. Recruitment started on May 6, 2015 and ended on July 18, 2018. The study protocol was approved by the Medical Faculty ethics committee of the Ruhr University Bochum (Nr. 2015-5251). All patients gave written informed consent to participate.

Upon recruitment, patients were randomized (via block randomization, five patients per block) to either group A or group B. Patients in group A first underwent suggestive induction; those in group B first underwent long-term monitoring. Whether each patient then went on to also undergo the other procedure was determined on clinical grounds by the clinical team, as they would normally decide, without consulting with the study coordinator.

Suggestive induction was performed in a dedicated examination room as described previously.9,14,21 Patients were informed beforehand in writing and in person about the procedure, and signed a consent form. It was explained that a range of conditions such as epilepsy, PNES, or syncope can cause episodes of neurological dysfunction or blackouts, and that recording a typical event on video and EEG can help determine the correct diagnosis. Three provocation techniques were introduced with brief explanation about their potential to trigger various kinds of seizures. Patients were informed that (a) hyperventilation can trigger epileptic seizures in some patients through a change in arterial blood gases, and that it can also trigger PNES in some patients, although the mechanism for that is not clear; (b) photic stimulation can trigger epileptic seizures in some patients through synchronous activation of neurons in the brain, and it can also trigger PNES through unknown mechanisms; and (c) in some patients, intravenous injection of an electrolyte solution can trigger their typical attacks through endogenous mechanisms. No claims regarding pharmacodynamic activity or epilepsy were made.

After a baseline recording of several minutes, patients were first asked to hyperventilate for 3 minutes. If no seizure occurred during or immediately after hyperventilation, photic stimulation was performed with increasing and then decreasing frequencies (1-30 Hz) for a total of 2 minutes. If those two procedures did not trigger a seizure, patients were administered a series of three to six doses of saline (1-8 mL) over a peripheral line. Seizures that occurred during suggestive induction were compared to the previously obtained seizure history, and patients (or their relatives) were asked to rate how much the provoked seizure resembled their usual events on a 1-10 scale, with ratings of 7 or higher necessary to consider the test diagnostic. The ictal EEG and electrocardiography (ECG) were reviewed to exclude ictal abnormalities suggesting epilepsy or arrhythmia.

Long-term video-EEG monitoring was performed according to German epileptology standards for at least 2 days, using 23 electrodes according to the international 10-20 system, including single-lead ECG, plus additional anterior temporal electrodes. It was performed in dedicated monitoring rooms equipped with cameras, microphones, and EEG stations, or using a mobile video-EEG system (Xltek, natus). Monitoring duration was counted in days based on start and end dates. Patient demographic and clinical data at admission was recorded at the time of recruitment through a custom questionnaire. Data regarding the diagnostic process was retrieved from electronic medical records. Chi-square tests, t test, and Mann-Whitney U test were used for between-group comparisons; level of significance was set at P < .05.

3 | RESULTS

3.1 | Recruitment and study population

Between May 6, 2015 and July 18, 2018, a total of 78 admitted patients who met inclusion criteria consented to inclusion in the study. Admissions were a mix of elective patients and acute seizure admissions through the emergency department. One patient was excluded shortly after randomization because German language proficiency proved insufficient for reliable history taking and verbal suggestion during suggestive induction. Two patients were recruited twice to the study (9 and 29 months apart, respectively) for different semiologies (this was not mentioned by the patients at the time and only noticed at a later date by the study coordinator; since the target seizure semiology was new at each admission, those recruitments did not violate study protocol). The two patients recruited twice were randomized to a different group each time (by chance). Finally, one patient was randomized to the wrong group due to a technical error. Overall, 77 study cases were considered for analysis, 39 in group A and 38 in group B.

The age range at admission across all participants was 16-77 years, with the median age at admission in group A and B 33 and 30.5 years, respectively (difference not significant). Groups A and B had 74% and 76% female patients, respectively (difference not significant).
3.2 | Diagnostic workup efficiency

Figure 1 provides a summary of the diagnostic workup in both groups. The overall length of in-hospital stay was not statistically different between groups (median stay of 5 and 6 days for group A and B, respectively; U = 580, P = .099).

In group A (participants underwent suggestive induction first and then long-term monitoring, if necessary) 19 of 39 (49%) of inductions were diagnostic. In eight of those cases, monitoring was then deemed unnecessary and was thus spared. In the remaining 11 cases, monitoring was still performed afterward because of additional seizure types and/or to evaluate interictal EEG at greater length. In the 20 patients from group A whose suggestive induction was not diagnostic, 17 underwent monitoring and 3 declined the procedure. In 3 of the 17, a PNES was then recorded; in another 3 patients, an epileptic seizure was recorded, and in 11 cases the procedure was nondiagnostic.

In group B, one patient aborted monitoring during setup and later had a PNES during suggestive induction. In the 37 patients who underwent monitoring, 6 had an epileptic seizure, 16 had a spontaneous PNES, and in 15 no event was recorded. Those 15 patients went on to undergo suggestive induction, in which PNES were recorded in 4. An additional 6 patients who had spontaneous PNES during monitoring underwent suggestive induction outside the study protocol for various reasons; 3 of those had provoked PNES. Two patients with epileptic seizures during monitoring underwent suggestive induction outside the study protocol with negative results.

In summary, in patients who underwent suggestive induction as a first step in their diagnostic workup (group A), long-term monitoring could be avoided entirely in 21% of patients (8/39). Results from group B showed that 13% of admissions with suspected PNES (5/38) would have remained inconclusive if suggestive induction had not been employed at all (illness duration ranged from 6 months to 24 years, median: 3 years). The rate of inconclusive workup was similar in both groups: 36% in group A (31% when the three patients who self-discharged prematurely are disregarded) and 29% in group B.

3.3 | Analysis of suggestive induction and long-term monitoring

Over the course of this study, suggestive seizure induction was performed a total of 63 times. Disregarding five patients in whom an epileptic seizure was recorded during long-term monitoring, this leaves 58 patients with suspected or confirmed PNES who underwent induction procedures, 27 of which were successful. Questionnaire data regarding seizure triggers and prodromal symptoms were incomplete for four patients. Patients with positive suggestive induction reported prodromal symptoms ("aura") before their habitual events at
a rate of 18 of 27 (67%); those with negative induction had a significantly lower rate of 10 of 27 (37%; missing data in four patients; $\chi^2(1) = 4.747, P = .029$). This translates to an odds ratio of 3.4 (95% CI 1.1-10.4) for experiencing a provoked seizure during suggestive induction for patients who report seizure prodromes. Common prodromal symptoms included dizziness (n = 3), headache (n = 2), minor motor phenomena (trembling, twitching, or muscle tension; n = 4), sensory disturbances (tingling, hotness, local discomfort; n = 3), and nonspecific feelings of unwellness (n = 3). Patients with positive suggestive induction reported habitual seizure triggers at a rate of 10 of 27 (37%); those with negative induction at a rate of 15 of 28 (54%; missing data in three patients; $\chi^2(1) = 1.516, P = .218$). Across all positive suggestive inductions, 15 of 27 (56%) of PNES were provoked by noninvasive procedures (one at the start of the procedure, nine during hyperventilation, and five during photic stimulation). In the remaining 12 cases (44%) a PNES occurred only after intravenous injection. Thus, across all 63 suggestive inductions during this study, saline injection was used on 48 occasions, inducing a PNES in 12 cases for a success rate of 25%.

No epileptic seizures or syncope were recorded during suggestive induction. In one case a nonhabitual PNES was recorded in a patient whose typical seizures had a semiology that was highly suggestive of PNES; this induction was considered negative and the cases “inconclusive” in the terms of this study, although he did receive a clinical PNES diagnosis. In another case, only generalized restlessness and arousal were induced and reported as typical prodromes, but not the entire semiology (suggestive induction was thus considered negative); the full semiology was later recorded through long-term monitoring and was found to be epileptic.

The median length of recording across all monitoring sessions without spontaneous PNES (n = 32, excluding those with epileptic seizures) was 3 days (interquartile range: 3-4.25 days). In cases when spontaneous PNES were recorded, they occurred within 2 days in 19 of 20 cases (95%), and on the third day in one case (data on seizure timing missing in three cases).

Patients with negative long-term monitoring at any point (n = 31, excluding those with epilepsy as well as excluding two patients with missing data) had a median seizure frequency of 2 per months (interquartile range: 1-12 per month), and those with spontaneous PNES during monitoring (n = 23) had a median seizure frequency of 4.7 per month (interquartile range: 2-12/month); the difference was not statistically significant ($U = 416.5, P = .293$).

4 | DISCUSSION

Suggestive seizure induction is used in many epilepsy centers to ascertain a suspected diagnosis of PNES, but its optimal use is debated. By randomizing the order of long-term monitoring and suggestive seizure induction in a prospectively recruited sample of patients with suspected PNES, we were able to address several open questions regarding its clinical utility.

The order of the induction and monitoring did not affect the overall rate of conclusive outcome, although this outcome measure is highly dependent on the pre-test probability of actually having PNES, epileptic seizures, or another paroxysmal disorder. The small difference in median length of in-hospital stay for patients who underwent suggestive seizure induction first vs second (5 vs 6 days) was not statistically significant. Previous studies had indicated that performing suggestive induction during the initial outpatient consultation can obviate the need for inpatient monitoring in 47%-66% of patients with suspected PNES. A large analysis of short-term EEG at UK neurophysiology centers (337 PNES across 51 departments) showed that the likelihood of inducing a PNES through suggestion is higher when additional professional personnel is present, and when suggestive techniques are employed repeatedly. Due to variations in local healthcare logistics and remuneration algorithms, integrating such comprehensive suggestive induction procedures (including explanation, consent taking, technical preparation, post-ictal care, debriefing, and so on) will not be feasible in many places.

Our results show that the lessons from outpatient diagnostics can be transferred to inpatient care. In one fifth of cases (21%), long-term monitoring was obviated following successful induction. The lower proportion compared to the above-mentioned outpatient studies might be due to a higher complexity of inpatient cases (eg, multiple seizure types) or a tendency to stick to previously scheduled workup, although the data offer no conclusive explanation. Long-term monitoring can be considered generally safe for patients with PNES, even though they are at an increased risk of ictal falls. Clinicians should consider starting inpatient workup with suggestive induction when patients are reluctant to undergo long-term monitoring, are unlikely to be sufficiently compliant, or have a single habitual seizure type and no ictal epileptiform EEG abnormalities. The primary goal of such procedural reordering should not be to save time or resources, although that might be a convenient side-effect.

Inpatient workup of patients with seizures of unknown etiology can remain inconclusive despite long-term monitoring in a considerable proportion of cases. Although suggestive induction is assumed to be useful in such situations, its utility has rarely been quantified prospectively. In a retrospective study at our center (n = 122) we found previously that in 26% of patients who remained inconclusive after long-term monitoring, positive suggestive induction could ascertain the PNES diagnosis. In this prospective investigation we found that 13% of patients in group B (monitoring first) would have
remained inconclusive had they not had a provoked PNES during suggestive induction. The median illness duration of these patients was 3 years, which highlights the major impact such facilitation of diagnosis (or its repeated failure, respectively) can have in the life of patients. One of those patients did not undergo monitoring because he could not tolerate the prolonged discomfort of scalp electrodes. This case illustrates the utility of suggestive induction for patients with suspected PNES who are unable or unwilling to complete long-term monitoring (eg, due to intellectual disability or psychiatric comorbidity).

To advance our understanding of suggestive seizure induction we investigated whether certain clinical features were associated with successful induction. We found that patients who reported having seizure triggers were not more likely to have seizures provoked through suggestion. However, patients who reported noticing prodromal symptoms (sometimes referred to as “auras”) were about three times as likely to have a PNES during suggestive induction. In a large database study of 258 patients with PNES, two thirds reported having seizure “auras,” so this might be a useful factor in deciding whether to try suggestive induction. The main principle of induction lies in the effective conveying of the expectation that a seizure is likely to commence, which in turn activates the mental representation and accompanying behavioral automatism of a PNES. The potency of the suggestion thus depends on the degree of confidence that a seizure is about to occur. If a patient perceives a known prodromal sensation (eg, dizziness or tingling), which in turn might be more readily suggestive than the entire semiology, the immediate expectation of a full seizure could be reinforced considerably.

The anticipation of a seizure might also be stronger when the provocation technique is perceived to be more “potent.” Placebo research has shown that effect sizes increase with the “invasiveness” of the procedure (pills < acupuncture < sham surgery). In line with previous findings from our group, most patients who experienced a seizure during suggestive induction did so through hyperventilation or photic stimulation, but 44% only did so after an intravenous injection (accounting for 25% of all placebo inductions performed across the study). Although some have argued for the abolishment of intravenous placebo for suggestive induction in favor of exclusively non-invasive, placebo procedures (hyperventilation or photic stimulation), our findings suggest that this will come at a significant cost to the diagnostic yield. Indeed, although Gogia et al reported a high diagnostic yield of 47% for non-invasive suggestion techniques among 169 patients with PNES, their initial study population also included 168 patients (40% of total) who remained without a diagnosis. However, in a large study that retrospectively compared two pair-matched cohorts of 170 patients each who underwent suggestive induction with or without saline injection, Chen et al showed there was no statistically significant difference in the induction rate between protocols. Our current study was not designed to re-examine this finding.

A major concern with giving placebo for diagnostic tests is that any purposeful deception regarding medical procedures is unethical, potentially illegal, and can undermine patients’ trust toward medical practitioners, which would be detrimental to future therapy (especially in patients with trauma history, who might feel particularly betrayed by deceptive behavior of authority figures). Our protocol attempts to mitigate these problems by including truthful information about the intravenous administration and its potential effects (eg, “we will inject an electrolyte solution, which can trigger certain types of seizure through endogenous mechanisms”) as well as careful debriefing. Informing patients in greater detail serves not only to mitigate ethical concerns, but has also been shown to increase the suggestive potency of a procedure. However, a certain degree of deception remains, as patients are likely to misinterpret the procedure as having a direct biochemical effect. The risks inherent in such deception need to be weighed against the potential harm of missing or delaying diagnosis and treatment due to inconclusive workup.

Finally, in one patient (eventually diagnosed with PNES based on clinical grounds) suggestive induction provoked a nonhabitual event. This highlights the known risk of inducing new semiologies in suggestible patients, and emphasizes the importance of careful debriefing. Similarly, in one patient, consciously experienced early elements of an epileptic seizure (restlessness and arousal) were induced through suggestion, again underscoring the importance of only regarding typical events as diagnostic evidence.

Previous studies had suggested that patients who did not experience a spontaneous PNES during long-term monitoring had, on average, lower seizure frequencies than those with diagnostic monitoring. Although patients with “negative” monitoring had a lower median seizure frequency in the current study, the group difference was not statistically significant. Another speculative explanation of nondiagnostic monitoring in suspected PNES has been that inpatient treatment protects from specific triggers (eg, family conflicts or occupational exposures). We found no significant difference in the rate of reported triggers between patients with and without spontaneous PNES during long-term monitoring.

Our study has several limitations. Although only a few patients who were approached for recruitment declined participation, this was not recorded, and so we cannot evaluate the potential for participation biases. Screening physicians were experienced epileptologists, well-acquainted with clinical indicators of PNES, but the suspicion of possible or probable PNES was established subjectively, and so liable to bias and variation. The median length of monitoring in patients without spontaneous seizures was just 3 days, which is short in comparison to current practice
in the United States, where EMU admissions usually last 5-10 days. Longer monitoring might have increased the rate of spontaneous events significantly, although a recent U.S. study on 150 admissions with suspected PNES suggests otherwise.28 Finally, our study was not blinded, possibly leading patients randomized to group B to believe that seizures need to be induced, making spontaneous occurrences during monitoring slightly less likely.

In conclusion, our study supports the use of suggestive seizure induction in inpatient workup of suspected PNES. When used as a first-line diagnostic procedure, suggestive induction can obviate the need for long-term monitoring in some patients, although a general reduction of the inpatient stay should not be expected. Suggestive induction is more likely to be diagnostic in patients who report prodromal symptoms.

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CONFICT OF INTEREST
SP has received a speakers fee from Novartis. JJ reports no conflicts of interest. WG has received speakers honoraria from UCB, Bial, and Eisai. TW has received speaker fees from Eisai and UCB and has served on an advisory board to Bial. US has received speaker’s honoraria from Novartis, GSK, and Medac; and advisory board honoraria from Roche and Optune/Novocure. JW has received speakers honoraria from UCB, Bial, Eisai, and Desitin. 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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