

Panic symptoms in transient loss of consciousness: frequency and diagnostic value in psychogenic nonepileptic seizures, epilepsy and syncope

REVISED MANUSCRIPT

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ABSTRACT

Purpose: Previous studies suggest that ictal panic symptoms are common in patients with psychogenic nonepileptic seizures (PNES). This study investigates the frequency of panic symptoms in PNES and if panic symptoms, just before or during episodes, can help distinguish PNES from the other common causes of transient loss of consciousness (TLOC), syncope and epilepsy.

Methods: Patients with secure diagnoses of PNES (n=98), epilepsy (n=95) and syncope (n=100) were identified using clinical databases from three United Kingdom hospitals. Patients self-reported the frequency with which they experienced seven symptoms of panic disorder in association with their episodes. A composite panic symptom score was calculated on the basis of the frequency of symptoms.

Results: 8.2% of patients with PNES reported “never” experiencing any of the seven panic symptoms in their episodes of TLOC. Patients with PNES reported more frequent panic symptoms in their attacks than those with epilepsy ($p<0.001$) or syncope ($p<0.001$), however, patients with PNES were more likely “rarely” or “never” to report five of the seven-ictal panic symptoms than “frequently” or “always” (45-69% versus 13-29%). A receiver operating characteristic analysis demonstrated that the composite panic symptom score distinguished patients with PNES from the other groups (sensitivity 71.1%, specificity 71.2%), but not epilepsy from syncope.

Conclusions: Patients with PNES report TLOC associated panic symptoms more commonly than those with epilepsy or syncope. Although panic symptoms are reported infrequently by most patients with PNES, a composite symptom score may contribute to the differentiation between PNES and the other two common causes of TLOC.

Keywords: Psychogenic nonepileptic seizures, epilepsy, syncope, panic, anxiety

Key points:

- Patients with epilepsy, PNES or syncope can report ictal panic.
- Ictal panic is more common in patients with PNES than epilepsy or syncope.
- Ictal panic symptoms are infrequent in most patients with PNES.
- Ictal panic can help to differentiate between PNES and epilepsy or syncope.
- Self-report questionnaires may have implications for diagnosis and treatment.

INTRODUCTION

Psychogenic nonepileptic seizures (PNES) superficially resemble epileptic seizures, but are not associated with epileptiform activity. Instead, most PNES can be understood as paroxysmal responses to distressing stimuli ^{1;2}. Along with syncope and epilepsy, PNES are the most common diagnoses in patients presenting to doctors with transient loss of consciousness (TLOC) ³.

Correctly diagnosing patients with TLOC can be challenging and high rates of delayed and incorrect diagnoses have been reported ⁴. Out of the three common causes of TLOC, PNES may be the most difficult to recognise ⁵. The failure to make the diagnosis of PNES has been associated with poor outcome ^{6;7}, iatrogenic harm ⁸, inappropriate emergency intervention ⁹, and even death ¹⁰.

The diagnosis of PNES is made typically based on the combination of data from multiple sources including the patient's history, witness accounts and the results of investigations ^{11;12}. Unfortunately, interictal investigations have a low sensitivity and specificity in this setting, and gold standard diagnoses are often not feasible ⁴. Furthermore, if episodes are captured during investigations they may not be typical of habitual events. For these reasons, the analysis of the patient's ictal symptoms remains the cornerstone of the diagnostic process.

Given the process of eliciting and interpreting the seizure history is quite subjective and often requires the expertise of a specialist, attempts have been made to develop diagnostic questionnaires or interviews to distinguish between tonic clonic seizures and syncope ¹³ or between epilepsy and PNES ^{14;15}.

Hendrickson et al.¹⁶ suggests the frequency of ictal panic symptoms, reported in response to a series of yes/no questions asked during history-taking, differentiates reliably between epilepsy (n=224) and PNES (n=130). The authors retrospectively

reviewed the records from clinical interviews of patients admitted for video-electroencephalogram (EEG) monitoring. Patients had been asked if they had ever experienced thirteen DSM-IV-TR¹⁷ panic attack symptoms. Overall, patients with PNES reported a greater number of panic attack symptoms compared to individuals with epilepsy ($p < 0.001$). A cut-off of four or more symptoms predicted the diagnosis of PNES with a sensitivity of 82.6% and a specificity of 65.4%.

Whilst this study suggests that panic symptoms are common in patients with PNES, other studies have suggested that PNES are characterised by a particular symptom profile that differs from experiences of panic attacks¹⁸ or epileptic seizures¹⁹. Goldstein and Mellers²⁰ demonstrated that, when compared to patients with epilepsy ($n=19$), those with PNES ($n=25$) reported similar levels of mental and cognitive ictal symptoms of panic, but were more likely to report somatic and autonomic arousal symptoms typically associated with panic attacks. As such, PNES could be considered a paroxysmal dissociative response to heightened arousal that may not be accompanied by subjective fear or distress - possibly reflecting dissociation during attacks (or “panic attack without panic” pg. 619).

In view of the fact that previous studies on ictal panic symptoms in patients with PNES were based on small samples, or on the retrospective evaluation of clinical records, which may have been affected by the interviewing clinicians not being blind to the patient’s likely diagnosis, the possible link between panic and PNES requires further investigation.

The first aim of the present study was to explore the frequency of ictal panic symptoms in a large dataset with secure diagnoses. The second aim was to determine whether ictal panic symptoms differentiate between PNES and the other two common causes of TLOC. We tested the hypothesis that patients with PNES would report a

greater frequency of ictal panic symptoms compared to patients with epilepsy or syncope, and that these symptoms could help to distinguish PNES from the other two common causes of TLOC.

METHODS

Patients

Patients with epilepsy or PNES were identified from clinical databases in the Departments of Clinical Neurophysiology at the Royal Hallamshire Hospital, Sheffield United Kingdom (UK), and the National Hospital for Neurology and Neurosurgery, London, UK. All patients in this study had gold standard diagnoses of epilepsy or PNES (recording of events involving TLOC during video-EEG monitoring confirmed as typical of habitual events)¹². Patients were excluded if the consultant neurologist responsible for their treatment suspected the presence of different types of attacks not captured during the video-EEG recording.

Some patients with a secure diagnosis of recurrent vasovagal or cardiac syncope were identified from the centres above, but most were identified using the database of the Falls and Syncope Service at the Royal Victoria Infirmary, Newcastle, UK. The diagnosis of syncope was made on clinical grounds by experts in the disorder and supported by investigations documenting physiological changes during typical attacks (heart rate and/or blood pressure changes during tilt-table examinations or heart rate changes during prolonged electrocardiographic recordings).

Patients were excluded if they were unable to complete the questionnaire without help i.e. had recognised learning difficulties. The Northern and Yorkshire Multi-Centre Research Ethics Committee granted ethical approval for this study. Different aspects of this dataset have been analysed and described previously^{15; 21}.

Protocol

To recruit 100 patients in each diagnostic group, 386 patients with epilepsy, 308 patients with PNES and 371 patients with syncope were sent invitation letters with an information sheet, a self-report questionnaire and a stamped addressed return envelope. If patients failed to respond, a second invitation letter was sent one month after the first. Recruitment ceased once we had 100 respondents from each condition. All participants were asked to complete the Paroxysmal Event Profile (PEP). The PEP asks respondents about symptoms before, during and immediately after episodes of TLOC. Each item is rated on a five-point Likert scale (Always, Frequently, Sometimes, Rarely or Never). Here, we focus on seven of 86 questions about panic symptoms which were extracted from the Present State Examination ²², and which reflect the symptomology of panic as described in the ICD-10 ²³ and DSM-V ²⁴. The seven questions were used to assess the subjective experience of panic during episodes and not to diagnose a panic disorder.

The following questions about panic during TLOC were included: (1) *During my attacks I feel very frightened*; (2) *During my attacks I feel that something terrible might happen*; (3) *During my attacks I am frightened that I am going to die*; (4) *During my attacks I am frightened that I will lose control*; (5) *During my attacks I am frightened that I will go crazy*; (6) *During my attacks my heart pounds and I feel shaky and sweaty*; and (7) *During my attacks I feel that I have to get out of the situation*.

Data analysis

Differences in sample characteristics were examined using chi-square or Mann-Whitney U test as appropriate. As significant differences in demographics

between the three conditions were observed we performed an analysis of covariance (ANCOVA) as an additional measure. For this report, all original scores were reversed so that higher scores reflect more frequent and diverse symptoms of ictal panic. The Shapiro-Wilk test demonstrated the data was not normally distributed. In view of this, and as data was collected using a Likert scale, non-parametric (two tailed) Kruskal –Wallis and Mann-Whitney U tests were used to compare frequency of ictal panic symptoms between PNES, epilepsy and syncope. Given multiple statistical comparisons (PNES vs. epilepsy, PNES vs. syncope and epilepsy vs. syncope), to reduce the risk of false positive findings the alpha level was adjusted using sequential Bonferroni²⁵, the most significant of the three *p* values had to <0.0167, the second most significant <0.025, and the third, <0.05.

To investigate if ictal panic symptoms can contribute to the differential diagnosis of the three conditions, a composite score was calculated as the sum of scores on the seven items - a higher score reflected more different and frequent ictal panic symptoms. A composite score was only computed for patients who completed all seven ictal panic related questions (epilepsy n=93, PNES n=90, syncope n=98). Creating a panic composite was justified as the seven questions for each of the three conditions were found to have good internal consistency (PNES $\alpha=0.843$, epilepsy $\alpha=0.882$ and syncope $\alpha=0.788$). An area under the receiver operating characteristic (ROC) curve statistic was conducted to investigate the sensitivity and specificity of the ictal panic composite as a test of diagnosis. The accuracy of the area under the ROC curve had to be >0.5 to be acceptable. Sensitivity and specificity was given equal importance. The data were analysed using SPSS 21.

RESULTS

Patient characteristics

Patient demographics are displayed in Table 1. Responses from 300 patients were recorded (epilepsy n=100, PNES n=100, syncope n=100). However, seven patients failed to complete any of the questions on ictal panic and were therefore excluded. Significant differences were observed between the three groups on age, age at onset of TLOC disorder and number of hospitalisations. This study captured significantly more responses from female (n=214) than male (n=79) patients ($\chi^2=62.2$, $p<0.001$), but there were not significant differences in terms of gender distribution between the three patient groups ($\chi^2=1.24$, $p=0.54$).

Table 1 Sample characteristics by group. Values are group medians (interquartile range) unless otherwise noted.

	P	E	S	P vs. E	P vs. S	E vs. S
n	98	95	100			
Gender (n)						
Female	69	68	77			
Male	29	27	23			
Age (years)	43 (22)	31 (15)	57.5 (44)	U=3371 p=0.001	U=3293.5 p<0.001	U=2520.5 p<0.001
Age at TLOC onset (years)	25 (18)	9 (10)	36.5 (45)	U=1775 p<0.001	U=3616.5 p=0.002	U=1545.5 p<0.001
Number of hospitalisations due to TLOC	2 (2)	1 (3)	(0) (0)	U=4085 p=0.423	U=1770 P<0.001	U=2236.5 P<0.001

n = number of patients, number of hospitalisations (0= never, 1= once, 2= between 3 and 5, and 3= more than 5), U = Mann-Whitney U analysis, P = psychogenic nonepileptic seizures, E = epilepsy, S = syncope, vs. = versus

Frequency of panic symptoms

Overall, 8.2% (n=8) of patients with PNES, 29.5% (n=28) of those with epilepsy and 43% (n=43) of those with syncope reported “never” experiencing any of

the ictal panic symptoms listed. To illustrate the frequency and distribution of TLOC associated panic symptoms, Table 2 shows the proportion of patients in each diagnostic group who stated that they “always” or “frequently” experience a particular symptom and those who “rarely” or “never” have a particular symptom. The fact that none of the percentages in the table approach 100 demonstrates the considerable variability of TLOC experiences for individual patients. It is also evident that in all diagnostic groups, patients were more likely to “rarely” or “never” report most TLOC associated panic symptoms than “always” or “frequently” (the only two exceptions being “feeling very frightened” and “heart pounds, feel shaky and sweaty” in the PNES group).

Table 2 Distribution of responses to symptoms of ictal panic.

Question	PNES		Epilepsy		Syncope	
	Always or Frequently	Rarely or Never	Always or Frequently	Rarely or Never	Always or Frequently	Rarely or Never
Feel very frightened	36%	30%	27%	57%	10%	73%
Feel that something terrible might happen	18%	59%	12%	77%	6%	87%
Frightened that I am going to die	15%	59%	5%	88%	4%	89%
Frightened that I will lose control	29%	45%	19%	72%	11%	82%
Frightened that I will go crazy	13%	69%	4%	88%	0%	97%
Heart pounds, feel shaky and sweaty	37%	29%	20%	67%	22%	59%
Feel I have to get out of the situation	16%	45%	16%	72%	11%	75%
Percentage mean	23%	48%	15%	74%	9%	80%

PNES = psychogenic nonepileptic seizures

Difference in ictal panic symptoms between diagnostic groups

There were significant group differences in ictal symptom reporting for all seven manifestations of panic sampled, with symptoms being reported most frequently in the PNES group. Six of the seven symptoms were reported least frequently in the syncope group. Differences were also significant for most comparisons of individual symptoms between the subgroups, although three of seven comparisons of the frequency of particular symptoms between the epilepsy and syncope group failed to reach significance (Figure 1 and Table 3).

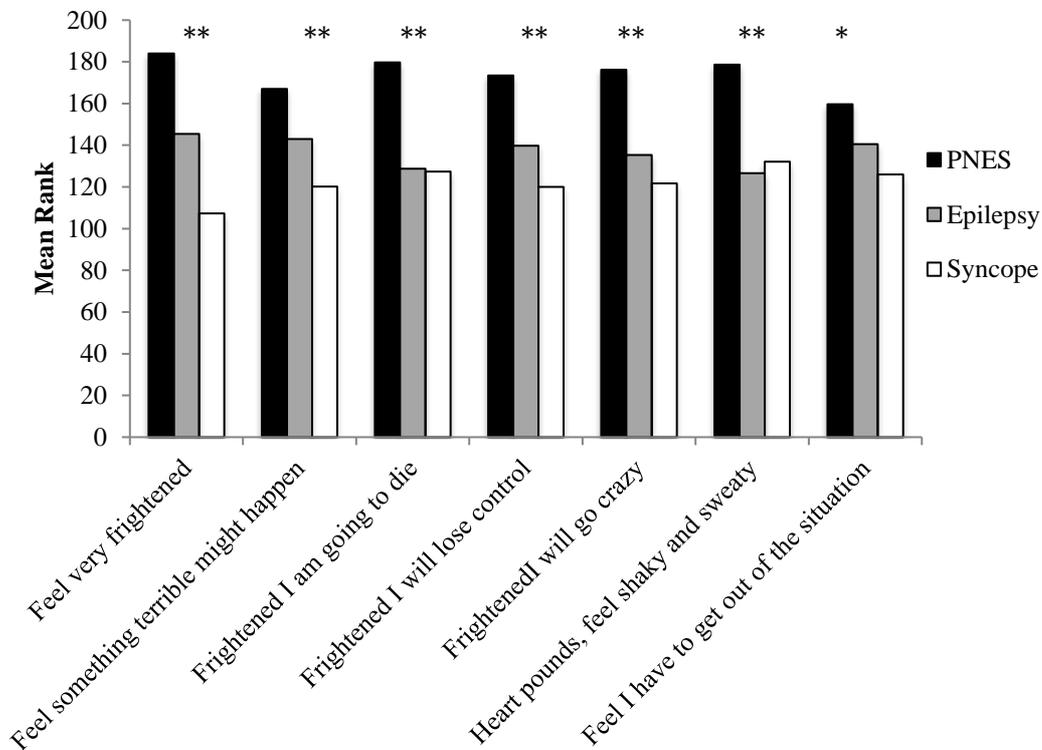


Figure 1 Significant differences between the PNES, epilepsy and syncope groups in the mean ranks (Kruskal-Wallis test) of ictal panic questions, (* $p < 0.01$ ** $p < 0.001$).

Table 3 Findings from Mann-Whitney-U analysis investigating pairwise comparisons (* significant using sequential Bonferroni).

Question	P		E		S		P vs. E	P vs. S	E vs. S
	Median	IQR	Median	IQR	Median	IQR			
Feel very frightened	3	2	2	3	1	2	p = 0.001*	p < 0.001*	p < 0.001*
Feel that something terrible might happen	1	2	1	1	1	0	p = 0.021*	p < 0.001*	p = 0.005*
Frightened that I am going to die	1.5	2	1	0	1	0	p < 0.001*	p < 0.001*	p = 0.879
Frightened that I will lose control	3	3	1	2	1	0	p = 0.003*	p < 0.001*	p = 0.043*
Frightened that I will go crazy	1	2	1	0	1	0	p < 0.001*	p < 0.001*	p = 0.03*
Heart pounds, feel shaky and sweaty	3	2.25	1	2	1	2	p < 0.001*	p < 0.001*	p = 0.625
Feel I have to get out of the situation	2	2	1	2	1	1	p = 0.074	p = 0.001*	p = 0.128

IQR= interquartile range, P = psychogenic nonepileptic seizures, E = epilepsy, S = syncope, vs. versus

Panic as a diagnostic tool

The composite score of ictal panic differed significantly between the three conditions ($\chi^2=47.5$, $p<0.001$, Figure 2). However, direct group comparisons were only significant for the comparison PNES vs. epilepsy ($p<0.001$) and PNES vs. syncope ($p<0.001$; epilepsy vs. syncope $p=0.052$).

To explore the possibility that group-level differences on the composite ictal panic symptom score could be explained by the observed demographic or clinical differences between the groups, a one-way ANCOVA was performed as an additional measure. This showed the ictal panic composite was still significantly different between the conditions when age ($F(2, 277) = 21.13$, $p<0.001$, partial $\eta^2=0.13$), age at TLOC onset ($F(2, 276) = 23.35$, $p<0.001$, $\eta^2=0.15$) and number of hospitalisations due to attacks ($F(2, 271) = 14.25$, $p<0.001$, $\eta^2=0.01$) were introduced as covariates.

When PNES was the state variable (PNES vs. epilepsy and syncope), the area under the ROC curve was 0.742, suggesting a statistically acceptable diagnostic accuracy of the composite ictal panic score. Scoring above the threshold cut-off score of 12.5 predicted a diagnosis of PNES with a sensitivity of 71.1% and specificity of 71.2%. However, when epilepsy (epilepsy vs. PNES and syncope) or syncope (syncope vs. PNES and epilepsy) was the state variable, the areas under the ROC curves were not acceptable (0.444 and 0.322 respectively). This suggests that, in patients with recurrent TLOC, self-report measures of the frequency of panic-related attack symptoms can help distinguish PNES from epilepsy and syncope, but not epilepsy from syncope.

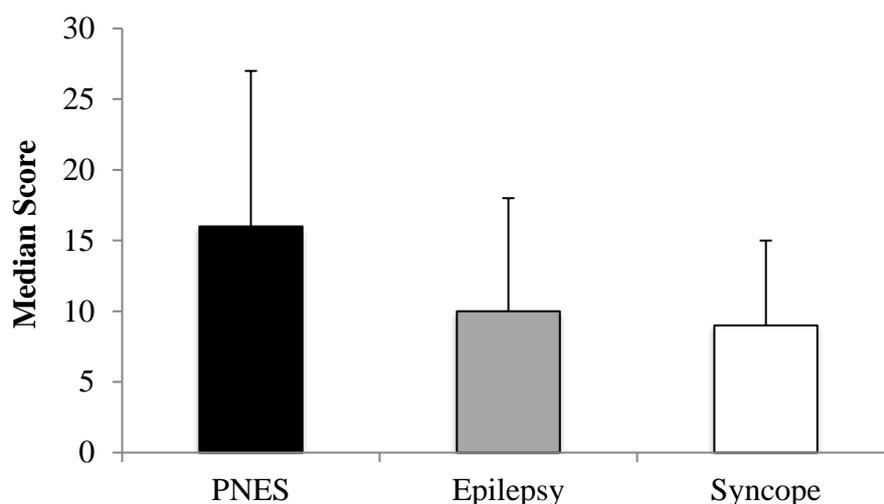


Figure 2 Median score of panic composite for PNES, epilepsy and syncope. Error bars reflect interquartile range.

DISCUSSION

This study investigated the frequency of panic symptoms associated with PNES, epilepsy and syncope. Whereas some previous studies in patients with PNES reported increased levels of ictal panic symptoms, others have given rise to the idea that PNES can be interpreted as “panic without panic” and may occur *instead of* more overt panic ²⁶. Panic symptoms are well recognised in association with epilepsy and syncope: focal epileptic seizures involving the limbic system commonly produce auras involving panic symptoms ²⁷, and panic symptoms are a common feature of syncope ²⁸. Furthermore, there is an overlap of the pre-syncope state and autonomic symptoms of panic ²⁹.

The results are consistent with previous studies demonstrating that patients with PNES are more likely to report symptoms of panic during their attacks than patients with epilepsy. Adding to this, we report that TLOC due to PNES is associated with more frequent ictal symptoms of panic than TLOC caused by syncope. Our findings support those of previous studies based on reports of subjective symptoms and objective measures of arousal that PNES often involve a subjectively adverse

experience associated with ictal manifestations of anxiety^{16; 18; 20; 30}. Having said that, even in the PNES group, patients were more likely “rarely “ or “never” to report most panic symptoms than “frequently” or “always”.

In terms of specificity, our findings closely match those of a previous study by Hendrickson et al. differentiating between PNES and epilepsy (71.2% reported in the current study vs. 65.4%), although we observed a lower sensitivity of panic symptoms as a diagnostic indicator of PNES (71.1% as opposed to 82.6%)¹⁶. It may be that the divergence of the findings is due to differences in the populations studied (outpatients with chronic disorders involving TLOC vs. inpatients undergoing video-EEG) and the mode of questioning (self-report questionnaire about symptom frequency vs. questioning by a clinician whether certain ictal panic symptoms had ever been experienced). The fact that more patients with PNES than those with epilepsy in our study, but not in the study by Hendrickson et al. reported that they experienced ictal fear of losing control or going crazy, and symptoms of shaking, certainly hints at differences between the patient populations.

It is also possible that the greater number of symptoms in the list of questions used in the previous study (thirteen vs. seven symptoms sampled here) improved the sensitivity of using panic symptom frequency as a diagnostic indicator of PNES. Whilst the findings of our study and those of that by Hendrickson et al. suggest that answers to questions about ictal panic symptoms may contribute to the differential diagnosis, other studies have demonstrated that a greater number of questions (including enquiries about non-panic symptoms) can improve differential diagnostic accuracy. For instance, Reuber et al.¹⁵, in the same patient cohort reported in this study, used a total of 86 questions about a wide range of possible subjective symptoms just before, during and immediately after episodes of TLOC, 74 of which

helped to differentiate between the three groups. These questions mapped onto five factors described by the labels “feeling overpowered”, “sensory experience”, “amnesia”, “mind/body/world disconnection”, and “catastrophic experience”. Using logistic regression analysis, PNES patients were correctly distinguished from those with syncope with 94% accuracy and from those with epilepsy with 77% accuracy. A correct differentiation between epilepsy and syncope was achieved in 91% of patients. Using a sample of 181 patients (PNES n=48, epilepsy n=116, PNES and epilepsy n=17), Syed et al. ¹⁴ started with 209 items to assess potential indicators of diagnosis and finished with 53 questions making a significant contribution to the differential diagnosis. These questions focused on ten predictors including age of onset, seizure frequency, depression, locus of control, and practical support seeking behaviours. Using this measure, the diagnosis of PNES was predicted with a sensitivity of 94% and specificity of 83%.

This evidence suggests that a short list of questions about panic symptoms may improve the quality of clinical assessments, although panic questions alone cannot be relied upon for the diagnosis and a more comprehensive assessment of ictal symptoms is recommended to capture patients TLOC experiences more fully ¹⁵.

When examining the distribution of responses to questions about individual symptoms of TLOC associated panic symptoms, our findings provide further evidence for the assertion that TLOC is experientially heterogeneous, in particular if it occurs in the context of PNES ²¹. Our results suggest that ictal panic symptoms only occur “always” or “frequently” in a (substantial) minority of patients with PNES. This subgroup of patients may indeed be experiencing dissociation arising out of panic attacks. In line with Clark’s model of panic ³¹, symptom escalation may result from catastrophic misinterpretation of the consequences of certain bodily sensations, which

happen to be normal anxiety responses leading to a heightened perceived threat and triggering of a dissociative response. Alternatively, the dissonance between anxious arousal and emotional self-perception in these patients may absorb attentional resources to such an extent that they feel and appear unconscious ³².

Our self-report data cannot prove that the pathogenesis of TLOC in the larger group of patients with PNES who “never” or “rarely” report ictal panic symptoms is truly different. It may simply be that patients in this subgroup dissociate more “effectively” from their anxious arousal and are therefore unable to report panic symptoms. Our previous analysis of the relationship between panic and dissociative symptoms in the same patient group demonstrated a positive correlation between symptoms considered as manifestations of anxiety and those thought of as characterising dissociation ¹⁵. Whilst this findings may be interpreted as an argument against the interpretation of dissociation as an “effective” way of dealing with anxiety, it is not at all clear that “effective” dissociation has to be associated with high scores on questionnaires asking about a broad range of so-called “dissociative” symptoms. What is evident from the data presented here is that PNES are an inter- and intra-individually heterogeneous phenomenon, indicating that one psychopathological mechanism (such as “panic without panic”) may not be relevant in all patients or at all times. This conclusion, based on self-reported ictal experiences in this study, resonates with the findings of other studies which have identified different subgroups of patients with PNES, for instance, one subgroup with markedly abnormal emotion regulation and another with an emotion regulation profile that does not differ from healthy controls ³³.

None of the studies focusing on ictal symptoms of panic examined the relationship between these symptoms and state or trait anxiety in the interictal state.

However, there is evidence that anxiety symptoms and anxiety disorders are found more commonly in patients with PNES³⁴, epilepsy²⁷ and syncope³⁵ than in healthy controls. A chronic and disabling disorder characterised by unpredictable and socially challenging episodes of TLOC might be expected to generate secondary anxiety. In addition, highly distressing ictal panic symptoms – however brief – could have effects on interictal functioning, and be an important reason for the increased levels of emotional and behavioural avoidance observed in patients with PNES³².

Limitations

The current study has a number of limitations. We note that there were significant demographic differences between PNES, epilepsy and syncope groups. However, we carried out an additional multivariate analysis of the differences in the composite panic symptom score, which suggested differences were observed even after age, age at TLOC onset and number of hospitalisations had been controlled for. It is not clear why responses were collected from a significantly higher proportion of females (n=214) than males (n=79). This gender difference would be in line with expectations in the PNES, but not in the other two patients groups.

Our insistence on gold standard diagnoses (including the observation of a typical episode of TLOC during physiological investigation) is likely to have introduced selection bias, favouring patients with chronic disorders with relatively frequent episodes of TLOC. This means that our findings cannot immediately be generalised to all patients with TLOC, especially those presenting with a disorder of recent onset. Given that the overwhelming majority of respondents had chronic conditions causing recurrent TLOC we cannot say what minimum number of episodes

of TLOC a patient has to have experienced before our questions focusing on the frequency of ictal panic symptoms could have been completed in a meaningful way.

As the aim of the present study was to determine distinguishing features between unselected cases of PNES, epilepsy and syncope, differences in ictal panic were not investigated between different subtypes of the same condition. It is possible that patients with different types of epilepsy or syncope would report different levels of ictal panic symptoms. While we do not have sufficient data firmly to subdifferentiate between different epilepsy syndromes or types of syncope, given our mode of recruitment, we expect that the overwhelming majority of patients in the epilepsy group (>80%) had focal epilepsy and a similar proportion of patients in the syncope group had neurovasogenic (vasovagal) as opposed to cardiac syncope.

Finally, despite the fact that all diagnoses had been objectively proven, our study is based on self-report and did not include any ictal assessments. This means that we cannot comment on the degree of objective ictal impairment of consciousness in the three patients groups. It is possible that one reason why patients with PNES reported panic symptoms more often is that they had a greater level of ictal awareness and recall.

Conclusion

Despite these limitations, based on a large sample of patients with a secure diagnosis of one of the three most common causes of TLOC, we have demonstrated that ictal panic symptoms are reported more frequently by patients with PNES than those with epilepsy or syncope. The reporting of ictal panic symptoms on a self-report questionnaire can contribute to the distinction of patients with PNES from those with epilepsy or syncope, but cannot distinguish reliably between epilepsy and syncope.

CONFLICTS OF INTERESTS

None declared.

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