# A brief update on psychogenic non-epileptic seizures: a challenge to overcome

Massimiliano Beghi[1], Cesare Maria Cornaggia[2], Ettore Beghi[3]

[1] Department of Mental Health, AUSL Romagna, Ravenna, Italy
[2] School of Medicine and Surgery, University of Milano Bicocca, Milan, Italy
[3] Deparment of Neuroscience, Istituto di Ricerche Farmacologiche Mario Negri, Milano, Italy

Received January 13, 2020
Accepted for publication on-line March 9, 2020
Published on-line March 31, 2020

**Correspondence**
Ettore Beghi, MD
Laboratory of Neurological Disorders,
Istituto di Ricerche Farmacologiche Mario Negri IRCCS,
Via Mario Negri 2, 20156 Milan, Italy
Tel: +390239014542
Fax: +390239001916
email: ettore.beghi@marionegri.it
https://orcid.org/0000-0003-2542-0469

**SUMMARY**
Psychogenic Non-Epileptic Seizures (PNES) are defined by their semiological resemblance to Epileptic Seizures (ES), not associated with specific epileptic discharges in an ictal EEG. PNES are, in fact, a feature of an underlying psychiatric disorder even if these patients are currently in the realm of epileptologists and for these reasons there is a large degree of confusion underlying the diagnosis (with an average delay of 3 years) and management of PNES. Documented PNES diagnosis would require the attack captured on video EEG (vEEG), but often it is not possible. The video registration of a seizure seen by an expert would make PNES "probable". Conversational analysis has been demonstrated to be a very useful tool in the differential diagnosis between PNES and ES with a good rate of reliability. From a psychological point of view, PNES could be the same phenotype of different underlying mechanisms and, also for this reason, should consider these underlying processes and treatment could be sometimes seriously deficient. Many psychological approaches are anecdotally reported, but controlled studies are still lacking, and interventions still rely on clinicians' experience. Moreover, pharmacological treatment may be recommended in adults or elderly with concomitant anxiety or depression. In conclusion, many symptoms and signs are valid but none is pathognomonic, the symptoms should be reported correctly and psychiatrists should be necessarily involved for the correct diagnosis and management of PNES.

## PNES: A PUBLIC HEALTH ISSUE

Psychogenic Non-Epileptic Seizures (PNES) are defined by their semiological resemblance to Epileptic Seizures (ES) but are not associated with specific epileptic discharges in an ictal EEG (Asadi-Pooya and Sperling, 2015). Most PNES are thought to be non-volitional responses to internal or external triggers perceived as threatening or challenging (Asadi-Pooya and Sperling, 2015; Brown and Reuber, 2016).

The incidence of PNES has been found to be 1.4–4.9/100,000/year and the prevalence estimated as up to 33 per 100,000 population (Asadi-Pooya and Sperling, 2015). PNES are one of the most frequent and difficult differential diagnoses in epileptology.

Studies have shown that there is a large degree of confusion underlying the diagnosis and management of PNES, not only among patients and their families,

but also within primary care physicians (Carton et al., 2003; O'Sullivan et al., 2006). Moreover, most studies have focused on PNES as a clinical condition to be contrasted to ES (De Timary et al., 2003; Cragar et al., 2005; Asadi-Pooya and Sperling, 2015; Gale et al., 2015; Anderson et al., 2017), when in fact they can be simultaneously present even in people with ES, making it a further diagnostic challenge.

Also, for these reasons, the ascertainment and characterization of PNES remain, in most cases, complicated and the correct diagnosis is obtained with a significant delay. Factors associated with this delay seem to be the presence of head trauma (Asadi-Pooya and Tinker, 2017), age at the onset of seizures, seizure frequency, a history of ictal injury, having comorbid epilepsy, and taking antiepileptic drugs (AEDs) (Bahrami et al., 2019).

On the other hand, failure to recognize the functional nature of PNES is also responsible of a delay in starting the appropriate psychological or psychiatric approach and treatment (Bodde et al., 2009, 2012), with consequent worsening of patients' quality of life, as the majority of patients with PNES remain in care, with a diagnosis of ES, in secondary or tertiary centers for epilepsy (Bodde et al., 2012; Zhang et al., 2009).

This assistance "overload" is inadequate and not corresponding to the true diagnosis, and a correct psychiatric and/or psychological intervention is not provided correctly.

## PNES: AN ECONOMIC BURDEN

PNES carry significant direct and indirect costs: a recent study conducted in Denmark (Jennum et al., 2019) revealed that patients with PNES had a lower employment rate than did controls for equivalent periods up to three years before the diagnosis was made. The additional direct and indirect annual costs for those aged older than 18 years, were €33,697 per patient. In contrast, on the patients' side, receiving a diagnosis of PNES can be associated with loss of trust in the health services. However, the detection of PNES carries a decrease in neurology care and inpatient stays (Razvi et al., 2008), with consequent reduction in care costs. A review chart conducted in the United States (Michigan) (Ahmedani et al., 2013) found that in the year following PNES diagnosis, a decline in average visits (1.45) and costs ($1784) were observed.

A report from the International League Against Epilepsy Non-Epileptic Seizures Task Force (LaFrance et al., 2013) proposed a staged diagnostic approach, classifying PNES diagnosis in possible, probable, clinically established and documented. This has perhaps improved the diagnostic delay from 7 to 2–3 years.

Finally, as the prognosis of these patients, compared to those with ES, is often less favorable (Kanemoto et al., 2017), a longer dependence on diagnostic and therapeutic services is required.

## PNES: A DIAGNOSTIC CHALLENGE

Elements useful to the diagnosis consist of patient history and description of attacks, and if at all possible, an eyewitness description of events.

Chen et al. (2019) confirmed the importance of eyewitnesses' report for the differential diagnosis between PNES and ES, with good accuracy (improvement from 76% to 83%). If home-video recording is available to caregivers and relatives, it can help to convey a clearer picture of the seizures (Erba et al., 2016; Beghi et al., 2017). If video footage can be reviewed by a clinician expert in PNES, it most likely adds to the degree of certainty of a clinical diagnosis ("clinically established"). Not being able to observe the onset of the seizure or a clinician who lacks experience in ictal assessment of patients would make PNES "probable". Documented PNES would, therefore, require the attack captured on video EEG (vEEG) to be reviewed by the clinician, coupling the behavior with the electrophysiology, but this is very difficult to undertake if seizures are rare and vEEG is not available in the epilepsy center, especially in middle-low income countries where its use is very limited (Kanemoto et al., 2017).

A recent review did not find validated diagnostic criteria to help clinicians assessing patients in primary or emergency care settings to discriminate between syncope, epilepsy, PNES, or other type of attack (Asadi-Pooya et al., 2019). Performance may be improved by combining sets of criteria in a clinical decision rule, but no such rule has been validated prospectively against gold-standard diagnostic criteria. Moreover, clinical characteristics of PNES in adult patients show significant differences across countries (Asadi-Pooya et al., 2019).

Some authors tried to correlate PNES with neurophysiological data. Naganur et al. (2019) showed that the evolutionary pattern of the frequencies of rhythmic movement artifacts on EEG during PNES differs from that of ES. Convulsive PNES were demonstrated to display a characteristic pattern of rhythmic movement artifact that remains stable over time during the

event, whereas the EEG activity during convulsive ES tends to evolve throughout. Sensitivity and specificity for artifacts were respectively 92.7% and 75.0%. Dogan et al. (2017) tried to assess the clinical utility of serum lactate levels for the differentiation of generalized tonic-clonic seizures, PNES, and syncope. Serum lactate levels in patients with generalized tonic-clonic seizures were significantly higher than in the patients with PNES ($p<0.001$). However, values are lower or unknown for other seizure types.

Tyson et al. (2018) compared 72 patients with ES and 33 patients with PNES on various tests of cognitive ability and performance validity. The utility of psychometric methods of differential diagnosis is limited by the complex neurocognitive profiles associated with ES and PNES.

At last, according to the literature, conversational analysis has been demonstrated to be a very useful tool in the differential diagnosis between PNES and ES (Schoendienst et al., 1991; Cornaggia et al., 2012, 2016) since a significant difference in seizures' description has been shown in these two categories of subjects (Schwabe et al., 2007): patients with PNES repeat their extraneousness to the attack, refuse to reply, express amnesia, reconstruct the happening by referring to descriptions provided by witnesses, and often describe their attacks using the image of an internal entity of which they were victims. By contrast, patients with ES describe their attacks in as much detail as possible and try to reconstruct the experience as fully as they can, making an effort to describe their subjective symptoms, quantify the duration of the phases preceding and following the seizure, and use the image of an external entity overcoming them.

## PNES: HOW TO OVERCOME ALL ISSUES

Other interesting challenges in PNES involve the nosography, the etiology, the underlying mental processes that could help in both diagnosis and treatment. DSM-5 and ICD-10 put PNES in different categories (respectively in the category "Somatic Symptoms and Related Disorders" and in the category "Dissociative Disorders"). This dual classification is a source of confusion among epileptologists and psychiatrists; moreover, the underlying mental processes could differ significantly, even in the presence of the same semiology. In our previous publications, we tried to explain the defense mechanisms involved in the development of PNES (Beghi et al., 2015a) and the significant role of childhood trauma as a risk factor for PNES (Beghi et al., 2015b). PNES could be the same phenotype of different underlying mechanisms and, also for this reason, treatment could be sometimes seriously deficient and should consider the underlying processes (Beghi et al., 2019).

PNES are, in fact, a feature of an underlying psychiatric disorder even if these patients are currently in the care of epileptologists. There are two major reasons:

1. Epileptologists are asked to make the differential diagnosis, and
2. It is usually difficult for these patients to accept the diagnosis of a psychiatric disorder, so when receiving the diagnosis from an epileptologist, they tend to refer to another epileptologist to get a "misled" diagnosis of epilepsy (Cornaggia et al., 2017; Beghi et al., 2019).

The classification proposed by Magaudda et al. (2016) is based on the neurological aspects of the problem (i.e. the semiology of seizures) and divide the PNES in to four categories: Hypermotor, Akinetic, Focal Motor, and with Subjective Symptoms (SS).

The table 1 is a synthesis of the contribution of key signs and symptoms to a diagnosis of PNES or ES, even if none of them is pathognomonic for PNES.

## A CONSENSUS STATEMENT ON THE DIAGNOSIS AND TREATMENT OF PNES

A recently published Consensus Conference on the diagnosis and treatment of PNES represents a synthesis of the best available evidence (Gasparini et al., 2019). The document illustrates the opinion of the main Italian experts in the field. The absence of high-quality scientific evidence limits the strength of recommendations for many of the addressed topics. Even though most questions were formulated separately for children/adolescents and adults, no major differences in evidence and recommendations exist. Ictal vEEG can still be considered the gold standard for the diagnosis. Video recording alone may be sufficient for the detection of PNES with motor phenomena. No robust data exist on the role of single signs or symptoms in confirming or excluding PNES, as sensitivity and specificity are generally suboptimal. Prolactin and creatinkinase are reliable serum biomarkers, as normal values within a few hours after an episode may help confirm the diagnosis of PNES. However, the sole normality of these levels does not exclude the diagnosis of ES. Many psychiatric conditions are common in people with PNES, including depression, anxiety, post-traumatic stress disorders,

**Table 1.** Frequency of key symptoms and signs in PNES vs ES

| | **PNES** | **ES** |
|---|---|---|
| **Etiology** | **Psychic** | **Organic** |
| Interictal EEG | Normal | Normal/with epileptiform abnormalities |
| Seizure length | Usually > 2 minutes | Usually < 2 minutes |
| Onset | Often gradual<br>EEG patterns are only in wakefulness | Usually sudden<br>Some patients describe altered sensations for a long time before the episode<br>Wakefulness/sleep |
| Frequency | Variable | Parossistic/in cluster |
| Triggers (light, noise) | Occasionally | Rarely |
| Aura | Variable | Variable |
| Seizures' place | Mostly at home | Everywhere |
| Witnesses | Yes | Variable |
| Seizures' pattern | Variable | Stereotyped |
| Rolling motor activity | Common | Very rare |
| Asyncronous movements of limbs | Common | Rare |
| Finalized movements | Occasional | Very rare |
| Rhythmic pelvic movements | Occasional | Rare |
| Opisthotonus, ("arc de circle") | Occasional | Very rare |
| Side to side movements | Common | Rare |
| Tongue biting (tip) | Occasional | Rare |
| Tongue biting (sides) | Rare | Common |
| Prolonged ictal atonia | Occasional | Very rare |
| Shout | Ictal phase (with dramatic, mystic or obscene content) with crying and sobs | At the big inning, with grunts, along with clonic movements |
| Mouth closure in tonic phase | Occasional | Very rare |
| Eyelid closure | Very common | Rare |
| Resistance to eyelid opening | Very common | Rare |
| Babinski sign | Negative | Positive if convulsions are present |
| Pupil reflex to light stimuli | Maintained | Usually absent |
| Reactivity while unconscious | Occasional | Very rare |
| Cianosis | Usually absent | Usually present |
| Post-ictal confusion | Rare | Common |
| Seizure induction | Triggering | None |
| Postictal stupor | Rare | Frequent |
| Urine or feces loss | Reported (more rarely) | Reported |
| Postictal amnesia | Variable | Usual |
| Seizure remembering under hypnosis | Yes | No |
| Effect of hypnosis | High | Mean |
| Injuries | Rare | Minor, frequent |

PNES – Psychogenic Non-Epileptic Seizures
ES – Epileptic Seizures

personality disorders, but none is pathognomonic, since prevalence in persons with PNES is not significantly different from persons with epilepsy. Many psychological approaches are anecdotally reported, but controlled studies are lacking and interventions still rely on clinicians' experience. Moreover, pharmacological treatment may be recommended in adults or elderly with concomitant anxiety or depression. Reports are conflicting on the ethical aspects of PNES management.

## UNANSWERED QUESTIONS AND FUTURE DIRECTIONS

There are 3 unanswered questions:

1. Since the symptoms and signs reported in the Table are all valid but none is pathognomonic, is it possible to include the variables with the best discriminatory power in a questionnaire that could weight every variable?
2. Are the seizures reported with valid diagnostic instruments (vEEG, video recording, etc)?
3. How the specific scientific background of the physician in charge (epileptologist, psychiatrist) matters for the correct management of PNES?

A critical appraisal of published reports (Giussani et al., 2020) emphasizes the importance of taking into consideration not only the presence (or absence) of certain symptoms and signs but also their association. The variety of methodologies and testing procedures reported in the literature has led to fragmentation of findings. There is a need to consolidate previous experiences in one comprehensive instrument easily available in resource-poor settings and accessible to lay people for self-reporting. Ideally, a structured questionnaire for patients should reflect the complex mosaic of individual features (historical, developmental, psychosocial and environmental) with particular attention to the risk factors, the personality and behavioral traits investigated in patients with PNES, ES and both. Instead, a questionnaire for eyewitnesses should inquire about concrete features of the event semiology. Though eyewitnesses are limited in their recall of the event details, some of these features are easily noticeable and may represent key elements in the differential diagnosis. In both cases, questions should be formulated in clear, direct, and intuitive format. Future research calls for validating these instruments prospectively in a multicenter study with a large cohort of patients whose diagnosis is well documented. Such a study has been recently planned and will be concluded in the forthcoming months.

## CONFLICT OF INTERESTS

Massimiliano Beghi and Cesare Cornaggia have nothing to disclose. Ettore Beghi reports grants from Italian Ministry of Health, grants from SOBI, personal fees from Arvelle Therapeutics, outside the submitted work.

## REFERENCES

**Ahmedani B.K., Osborne J., Nerenz D.R., Haque S., Pietrantoni L., Mahone D. et al.:** *Diagnosis, costs, and utilization for psychogenic non-epileptic seizures in a US health care setting*. Psychosomatics, 2013, 54: 28–34.

**Anderson D.G., Damianova M., Hanekom S., Lucas M.:** *A comparative retrospective exploration of the profiles of patients in South Africa diagnosed with epileptic and psychogenic non-epileptic seizures*. Epilepsy Behav., 2017, 69: 37–43.

**Asadi-Pooya A.A., Myers L., Valente K., Restrepo A.D., D'Alessio L., Sawchuk T. et al.:** *Sex differences in demographic and clinical characteristics of psychogenic nonepileptic seizures: A retrospective multicenter international study*. Epilepsy Behav., 2019, 97: 154–157.

**Asadi-Pooya A.A., Tinker J.:** *Delay in diagnosis of psychogenic nonepileptic seizures in adults: a post hoc study*. Epilepsy Behav., 2017, 75: 143–145.

**Asadi-Pooya A.A., Sperling M.R.:** *Epidemiology of psychogenic non-epileptic seizures*. Epilepsy Behav., 2015, 46: 60–65.

**Beghi M., Negrini P.B., Perin C., Peroni F., Magaudda A., Cerri C., Cornaggia CM.:** *Psychogenic non-epileptic seizures: so-called psychiatric comorbidity and underlying defense mechanisms*. Neuropsychiatr. Dis. Treat., 2015, 30: 2519–2527.

**Beghi M., Cornaggia I., Magaudda A., Perin C., Peroni F., Cornaggia C.M.:** *Childhood trauma and psychogenic nonepileptic seizures: A review of findings with speculations on the underlying mechanisms*. Epilepsy Behav., 2015, 52: 169–173.

**Beghi M., Erba G., Cornaggia C.M., Giussani G., Bianchi E., Porro G. et al.:** *Engaging psychiatrists in the diagnosis of psychogenic nonepileptic seizures. What can they contribute?* Seizure, 2017, 52: 182–187.

**Beghi M., Cornaggia C.M., Beghi E., LaFrance W.C. Jr.:** *Is drug treatment of psychogenic nonepileptic seizures effective? Epilepsy Behav*., 2019, 98: 288–289.

**Bodde N.M.G., Brooks J.L., Baker G., Boon J.M., Hendriksen J.G.M., Mulder O. et al.:** *Psychogenic non-epileptic seizures –definition, etiology, treatment and prognostic issues: a critical review*. Seizure, 2009, 18: 543–553.

**Bodde N.M., Lazeron R.H., Wirken J.M., van der Kruijs S.J., Aldenkamp A.P., Boon P.A.:** *Patients with psychogenic non-epileptic seizures referred to a tertiary epilepsy centre: patient characteristics in relation to diagnostic delay*. Clin. Neurol. Neurosurg., 2012, 114: 217–222.

**Brown R.J., Reuber M.:** *Towards an integrative theory of psychogenic non-epileptic seizures (PNES)*. Clin. Psychol. Rev., 2016, 47: 55–70.

**Carton S., Thompson P., Duncan J.:** *Non-epileptic seizures: patients' understanding and reaction to the diagnosis and impact on outcome*. Seizure, 2003, 12: 287–294.

**Chen M., Jamnadas-Khoda J., Broadhurst M., Wall M., Grünewald R., Howell S.J.L. et al.:** *Value of witness observations in the differential diagnosis of transient loss of consciousness*. Neurology, 2019, 26: e895–e904.

**Cornaggia C.M., Di Rosa G., Polita M., Magaudda A., Perin C., Beghi M.:** *Conversation analysis in the differentiation of psychogenic nonepileptic and epileptic seizures in pediatric and adolescent settings*. Epilepsy Behav., 2016, 62: 231–238.

**Cornaggia C.M., Gugliotta S.C., Magaudda A., Alfa R., Beghi M., Polita M.:** *Conversation analysis in the differential diagnosis of Italian patients with epileptic or psychogenic non-epileptic seizures: a blind prospective study*. Epilepsy Behav., 2012, 25: 598–604.

**Cornaggia C.M., Beghi M., Beghi E.:** *Why talking about psychiatric comorbidity in PNES?* Epilepsy Behav., 2017, 75: 276.

**Cragar D.E., Berry D.T.R., Schmitt F.A., Fakhoury T.A.:** *Cluster analysis of normal personality traits in patients with psychogenic nonepileptic seizures*. Epilepsy Behav., 2005, 6: 593–600.

**De Timary P., Fouchet P., Sylin M., Indriets J.P., De Barsy T., Lefèbvre A. et al.:** *Nonepileptic seizures: delayed diagnosis in patients presenting with electroencephalographic (EEG) or clinical signs of epileptic seizures*. Seizure, 2002, 11: 193–197.

**Doğan E.A., Ünal A., Ünal A., Erdoğan Ç.:** *Clinical utility of serum lactate levels for differential diagnosis of generalized tonic-clonic seizures from psychogenic nonepileptic seizures and syncope*. Epilepsy Behav., 2017, 75: 13–17.

**Erba G., Giussani G., Juersivich A., Magaudda A., Chiesa V., Laganà A. et al.:** *The semiology of psychogenic nonepileptic seizures revisited: Can video alone predict the diagnosis? Preliminary data from a prospective feasibility study*. Epilepsia, 2016, 57: 777–785.

**Gale S.D., Hill S.W., Pearson C.:** *Seizure semiology in males with psychogenic nonepileptic seizures is associated with somatic complaints*. Epilepsy Res., 2015, 115: 153–157.

**Gasparini S., Beghi E., Ferlazzo E., Beghi M., Belcastro V., Biermann K.P. et al.:** *Management of psychogenic non-epileptic seizures: a multidisciplinary approach*. Eur. J. Neurol., 2019, 26: e205–e215.

**Giussani G., Erba G., Bianchi E., Beghi E.:** *Self-report quetionnaires for the diagnosis of psychogenic non-epileptic seizures in clinical practice. A comprehensive review of the available instruments*. Seizure, 2020 (in press).

**Jennum P., Ibsen R., Kjellberg J.:** *Welfare consequences for people diagnosed with nonepileptic seizures: A matched nationwide study in Denmark*. Epilepsy Behav., 2019, 98: 59–65.

**Kanemoto K., LaFrance W.C. Jr, Duncan R., Gigineishvili D., Park S.P., Tadokoro Y. et al.:** *PNES around the world: Where we are now and how we can close the diagnosis and treatment gaps-an ILAE PNES Task Force report*. Epilepsia Open., 2017, 23: 307–316.

**LaFrance W.C. Jr, Baker G.A., Duncan R., Goldstein L.H., Reuber M.:** *Minimum requirements for the diagnosis of psychogenic nonepileptic seizures: a staged approach: a report from the International League Against Epilepsy Nonepileptic Seizures Task Force*. Epilepsia, 2013, 54: 2005–2018.

**Magaudda A., Laganà A., Calamuneri A., Brizzi T., Scalera C., Beghi M. et al.:** *Validation of a novel classification model of psychogenic nonepileptic seizures by video-EEG analysis and a machine learning approach*. Epilepsy Behav., 2016, 60: 197–201.

**Naganur V.D., Kusmakar S., Chen Z., Palaniswami M.S., Kwan P., O'Brien T.J.:** *The utility of an automated and ambulatory device for detecting and differentiating epileptic and psychogenic non-epileptic seizures*. Epilepsia Open, 2019, 4: 309–317.

**O'Sullivan S., Sweeney B., McNamara B.:** *The opinion of the general practitioner toward clinical management of patients with psychogenic nonepileptic seizures*. Epilepsy Behav., 2006, 8: 256–260.

**Razvi S., Mulhern S., Duncan R.:** *Newly diagnosed psychogenic nonepileptic seizures: health care demand prior to and following diagnosis at a first seizure clinic*. Epilepsy Behav., 2012, 23: 7–9.

**Schoendienst M., Guelich E.:** *Das ist unheimlich schwer zu beschreiben: Formulierungsmuster in Krankheitsbeschreibungen anfallskranker Patienten: Differential diagnostische und therapeutische Aspekte*. Psychother. Sozialwissensc., 1991, 1: 199–227.

**Schwabe M., Howell S.J., Reuber M.:** *Differential diagnosis of seizure disorders: a conversation analytic approach*. Soc. Sci. Med., 2007, 65: 712–724.

**Tyson B.T., Baker S., Greenacre M., Kent K.J., Lichtenstein J.D., Sabelli A., Erdodi L.A.:** *Differentiating epilepsy from psychogenic nonepileptic seizures using neuropsychological test data*. Epilepsy Behav., 2018, 87: 39–45.

**Zhang Y.C., Bromfield E.B., Hurwitz S., Nelson A., Sylvia K., Dworetzky B.:** *Comparison of outcomes of video/EEG monitoring between patients with epileptic seizures and those with psychogenic nonepileptic seizures*. Epilepsy Behav., 2009, 15: 303–307.