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**PNES Epidemiology:**

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## **Structured abstract**

Psychogenic non-epileptic seizures (PNES) are clinically defined as events resembling epileptic seizures but presumed to be not conscious and an involuntary expression of emotional distress similar to panic attacks. Their neurobiological physiopathology is different. However, PNES-like states are recognized in some cultures as a cultural phenomenon.

PNES rank among the top three neuropsychiatric problems and are targeted by an International League Against Epilepsy Task Force that published in 2017 an actualization concerning PNES epidemiology renewing the interest concerning PNES. Studies concerning PNES are complicated: these patients are difficult to identify, and a have tendency to disengage from medical services after diagnosis.

The incidence and prevalence estimates in the literature are based on diagnoses from tertiary care epilepsy monitoring units, where approximately 20 to 40% of adult patients and 10 to 23% of children presenting with “drug-resistant epilepsy” are diagnosed with PNES, making the incidence of PNES to be 1.4–4.9 cases per 100,000 people per year and the prevalence range of 2–33/100,000. However, epilepsy can be associated with PNES with estimated comorbidity range from 5 to 50%.

75% of patients with PNES are young adult women. PNES are uncommon under 6 and after 50 years of age. The female predominance is classically not found in children, late-onset or intellectual disability (ID) subgroups (about 10% PNES patients). Psychiatric comorbidities such as anxiety, post traumatic stress disorders and history of trauma are frequent in PNES patients.

One recent change concerning the epidemiology of PNES is the awareness that this condition is present worldwide, and not only in western developed countries.

## **Highlights**

- 1) PNES epidemiology study is of growing interest after ILAE task force publication.
- 2) PNES are found worldwide and sometimes recognized as a cultural phenomenon.
- 3) New studies are warranted to improve PNES epidemiology knowledge worldwide.

## **Keywords**

PNES, depression, epilepsy, anxiety, epidemiology, functional disorder.

## INTRODUCTION

Psychogenic Non-Epileptic Seizures (PNES) are clinically defined as events resembling epileptic seizures but presumed to be not conscious and involuntary expression of emotional distress similar to panic attacks. They mimic epileptic seizures, but their neurobiological physiopathology is different. PNES are the most common type of conversion disorders or functional neurologic symptom disorders, both terms used interchangeably in the Diagnostic and Statistical Manual - Fifth Edition (DSM-5) (1). The Scottish Neurological Symptom study (2) stated that functional and psychological symptoms are the second most frequent referral symptom in neurology (after headache), PNES being the most frequent motive in this category.

The International League Against Epilepsy (ILAE) established that “gold standard” diagnosis of PNES is based on a history consistent with PNES and the recording of a typical event with semiological features of PNES such as resistance to eye opening but no epileptiform activity on the electroencephalogram (EEG) **before, during, or after** the ictus. The combination of a history, semiology, and video EEG findings consistent with PNES provides the level “**documented**” PNES (3).

It is estimated that 20–30% of patients referred to epilepsy centers with intractable seizures have been misdiagnosed with epilepsy. The vast majority of these patients are eventually diagnosed with PNES (4).

An international consensus clinical practice statement issued in 2011 (5) ranked PNES among the top three neuropsychiatric problems : Assessment and management of nonepileptic seizures and imitators of epilepsy was preceded by assessment and management of depressive disorders in epilepsy and assessment and management of concomitant anxiety disorders in epilepsy.

Followingly, an ILAE PNES Task Force published in 2017 an actualization concerning PNES epidemiology in adults and in patients subgroups, such as children, older adults, and those with intellectual disability (3). We searched PubMed central using the keywords “psychogenic non epileptic seizure”, “PNES”, “epidemiology” on August 27th, 2019. We obtained 122 results. We selected among the results reviews and studies in French or English that we considered of interest, concerning aspects of PNES epidemiology. We were careful that the methodology of PNES diagnosis in the selected papers used Video-EEG exploration.

## Findings

PNES epidemiology is a topic of growing interest. The most ancient publication we found dated from 1984. Between 1984 and 2009, there were less than 10 publications per year. This number increased in the last years with a maximum of 25 publications in 2018.

PNES are a topic of interest not only from the medical and caregiver point of view but also from the societal and economical health aspect. Studies concerning PNES **medico-economic consequences** report a heavy burden for healthcare systems and societies at large, as well as for affected individuals and their families (6). The lack of money for treatment concerns 70% and 50% of the low and middle-income countries respectively and is identified as one of the major hurdles to the diagnoses and treatment of PNES (7). In addition to the direct healthcare costs associated with PNES, indirect costs to patients and caregivers caused by loss of employment and reduced availability for household work have great societal impact (8). Several studies have found that direct healthcare costs decline following the diagnosis of PNES because of substantial reductions in healthcare resource utilization (9)(10).

The early reduction in healthcare use is often sustained over the longer term, although long-term employment outcomes do not seem favorable (11) (12).

Studying PNES epidemiology is complicated. One major recent improvement is the publication of clearly defined diagnostic criteria after ILAE interest in this domain, that allowed to harmonize PNES patient’s definition around the world.

PNES **diagnosis delay** from first seizure to definitive diagnosis of PNES is usually reported (13) (14)(15) (16) between 3 and 8,4 years. Two recent studies (15) (17) noticed that the presence of antiseizure medication is associated with longer diagnostic delay (odds ratio 6,1) and each anti-seizure medication trial extends this diagnostic delay. Younger age at onset and the presence of ictal injury (odds ratio 3,6) are also associated with longer diagnostic delay in PNES patients (17). This long diagnosis delays and a tendency for patients with PNES to disengage from medical services after diagnosis are two issues that make patients with PNES disorders difficult to identify, even in developed countries.

One limitation concerning PNES epidemiology, clearly underlined by ILAE, is the absence of well-resourced, formal population-based epidemiological studies. Most estimates of the **incidence and prevalence** in the literature are based on diagnoses from tertiary care epilepsy monitoring units (EMU), where approximately 20 to 40% of adult patients and approximately 10 to 23% of children presenting with “drug-resistant epilepsy” are diagnosed with PNES (18)(19) (20) (21). A study in Tanzania (22) observed a higher proportion with half the patients referred to a tertiary medical center with functional neurological disorders presenting PNES. A study by Salinsky et al. indicated that up to 25% of veterans entering epilepsy monitoring units were finally diagnosed with PNES (23).

The incidence of PNES has recently been determined to be 4.09/100,000 in a study based in the United Kingdom (24). Other studies estimated the incidence of PNES to be 1.4–4.9 cases per 100,000 people per year (25) (26).

Two prevalence estimates are suggested by ILAE (3): one based on the number of patients referred to epilepsy centers who are thought to have severe epilepsy but who turn out to have PNES. This solution yields a possible prevalence range of 2–33/100,000 (0.002–0.033%) (27).

The second one is based on the assumption of a similar long-term course for PNES and epilepsy and an extrapolation from incidence figures. Following this approach, an incidence figure of 5/100,000/year would yield an estimated prevalence of approximately 1/10 that of epilepsy, or 5/100,000.

There is a **predominance of female gender** among patients with PNES with a ratio classically considered of 3 to 1 in favor of women. This may vary as published in a recent study concerning 330 patients retrospectively included over 10 years (17), in which sex ratio was only 1,89 in favor of women. The female sex preponderance occurs after puberty but is also found in some pediatrics studies (28) and does not vary with the country development status ((7),(29) (30) (31). This sex ratio is also found in other conversion disorders such as functional movement disorders (32). Neurobiological, social and vulnerability differences may explain why PNES are predominantly seen in female gender (33)(34) (35) (36)(37) : many of the PNES risk factors are more common in women (1). Studies have reported differing but high rates of previous sexual abuse in women with PNES in Eastern and Western countries (38) (39) (21) (30). (33). Yet, one study comparing men and women with PNES found similar overall rates of psychiatric comorbidity between the two genders (40). Interestingly, another study using a personality profile evaluation showed worse emotional adjustment in men compared with women with PNES (41).

The clinical course of PNES in men and women may differ : a recent study including 41 video-EEG diagnosed PNES patients found that PNES started later in women compared to men (24,3 versus 17,5 years), with longer PNES episode duration in women (10 versus 2 minutes) and no gender specific difference in the semiologic expression of PNES (42).

PNES occur mainly in **young adults** (second and third decades) but are also reported **in children** (43). A recent study in Brazil (28) about 53 children aged between 7 to 17 with video-EEG documented PNES showed an average delay until referral of 17,76 month (elongating with an earlier age of onset), and a female predominance (60,4%). However, there is a lack of population-based data on the prevalence or incidence of PNES in the pediatric population.

Studies of children up to 12 years of age have identified the following patient characteristics:

- PNES have been reported from the age of 3 years but are uncommon under 6 years of age (44);

- Unlike in adults, there is no female predominance (45);
- Motor inhibition (dialeptic attacks) are more common than hyper-motor-type events (46) (47);
- A history of physical or sexual abuse is reported less commonly by pediatric than by adult patients (43);
- School phobia or difficulties in school (including bullying, specific learning difficulties, or unrealistic expectations) are the most common precipitating or perpetuating factors (43);
- A better outcome for children than for adults with PNES (48).

Concerning older patients, PNES are uncommon after the age of 50 years and little is known about patients with **late onset PNES**. In Duncan et al. (24) cohort, late onset PNES were more likely to be male, less likely to report history of sexual abuse and more likely to have severe physical health issues and to report health-related traumatic experiences. PNES semiology and mental health status seemed similar between early and late onset PNES.

**Psychiatric comorbidities** are very common in PNES, with estimates ranging between 53 and 100% of PNES patients with at least one comorbid psychiatric disorder (49).

When compared to patients with conversion disorders such as functional movement disorders (32), PNES patients have more anxiety disorders (56% versus 44%), and similar rates of mood disorders. Study using personality measure scales (such as the Personality Assessment inventory) (50)(51) have found significantly higher somatic, conversion, depressed, anxious and suicidal symptoms in PNES patients.

In comparison with epileptic patients, PNES patients have significantly elevated risks found for Post-Traumatic Stress Disorder (PTSD), personality disorder, and anxiety but not depression (52) but this result is not consistent in every study (53). In a recent review (53), considering only video EEG proven PNES and ES, Walsh et al. concluded that PNES patient's depression level was better explained by interpersonal factors whereas epileptic patient's depression level were influenced by illness related factors. When PNES are associated with depression (21% to 60% patients) (54), patients have lower level of functioning and worse quality of life (55) (56). The reduction in quality of



life experienced by people with PNES is well documented and is a major global public health issue (57).

**Traumatic life experiences in childhood or adulthood** are associated with PNES :

Adverse childhood experiences have been identified as a factor predisposing to the development of PNES in later life (58) (59). Childhood sexual abuse is reported between 5,9 to 84,6% PNES patients (PNES patients are three time more likely to report sexual abuse than controls) (59). In a study comparing subjects with epilepsy or PNES, using the 28-item brief screening version of the Childhood Trauma Questionnaire, the prevalence of childhood trauma was significantly higher (36% vs 16%) in PNES patients than epilepsy patients (60). Patients with PNES scored significantly higher across all childhood trauma domains, including emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect. Patients with PNES and a history of childhood repeated trauma have more frequent dissociative experiences and psychiatric comorbidities, with an association between their psychiatric symptoms and diagnosis criteria of complex PTSD (61).

Concerning trauma in adulthood, a review of 7 studies by Fiszman et al (38) indicated that 82,6% PNES patients report trauma in adult life (“general traumatic events other than abuse”) (38). Among veterans, in a retrospective study including 50 PNES confirmed patients, PTSD was the most frequent DSM-axis 1 diagnosis preceding admissions (58%), followed by depression (46%) and alcohol abuse. These axis 1 diagnosis were frequently associated in those patients (34% had all 3 diagnoses and 58% had at least 2). In addition, 36% patients had a personality disorder (62).

PNES clinical presentation is close from epileptic seizure. Video-EEG is key to differential diagnosis between those conditions. However, it is not unusual to find both epileptic seizure and PNES in a single patient : the **association of PNES and epilepsy** is not consistently reported in the literature, with estimates ranging from 5 to 50% (21) (27) (63) (64) (65) (66) (18) (67) (68). The criteria for diagnosis of concomitant epilepsy are not consistent among studies. Some considered interictal spikes sufficient to define epilepsy even if interictal epileptiform abnormalities have been reported in nonepileptic conditions (69) and even in normal people (67).

After temporal lobe epilepsy surgery, patients presenting with epileptic seizures and PNES improve in both (70), but rarely PNES occur de novo after epilepsy surgery (>5%).

A recent study from Wissel et al. (71) used video-EEG proven events to separate patients with combined epileptic (ES) and psychogenic nonepileptic seizures (PNES) and age- and gender-matched patients with ES-only and PNES-only. The study (138 patients) showed that in patients with PNES and ES, ES antedated PNES in 70% cases. The PNES-ES patients had higher depression and anxiety scores and had more often epileptic discharges originating the right hemisphere.

The proportion of patients with **PNES and comorbid intellectual disability (ID)** is similar to that of patients with PNES and additional epilepsy (i.e., about 10%) (72) (73). In a recent study (74) that focused on patients living at an epilepsy day-care facility in the Netherland, the prevalence of PNES in patients with ID was 7,1%.

One study focusing on patients with PNES and ID suggested differences from patients with PNES without ID : trend towards a male preponderance, relative paucity of antecedent sexual abuse, frequent episodes of psychogenic nonepileptic status, as well as a greater proportion of patients in whom situational or emotional triggers immediately preceding individual PNES were reported (75). Another study (74) showed that they had more depressive symptoms, experienced more negative life events and had more often an ID discrepancy (ID profile with one domain particularly more impaired than another).

Gates and Erdahl proposed “a reinforced behavior pattern” as a particularly important pathogenetic factor leading to PNES in patients with comorbid ID (76) (77).

Unfortunately, no other data are available about PNES in these specific subgroups from less highly developed regions of the world. (3)(78).

#### Discussion:

PNES is a chronic and not rare medical condition that implies long term care and follow-up.

Before PNES diagnosis criteria were clearly defined, PNES patients were mistakenly thought to have drug resistant epilepsy and were treated with anti-seizure medication (62). After ILAE interest in this

condition, our knowledges are increasing with numerous studies associating neurologists, psychiatrists, and epilepsy specialists located around the world.

The sex ratio in favor of women, the highest prevalence among young adults, the association with a history of trauma and psychiatric comorbidities is more and more established. Our knowledges concerning PNES in less frequent patients' subgroups such as children, older adults, or ID subjects improve slowly.

The better knowledge of PNES patients' characteristics improves our understanding of this condition. In a study that investigated and compared psychiatric features of 25 consecutive patients with PNES on the basis of presence of reported trauma, Hingray et al. (79) observed two different patients profiles : patients with trauma antecedents correlated with a high rate of psychiatric comorbidity and a strong dissociative mechanism. Patients without trauma had a weaker dissociative mechanism, lower female predominance, less psychiatric comorbidities, more frequent "frustration situations" as a factor triggering PNES and sick leaves as perpetuating factors. Another study observed 2 clusters of patients on the basis of differences concerning alexithymia and emotion regulation (80). Theoretical models are developed to increase the understanding of PNES (81).

One recent change concerning the epidemiology of PNES is the awareness that this condition is not present only in western developed countries but present worldwide, as suggested by some authors since 2000 (29)(30). In addition to presentations closely resembling those observed in western and other highly industrialized societies, PNES-like states are also recognized in some cultures around the world as a cultural phenomenon (82).

PNES repartition among a single country population can be heterogenous as in Georgia, where PNES are more frequent in the minority religions and ethnic groups (3)

ILAE publication encouraged studies describing PNES in several countries increasing our knowledge concerning PNES patients' care discrepancies : in Subsaharian Africa, diagnosis is more difficult due to the frequent lack of national healthcare and PNES diagnoses rely mostly on clinician expertise (22). But western countries findings are also found in other part of the world : in South Africa (83) a retrospective study comparing video-EEG diagnosed PNES and epilepsy patients showed a high rate

of initially misdiagnosed patients (50% epilepsy, 50% PNES), a female predominance, and a tendency toward overmedication with antiepileptic drugs in PNES patients.

The future challenge concerning PNES epidemiology study is the elaboration of well-resourced, formal epidemiological studies with strong methodology, issued from less highly developed regions of the world.

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