Seizure 59 (2018) 108–115

Contents lists available at ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

Review

The association of panic and hyperventilation with psychogenic non-epileptic seizures: A systematic review and meta-analysis

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ARTICLE INFO

Article history:
Received 14 November 2017
Received in revised form 9 May 2018
Accepted 11 May 2018

Keywords:
Psychogenic non-epileptic seizures
Panic
Panic attack
Panic symptoms
Panic disorder
Hyperventilation

ABSTRACT

Introduction: Psychogenic Non-Epileptic Seizures (PNES) are events that appear epileptic but are instead thought to have a psychological origin. Increased rates of several psychiatric disorders have been reported in PNES, including anxiety and panic disorders. Some theories suggest panic and/or hyperventilation have aetiological roles in PNES, though these remain unproven.
Methods: We conducted a systematic review of associations of panic and hyperventilation with PNES using Ovid Medline and PubMed, and a *meta*-analysis where appropriate.
Results: We found eighteen studies reporting rates of panic in PNES and eight studies reporting hyperventilation. The reported rate of panic attacks in PNES ranged from 17% to 83%, with physical symptoms more commonly reported, and affective symptoms less so. 'Dizziness or light-headedness' was found to be more prevalent than 'fear of dying' by random-effects meta-analysis (68% vs. 23%). A proportion meta-analysis found a weighted occurrence of 20% of panic disorder in PNES. A pooled meta-analytic rate of PNES events following voluntary hyperventilation induction was 30%, while the clinically observed rates of peri-ictal hyperventilation in PNES without induction varied from 15 to 46%.
Conclusions: Previous studies have reported moderate rates of association of panic in PNES, though the proportions varied considerably across the literature, with physical symptoms more commonly reported than affective. Hyperventilation is an effective inducer of PNES events in a minority, and can be observed occurring in a minority of patients without induction. These results support an important, albeit not essential, role for panic and hyperventilation in the pathogenesis of PNES events.

1. Introduction

Psychogenic non-epileptic seizures (PNES) are events that superficially resemble epileptic seizures but without evidence of typical epileptic discharges on electroencephalography (EEG), and which are thought to have a psychological origin [1]. PNES are a form of Conversion Disorder, which psychiatric orthodoxy holds results from the 'conversion' of intrapsychic stress into neurological symptoms, though the aetiology and mechanism of this are unclear. Psychological states are thought to play a role [2], as well as a history of trauma [3,4] and abuse [3,5], though by no means invariably [6]. It is associated with a range of psychiatric comorbidities, including depression, anxiety and personality disorders [3,7], though these again are not always found.

Panic symptoms have been particularly commonly reported in PNES [8], and it has been claimed that panic plays a specific aetiological role in PNES events: Goldstein and Mellers speculated that the events occur as a response to heightened arousal in the absence of raised anxiety levels ('panic without panic') [9]. This is supported by reports of increased autonomic arousal in PNES [10], and by the use of hyperventilation, perhaps the cardinal feature of panic [11], to provoke non-epileptic events in EEG suites [12]. As the mechanisms of PNES remain elusive, the investigation of associated panic may potentially be informative as to their production or predisposition.

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https://doi.org/10.1016/j.seizure.2018.05.007
1059-1311/

This systematic review aims to capture the available literature on the associations between PNES and panic and panic symptoms, including hyperventilation, to allow appraisal of the evidence examining the possible role of panic in the aetiology of PNES.

2. Methods

2.1. Inclusion & exclusion criteria

We included any article presenting original data in a peer-reviewed journal that reported a specific rate of either panic, hyperventilation or panic symptoms with PNES. As the individual symptoms of panic (such as shaking) are very non-specific, we included studies of symptoms only if they were reported in a study of panic specifically. Studies were excluded if they were not in English, were not available in full text, were reviews or case studies.

2.2. Search strategy

A search was conducted with the terms ("panic" OR "panic disorder" OR "panic attack" OR "panic symptoms" OR "hyperventilation") AND ("psychogenic seizures" OR "psychogenic non-epileptic seizures" OR "pseudoseizures" OR "functional seizures" OR "hysterical seizures" OR "non epileptic seizures" OR "functional epilepsy"). No date limits were specified, so the search would have covered from the start of each database to the date of the search, which was conducted on February 6th, 2017. This yielded 153 results on Ovid covering Embase, Ovid Medline, and PsychINFO, and 42 results on PubMed. After duplicates were removed, there were a total of 99 results. The abstracts were then read and studies excluded if they were: reviews or meta-analyses, books or book chapters, articles in languages other than English, single-case studies, and studies without psychogenic non-epileptic seizures or its synonyms. This left a total of n = 52 studies for which full text was sought. Unavailable papers, such as conference proceedings, were then excluded, and the Methods and Results sections of available articles were screened to confirm inclusion of panic, panic symptoms, or hyperventilation in PNES. Of the remaining 25 papers, 13 were excluded after full-text review because they did not meet the inclusion criteria. A review of the references of the remaining 12 papers plus a recent review [13] was conducted, yielding a further seven studies meeting inclusion criteria. Seven additional papers meeting inclusion criteria were also found from consultation with experts, five of which were recommended by a reviewer, including two studies published after the search date. This gave a final total of 26 studies – 18 studies of panic and eight studies of hyperventilation – included in the qualitative review (see Fig. 1); the studies excluded after full-text review, as well as the reasons for their exclusion, are noted in Appendix A (Table 6.-Supplementary file 1); the two main reasons for exclusion were either that an association was reported without quantitative support, or that the rate reported was mixed with another condition or procedure (e.g. hyperventilation with photic

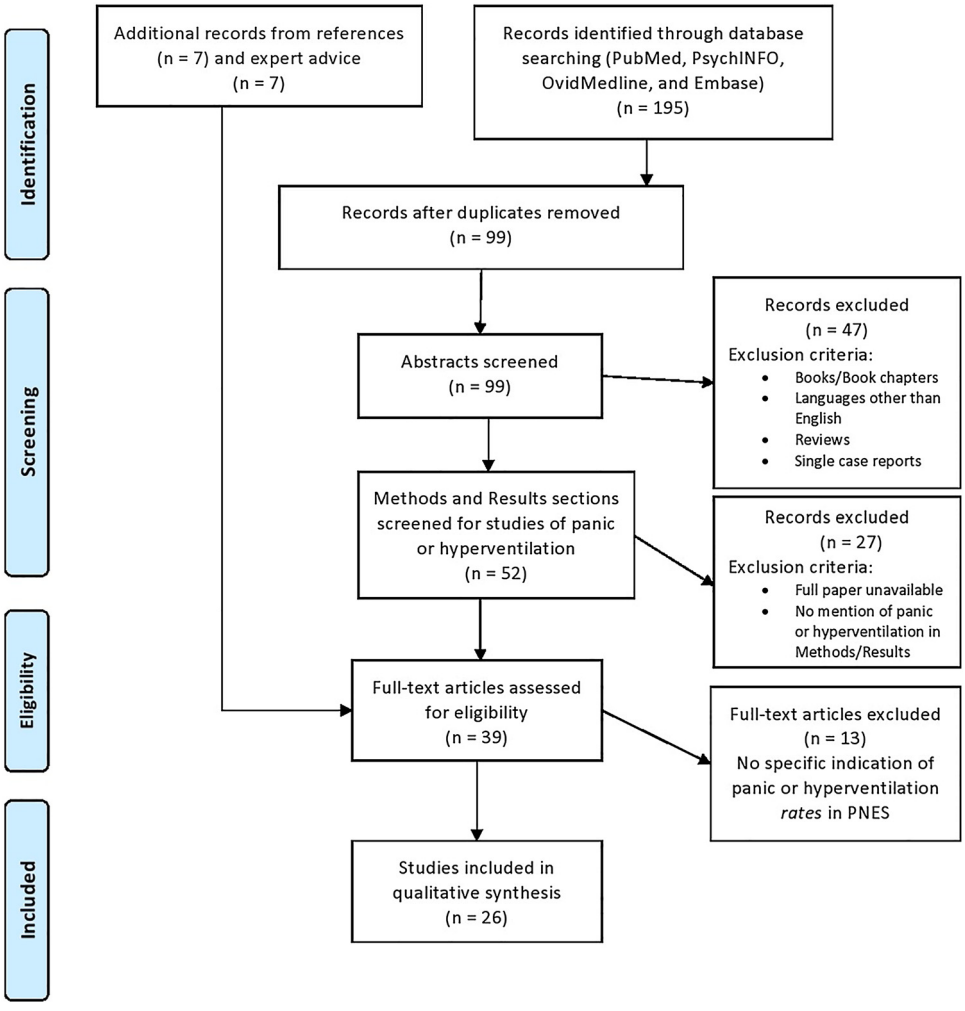

Fig. 1. PRISMA diagram of study selection.

stimulation). Where the data presented could not be sufficiently determined from the paper, the authors were contacted to provide clarification. Included studies were published between 1990 and 2017.

2.3. Quality appraisal

A quality assessment for each of the included papers was undertaken, based on the rubric developed by Reuber and Brown [14], using guidelines from the Centre for Reviews and Dissemination [15]. A percentage of ≥80 'yes' answers to features of the study method and a 'good' sample size (n ≥ 64) indicated a high-quality study, while 50–79% or ≥80% with a 'moderate' sample size (n = 26–63) indicated a medium-quality study. A 20–49% 'yes' rate or 'poor' sample size (n = 15–25) indicated a low quality study, while <20% 'yes' or a 'very poor' sample size (n < 15) indicated a very low quality study. Sample size ratings were applied to each group in case-control studies. The quality appraisal for each included study can be found in Appendix B (Table 7.- Supplementary file 2).

2.4. Data analysis

Given sufficient methodological similarity, random-effects meta-analyses of proportion for panic disorder in PNES, for the panic symptoms of 'dizziness' and 'fear of dying', and for PNES induction with voluntary hyperventilation were conducted using MedCalc for Windows, version 15.0 (MedCalc software, Ostend, Belgium).

3. Results

3.1. Panic in PNES

3.1.1. Panic attacks in patients with PNES

We identified six studies that measured the rates of panic attacks in patients with PNES (Table 1). Hendrickson et al. retrospectively reviewed records of face-to-face clinical interviews of a large population of 224 patients with PNES and 130 patients with epilepsy [8]. Subjects were previously asked if they had experienced any of the DSM-IV-TR criteria for panic symptoms in the peri-ictal period, and whether they were 'always' or 'sometimes' experienced before, after, or during their PNES events. The investigators found a significantly higher average number of panic symptoms in the PNES population than in the epilepsy group (6.4 vs. 3.4 respectively, $p < 0.001$) in and around the time of the ictal event, as well as increased rates of having four or more panic symptoms (82.6% vs. 34.6% of patients respectively, $p < 0.001$).

Witgert et al. also retrospectively reviewed panic symptoms in the ictal period of PNES events in 21 adolescent (aged 13–18) and 18 adult patients [16]. In contrast to Hendrickson et al. however, they collected information from a range of sources, including seizure symptomatology, interviews with patients and their caregivers, and videos of events. They then tabulated behavioural and cognitive symptoms and compared them to the DSM-IV criteria for panic attack, though it was unclear if the clinical information was gathered in a structured manner. Nevertheless, they found that 16.7% of adolescent patients met criteria for a panic attack in the ictal period while none of adult patients did ($p < 0.09$).

Duncan and Oto retrospectively analysed a database of patients presenting to their specialised epilepsy clinic, with the aim of comparing patients with PNES and learning disability versus patients with PNES without learning disability in several historical and clinical features, including past psychiatric diagnoses [17]. Of the 288 patients in both groups, 123 patients (42.7%) were found to have a past or current history of panic attacks, with no statistical difference between groups. A notable weakness of this study was that the method of determining panic attack presence or history was unclear.

Duncan et al. undertook another comparison study in which they retrospectively searched for patients presenting to a subspecialised PNES service who had their first PNES attack occurring over the age of 55, termed 'late-onset PNES' by the authors [18]. They were compared to patients with earlier onset PNES on a number a of clinical indicators, including a history of panic attacks. Of a total of 267 patients studied, 113 patients (42.3%) had a history of panic attacks, again with no difference between groups. Panic attack diagnosis was determined by clinical history at the time of initial patient presentation.

The low quality ratings, despite the large sample size, in the two case-control studies performed by Duncan et al. were because not all patients were diagnosed using vEEG, and because it was unclear whether patients were recruited consecutively.

Vein et al. compared 15 patients with PNES and 32 patients with panic attacks for prevalence and severity of DSM-III-R panic

Table 1
Studies of panic attacks in patients with PNES.

Study	Study type	Method of PNES diagnosis	Number of patients with PNES	Average number of panic symptoms (out of 13)	Occurrence in relation to ictal event	Patients with panic attack, or with four or more panic symptoms	*Quality assessment*
Hendrickson et al. [8]	Retrospective analysis	vEEG	224	6.4	Pre-ictal, ictal, and post-ictal	82.6%	Medium quality study
Duncan & Oto [17]	Retrospective comparison analysis	vEEG + witness accounts of typical PNES semiology	288	Unspecified	Unspecified	42.7%	Low quality study
Duncan et al. [18]	Retrospective comparison analysis	vEEG + witness accounts of typical PNES semiology	267	Unspecified	Unspecified	42.3%	Low quality study
Witgert et al. [16]	Retrospective review	Observation of at least three events identified as typical by a family member or friend + vEEG	18 adolescents, 21 adults	2.4 in adolescent patients, 0.9 in adult patients	Ictal	16.7% of adolescents, 0% of adults	Medium quality study
Frolov et al. [20]	Prospective case-control	Unspecified	11	Unspecified	Unspecified	70.0%	Very low quality study
Vein et al. [19]	Retrospective review	Minor periods of conversion symptoms as assessed by three experienced researchers, after ruling out neurological disease.	15	9.7	'in the paroxsym'	70.0%	Very low quality study

symptoms 'in the paroxysm' [19]. They found the average number of panic symptoms in PNES patients to be large (9.7), though significantly less than those found in patients with panic attacks (11.19, $p < 0.05$). This study was rated as very low quality as it did not use vEEG in diagnosing PNES, and there were demographic differences between patients with PNES and panic attacks.

Frolov et al. reported that 70% of their 11 patients with PNES experienced panic attacks [20]. However, they did not specify the process by which the diagnosis of panic attack was established, had between-group demographic differences and was also rated very low quality.

Due to the differences in diagnostic methods and data collection in these studies, the heterogeneity between them was too great to warrant a meta-analysis of the panic attack rate.

3.1.2. Panic symptoms

Three of the studies in Section 3.1.1 also listed the prevalence of specific panic symptoms in PNES patients (Table 2). In addition, we found three more studies that reported panic symptoms: Rawlings et al. reported the frequency of several panic symptoms in 98 patients with PNES using the Paroxysmal Event Profile (PEP), an 86-item self-report questionnaire of symptoms and phenomena in the ictus [21]. This questionnaire included seven questions derived from the ICD-10 and DSM-5 symptomatology criteria for panic. Additionally, the rates of two more symptoms typical of panic (PEP question 16.:'feeling dizzy, lightheaded' and question 58.: 'shortness of breath, choking') were obtained from correspondence. Their study compared the presence of these symptoms between patients with PNES, epilepsy, and syncope. Using the same questionnaire to study PNES phenomenology, Reuber et al. surveyed 100 patients with PNES contacted by mail to undertake the PEP [22].

In their seminal study, Goldstein and Mellers compared 25 patients with PNES to 19 patients with epilepsy regarding the presence of panic symptoms in their most severe attacks [9]. Twenty-six different panic symptoms were grouped into five symptom categories –'Autonomic arousal symptoms', 'Chest and abdomen symptoms', 'Mental state symptoms', 'General symptoms' and 'Cognitive symptoms' – but the authors provided the frequency of each panic symptom in their PNES sample at our request (Table 2).

The weaknesses of using the PEP is that there was only selective reporting of panic symptoms and not the full set found in DSM. This poses a limitation for quantitative comparison to the other symptoms of panic that were not reported. However, both PEP studies were notably strong in other aspects, particularly in standardising patient groups. Goldstein & Mellers' study rated well in its methodology, except for its low sample size, resulting in a final 'low' quality rating.

Hendrickson et al. noted that all panic symptoms except 'trembling' and 'fear of losing control' were more common in PNES than epilepsy (all $p < 0.001$). Rawlings et al. reported the symptoms of 'pounding of heart, sweating, and shaking', 'fear of losing control' and 'going crazy' and 'fear of dying' to be significantly more prevalent in patients PNES over epilepsy patients and syncope patients (all $p < 0.001$). And Goldstein and Mellers found autonomic arousal symptoms, chest and abdomen symptoms, and general symptoms to be significantly more prevalent in the ictus of PNES events over epilepsy. Furthermore, they reported significantly higher symptoms of 'chest pain', 'racing heart', 'shortness of breath', 'sweating', 'paraesthesias', and 'fear of dying' in PNES compared to epileptic events. By contrast, Vein et al. found that 'fear of dying' was significantly less prevalent in PNES events than in patients with panic attacks ($p < 0.001$).

'Trembling and shaking' was prevalent across all studies of symptoms, though clearly this may have reflected seizure semiology. Hyperventilation, and related symptoms of dizziness and paraesthesia, were also commonly reported. A random effects meta-analysis of proportion for 'dizziness or light-headedness' was found to be 68.0% (CI: 55.4 to 79.5%). By contrast, the percentage of patients who reported fear symptoms such as 'fear of losing control' and 'fear of dying' were relatively lower in almost all reported studies; a meta-analysis showed a mean proportion of

Table 2
Frequencies of specific panic symptoms in PNES patients.

Symptoms	Rawlings et al. [21] (n = 98)	Hendrickson et al. (n = 224)	Reuber et al. [22] (n = 100)	Goldstein & Mellers [9] (n = 25)	Witgert et al.- adolescent patients (n = 18)	Witgert et al.- adult patients (n = 21)	Vein et al. (n = 15)
Palpitations, pounding of heart	71%	46.0%	70%	60%	0%	0%	93%
Sweating		50.9%		64%	0%	0%	80%
Trembling, shaking		84.8%		76%	56%	29%	80%
Shortness of breath, smothering	83%	55.8%	34%	64%	56%	5%	93%
Feelings of choking		22.8%		24%	6%	0%	Unspecified
Chest pain/ discomfort	Unspecified	36.6%	Unspecified	44%	11%	0%	73%
Nausea or abdominal distress	Unspecified	30.8%	Unspecified	64%	11%	10%	80%
Feeling dizzy, lightheaded	63%	78.1%	68%	72%	61%	10%	93%
Chills or heat sensations	Unspecified	53.1%	Unspecified	60%	11%	0%	60%
Paraesthesias	Unspecified	58.0%	Unspecified	68%	28%	19%	73%
Derealisation or depersonalisation	Unspecified	61.6%	Derealisation- 21% Depersonalisation- 25%	Derealisation-64% Depersonalisation- 60%	6%	5%	Unspecified
Fear of losing control or going crazy	Losing control- 55% Going crazy- 31%	17.9%	Losing control- 50% Going crazy- 26%	Losing control- 68% Going crazy- 44%	0%	0%	7%
Fear of dying	41%	28.1%	37%	24%	0%	0%	20%
Quality assessment	Medium quality study	Medium quality study	High quality study	Low quality study	Medium quality study		Very low quality study

Where extracted from Likert scales, the percentages represent symptoms that were 'always', 'frequently', or 'sometimes' present during patients' events.

23.7% (CI: 12.2 to 37.4%) of patients experienced fear of dying in their attacks.

3.1.3. Panic disorder

We found nine studies reporting a rate of panic disorder (the syndrome of recurring, unexpected panic attacks) in patients with PNES. Snyder et al. prospectively interviewed 20 patients with PNES using a structured DSM-III-R schedule and found that 14 (70%) met the diagnosis for panic disorder (Table 3) [23]. Other studies found much lower rates. Bowman and Markland conducted a structured DSM-III-R interview of 45 patients with PNES, and found that 12 (27%) warranted a diagnosis of panic disorder at some point during their lifetime [7]. Schramke et al. retrospectively reviewed clinical psychological evaluations of 61 patients admitted for long-term vEEG to assess possible risk factors for a diagnosis of PNES [24]. Although they concluded that panic disorder was significantly more prevalent in PNES than epilepsy (25% vs. 9% respectively, $p \leq 0.01$), they found 'anxiety disorder symptoms other than panic disorder' to be one of the variables that best predicted a PNES diagnosis as opposed to an epilepsy diagnosis. Arnold and Privitera aimed to identify various psychiatric diagnoses present in a sample of epilepsy patients and those with PNES [25]. Of 14 inpatients with PNES studied, three (21%) had a DSM-III-R diagnosis of panic disorder in their lifetime, diagnosed through a structured clinical interview in which the study psychiatrist was blinded to the seizure diagnosis.

We found several studies that reported rates of panic disorder in PNES with the aim of determining which neurologic and psychiatric variables were more prevalent in PNES. Baslet et al. analysed three separate groups of patients with PNES and found a total of eight patients with comorbid panic disorder out of their total sample of 44 (18%) [26]. Bailles et al. found that two patients out of their sample of thirty (7%) met criteria for panic disorder within their lifetime [27]. Kanner et al. studied 45 patients with PNES from the time of the communication of diagnosis and 6 months afterwards, aiming to find possible variables that may alter the prognosis and outcome of these patients, but found that only one patient (2%) met the DSM-III-R criteria for panic disorder [28].

A more recent study by Ekanayake et al. studied several measures to distinguish between patients with PNES and those with Psychogenic Motor Disorders (PMD), and found panic disorder in eight out of 43 patients (19%) with PNES, significantly more than in patients with PMD ($p = 0.0009$) [29].

In a paediatric study of PNES, Wyllie et al. had 34 child or adolescent patients with PNES undergo evaluation by a paediatric psychiatrist at the time of their PNES diagnosis, and found that only three (8.8%) met the DSM-IV criteria for panic disorder [30].

Most of the studies reporting panic disorder were rated as low quality. This was mainly due to their not excluding epilepsy or, perhaps understandably, ictal panic attacks in the PNES subjects studied.

A random-effects meta-analysis of proportion combining the studies investigating panic disorder found the weighted proportion to be 20.8% (10.8 to 31.3%; Fig. 2). A Chi-squared test showed a high-moderate level of heterogeneity ($I^2 = 82.7\%$, $Q = 46.1$, $p < 0.0001$).

3.2. Hyperventilation in PNES patients

3.2.1. Hyperventilation for induction of PNES

We found five studies that quantified the success of voluntary hyperventilation for induction of PNES events (Table 4). Craciun et al. aimed to test whether 5 min of hyperventilation increased the diagnostic yield of EEG for clinical events compared to 3 min of hyperventilation [31]. They found that ten out of 22 PNES patients (45.5%) had an event during the 5-min hyperventilation, while

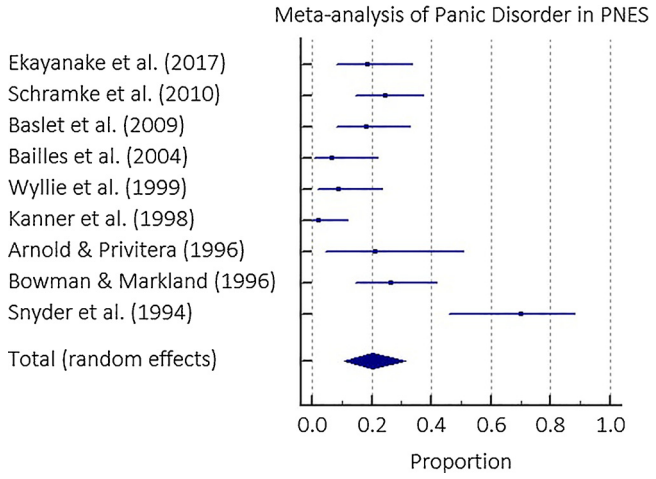

Fig. 2. Forrest plot of the proportion of PNES with panic disorder.

Table 3
Panic disorder in PNES patients.

Study	Study type	Method of PNES diagnosis	Number of PNES patients	Panic disorder diagnosis	Method of panic disorder diagnosis	*Quality assessment*
Ekanayake et al. [29]	Retrospective case-control study	vEEG	43	18.6%	Structured clinical interview for DSM-IV	Medium quality study
Schramke et al. [24]	Retrospective review	vEEG	61	24.6%	'Clinical interview'	Low quality study
Baslet et al. [26]	Prospective cohort study	vEEG in 41 patients, semiology in 3 patients	44	18.2%	DSM-IV-TR	Low quality study
Bailles et al. [27]	Cohort study	vEEG	30	6.7%	DSM-IV	Medium quality study
Wyllie et al. [30]	Prospective cohort of paediatric patients	vEEG and identified as typical by patient and family	34	8.8%	DSM-IV	Low quality study
Kanner et al. [28]	Prospective cohort study	vEEG	45	2.2%	Structured clinical interview for DSM-III-R	Medium quality study
Arnold & Privitera [25]	Prospective case series	vEEG	14	21.4%	Structured clinical interview for DSM-III-R	Medium quality study
Bowman & Markland [7]	Retrospective review	vEEG	45	26.7%	DSM-III-R	Low quality study
Snyder et al. [23]	Prospective case series	vEEG	20	70.0%	Structured clinical interview for DSM-III-R	Low quality study

Table 4
Studies examining use of hyperventilation induction in PNES.

Study	Study type	Method of PNES diagnosis	Number of PNES patients	Minutes of hyperventilation	Relationship to ictus	Patients with PNES event	*Quality assessment*
Craciun et al. [31]	Prospective procedural study	unclear	22	3	During	36.4%	Low quality study
Popkirov et al. [32]	Retrospective review of procedure	vEEG	32	2–3	Unclear	37.5%	Medium quality study
Hoepner et al. [33]	Retrospective analysis	vEEG	34	5	During	11.8%	Medium quality study
Abubakr et al. [12]	Retrospective analysis of inpatient population	vEEG	16	3	During or 5 min following	37.6%	Medium quality study
Arain et al. [34]	Prospective study of long-term vEEG monitoring	vEEG	24	3	During or 3 min following	33.3%	Medium quality study

eight (36.4%) had an event during the 3-min hyperventilation. Popkirov et al. tested a protocol of PNES event induction that involved thoroughly informing PNES subjects of the suggestion techniques to be used, including hyperventilation [32]. Of 32 patients undergoing this protocol, 12 (37.5%) had an induced event with 2–3 min of hyperventilation. However, the authors were unclear as to what constituted a PNES event and did not define the time period of occurrence relative to the hyperventilation.

Hoepner et al. tested whether PNES induction methods, including hyperventilation, were more effective if patients were given written information on their effectiveness [33]. Out of 34 patients with PNES that were given this information, four (11.8%) had a PNES event during 5 min of hyperventilation. Notably however, their sample also included seven patients with both PNES and epileptic seizures, and it was unclear whether patients with PNES events in hyperventilation had a double diagnosis.

Abubakr et al. retrospectively reviewed clinical records of PNES and epilepsy patients who underwent a routine, 3-min hyperventilation manoeuvre in an epilepsy monitoring unit [12]. Out of 16 PNES patients, six (37.5%) had a clinical event during hyperventilation or within 5 min following its completion. Only 4.6% patients with generalised epilepsy and no patients with partial epilepsy had a seizure using the same procedure. Arain et al. prospectively put 24 PNES patients through once-daily 3-min hyperventilation, with the suggestion that 'it may precipitate a seizure/spell' [34]. They found that eight patients had activation of non-epileptic events during or within 3 min following the hyperventilation, and found the number of events induced by hyperventilation to be significantly higher than that of spontaneous PNES events (rate ratio 16.6, $p < 0.001$). Furthermore, they found that 'motionless staring events' were more likely to be induced by hyperventilation than events with predominantly motor symptoms (seven patients and one patient, respectively). Additionally, they reported a significant difference using hyperventilation to induce events in PNES patients over epilepsy patients ($p = 0.016$).

A random-effects meta-analysis of proportion combining the hyperventilation studies found the weighted proportion of PNES induction to be 30.6% (19.7–42.6%; Fig. 3). A Chi-squared test showed some heterogeneity ($I^2 = 52.8\%$, $Q = 8.4$, $p = 0.08$).

3.2.2. Hyperventilation as a peri-ictal association with PNES

We found three studies that reported peri-ictal hyperventilation occurring without induction in clinically observed non-epileptic seizures (Table 5). Aguglia et al. reviewed 60 video-captured PNES events in 60 patients (one event per patient), and found hyperventilation to be associated with 21.7% of them, as part of the development of a clinimetric scale [35]. Seneviratne et al. studied the semiology of 330 PNES events to form a classification system [36]. They found differing rates of associated hyperventilation depending on the subtype in their system: 13.6% of 'Rhythmic Motor', 36.4% of 'Hypermotor', 15.2% of 'Complex Motor', 16.2% of 'Dialeptic' and 88.2% of 'Mixed' PNES. This totalled fifty-one events with hyperventilation as an observed feature, giving an overall percentage of 15.4% of PNES events. Finally, Wadwekar et al classified 54 South Indian patients according to the classification scheme of Hubsch et al. [1], and found that hyperventilation was associated with 46.3% of the patients [37]. None of these studies described the method used to measure hyperventilation, nor its timing relative to the PNES event. Therefore, given the obscurity of measurements, a meta-analysis of hyperventilation was not performed as its significance would be uncertain. It was also clear that the main aim of these studies was to describe clinical features of PNES, rather than hyperventilation specifically.

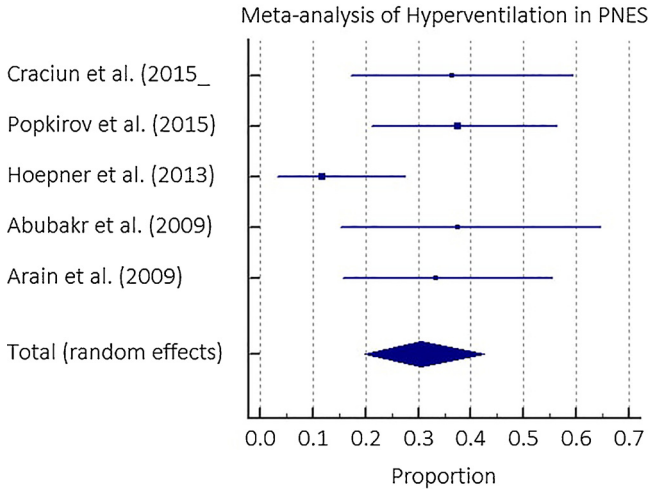

Fig. 3. Forrest plot of the proportion of PNES induced by hyperventilation.

4. Discussion

Based on our review, panic and panic symptoms have moderate associations with PNES. All of the included studies reported an association between panic and PNES, although the methods used and the reported rates of association varied widely. There were differences in methods of patient recruitment [22,23], methods and timing of psychological evaluation [23,24,27,29,30], and potential selection bias [8,17–20]. Furthermore, panic attack symptoms were recorded retrospectively in all but one study [20]. The rates of associated hyperventilation also varied greatly. This was perhaps due to the heterogeneity of the PNES populations [36], as well as variation in the method of hyperventilation used. The quality of the studies was generally low to medium, with most being low quality (Appendix B).

Table 5
Studies examining hyperventilation as an association with PNES.

Study	Study type	Method of PNES diagnosis	Number of PNES patients	Patients with hyperventilation as an association	*Quality assessment*
Wadwekar et al. [37]	Retrospective analysis of vEEG	vEEG	54 patients	46.3%	Medium quality study
Aguglia et al. [35]	Retrospective analysis	Positive response to suggestion manoeuvres	60 patients and events	21.7%	Low quality study
Seneviratne et al. [36]	Retrospective vEEG review of seizure semiology	Consensus of two epilepsy specialists based on vEEG and clinical details	330 events	15.4%	Medium quality study

Panic attacks should be considered as a diagnosis when at least four panic symptoms are present in a patient, along with a discrete period of intense fear or discomfort. In DSM-5, panic disorder should be diagnosed if there are recurrent, unexpected occurrences of these attacks [38]. While many people will have some somatic symptoms of panic, panic attacks and panic disorder are not diagnosed until these criteria are fully met.

Panic attacks are recognised as a differential diagnosis for both psychogenic and epileptic seizures [39], and some of the symptoms of panic can be identified during a PNES event [19], leading to speculation regarding their pathophysiological role [9,40]. Nine of our reviewed studies reported on panic disorder as an associated diagnosis, while six focused on panic attacks, and six reported on panic symptoms in PNES events. The combined rate of 20.8% of panic disorder diagnoses in PNES patients is markedly higher than even the lifetime prevalence of panic disorder in the general population (4.7% in a surveyed US study [41]); both Schramke and Arnold & Privitera also noted a higher number of panic disorder diagnoses in PNES compared to epilepsy in their studies –[24,25] noteworthy given the elevated incidence of anxiety disorders in epilepsy [16]. While this association appears relatively robust, and supports a possible mechanistic role, the relationship between the two is not defined or clarified by such studies of association. More plausible support for a mechanistic role come from the studies showing panic attacks or panic symptoms preceding or during the ictus. Increased rates of panic attacks and panic symptoms in the peri-ictal period support models of PNES that emphasise increased anxiety and autonomic arousal in their aetiology. Goldstein and Mellers argue that PNES events arise from raised levels of anxiety though without subjective anxious feelings [9]; Stone and Carson propose that PNES patients experience a pre-ictal 'aura' of somatic symptoms of panic, and that patients willingly dissociate in response to these uncomfortable prodromal symptoms [40]; Brown and Reuber argue that increased anxiety and autonomic arousal are, similarly, precursors but not determinants of a non-epileptic seizure [2], and that cognitive factors are responsible for dissociation into an event by activation of a 'seizure scaffold', influenced by a number of predisposing factors, including trauma. All of these theories would argue for panic symptoms or attacks preceding the ictus, but receive limited support from these data – largely due to limited reporting of the temporal relation of the panic and the ictus in the studies – and only Hendrickson et al. explicitly stated their recording of panic symptoms pre-ictally, though their rates were mixed with ictal and post-ictal occurrences of symptoms [8]. To address these theories fully, future studies will need to examine the temporal sequence directly.

There was support for the relative somatic focus of the panic symptoms – the 'panic without panic': there was a marked difference in the meta-analytic rates of somatic symptoms of 'dizziness' and 'fear of dying'. Fear was relatively low in the ranking of panic symptoms in PNES events, consistent perhaps with the high rates of alexithymia found in patients with PNES [42], as well as a more general difficulty in describing their ictal experiences [43], whereas shortness of breath and related symptoms were highly associated, which may reflect a specific function of hyperventilation. This contrasts with panic disorder in general, where fear symptoms, though not universal, are clearly endorsed by most [44].

Respiratory symptoms are very common in both spontaneous panic attacks and in panic disorder, and constitutes a hallmark of these conditions –[11] at least for most [44]. As voluntary hyperventilation has been used to induce non-epileptic events, review of hyperventilation studies in PNES is important, as it may be a crucial part of the pathogenesis of PNES events [40], perhaps on its own or as a symptom subset of panic attack. Our meta-analysis of hyperventilation for seizure induction suggests a moderate but consistent effect of voluntary hyperventilation in PNES induction. While there were differences in procedure for induction of seizures in the studies reviewed, the rates of induction were very similar, and there was consistent evidence of its greater effectiveness in inducing PNES over epileptic and spontaneous events. These results suggest a role in PNES event pathogenesis in these 'laboratory conditions' at least, if not 'in the wild', as they are definitively pre-ictal (though they extend to ictus in some cases). The studies of clinically observed hyperventilation would support a role in at least some patients, though the temporal relationship is again unclear. Nevertheless, not every PNES event (nor even a majority) can be successfully induced by hyperventilation, and clinically, it appears to be variably associated with semiology. If it has an aetiological role, on these data, it is only for a subgroup.

4.1. Limitations

This review has several limitations. Firstly, the studies did not report specifically at which stage the patients were at in their presentations of PNES; it is reasonable to conclude that the length of knowledge of diagnosis can contribute to habituation and dampen response to panic and hyperventilation, hence affecting the results. Secondly, while there are diagnostic criteria in DSM, there is no absolute biological demarcation by which panic disorder can be distinguished from other anxiety disorders. Future studies could exploit more objective, biological measures of panic or hyperventilation, particularly as the patient's subjective report is in question. Furthermore, this review did not include studies that explored the association between other anxiety disorders and PNES, and important data for review may have been missed. Many items in the Beck Anxiety inventory contain symptoms included in the DSM-5 classification of panic disorder, for example, and this questionnaire was used in several PNES studies that were not included in this review, as they did not meet our criteria. Thirdly, the papers were reviewed by only one member of this research team (AMI), and thus there was potential for bias in ratings. A team of reviewers along with a kappa agreement value would have

served to strengthen this study. Finally, the methodological quality of the studies in this review were mainly low to medium quality. The limitations of the source data may hence limit the impact of the review findings.

5. Conclusions

This review finds evidence for moderate prevalence of panic symptoms and panic disorder in PNES, although the reported rates of association vary. This could be due to several factors, including the period in which the symptoms were noted, the voluntary nature of patient self-report, and the quality of the reviewed studies themselves. Hyperventilation is an effective inducer of PNES events, with consistent rates of induction across studies. The mechanistic relevance of these findings are the subject of several theories, all open to further study.

Conflicts of interest and source of funding

None declared.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.seizure.2018.05.007.

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