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Psychogenic Nonepileptic Seizures in Patients Living with Neurocysticercosis

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<http://dx.doi.org/10.5772/intechopen.74243>

Abstract

Very little is known about psychogenic nonepileptic seizures (PNES) in patients with cysticercosis in the brain. We review the available medical literature on PNES in patients with neurocysticercosis and found no reports on this matter apart from our publications. Based on our previous experiences with patients presenting neurocysticercosis and associated epileptic seizures and/or PNES, we compared our results with the current advances published up to date. We also discuss the available information about epidemiology including frequency and prevalence, the role of sexual abuse on the ethiopathogenesis of PNES, clinical diagnosis and its differential diagnosis, laboratory investigations and video electroencephalogram, methods to induce PNES, medical treatment, and psychological intervention.

Keywords: psychogenic nonepileptic seizures, epileptic seizures, epilepsy, neurocysticercosis, epidemiology, diagnosis, video electroencephalogram, treatment and ethical aspects

1. Introduction

Neurocysticercosis (NCC) is a parasitic disease of central nervous system (CNS) caused by the larval stage (cysticercus cellulosae) of the pig tapeworm *Taenia solium*. This parasite is the most common helminthes to produce CNS infection in humans. The presence of acquired epilepsy in a person from an endemic region for cysticercosis or even in one living in close contact with patient who have taeniasis should suggest a diagnosis of cysticercosis of the CNS; the NCC

may remain asymptomatic for months to years, and sometimes its diagnosis is made incidentally when CT/MRI scan is done. Symptoms and signs are related both to the parasite and to the inflammatory-immunological response of the host but in almost all symptomatic patients, headache and epileptic seizure (ES) are the most frequent problem. NCC is the most common cause of acquired epilepsy worldwide and most of the patients taking first line antiepileptic drugs (AED) respond very well [1]. For interested people, other aspects concerning to NCC are available online [2].

NCC is a common parasitic disease of the brain in developing countries. The clinical and pathologic features of NCC vary depending on the inflammatory/immune response around cysticerci, their number, size, and localization. Inflammation around degenerating cysticerci may have severe consequences, including focal encephalitis, edema, and vasculitis. NCC can cause a wide variety of clinical syndromes from chronic meningitis and cranial nerve palsy to spinal infarction and symptoms due to either as mass effect or, particularly in racemose disease, raised intracranial pressure.

Almost all patients living neurocysticercosis (PLNCC) have epileptic seizures (ES) due to this zoonotic parasitic infection [2]. However, an important number of those epileptic patients also present psychogenic nonepileptic seizures (PNES) because epileptic and nonepileptic seizures are not mutually exclusive phenomena and may coexist in the same patient. PNESs are defined as change in behavior or consciousness resembling epileptic seizures but which have a psychological origin. PNESs are categorized as a manifestation of dissociative or somatoform (conversion) disorders. Predisposing, precipitating, and perpetuating factors should be carefully assessed individually. The complex process of communicating the diagnosis to patients and their relatives using a multidisciplinary approach is an important and effective therapeutic step than should be performed by good skilled physician. Video-EEG (vEEG) recording of an event is the gold standard for diagnosis [3], but in many developing countries where NCC is endemic, this technology is not available.

To distinguish ES from PNES, an accurate clinical assessment is mandatory apart from other technologies. Frontal lobe seizures can be mistaken for PNES, though these tend to have shorter duration, stereotyped patterns of movements, and occurrence during sleep in spite of vEEG technology. Sometimes, elevated blood levels of serum prolactin following most tonic-clonic or complex partial ES can support a diagnosis, but because the frequency is false positive, it is not a gold standard test. The psychological mechanisms underlying PNES are poorly understood, and there is a lack of well-established, evidence-based treatments [4].

To differentiate PNES from ES in PLNCC is an important challenge for neurologists, epileptologists, internists, and pediatricians but even more for general practitioners and family doctors. PNESs, also known as nonepileptic attack disorders, are events resembling an epileptic seizure but without the characteristic electroencephalographic anomalies associated with epileptic seizures. They are common in neurological settings and often associated with considerable distress and disability.

Brown and Markus described PNES (nineteenth century), as *seizure-like attacks not related to an identified central nervous system lesion*, and are currently classified as a conversion disorder,

according to the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) [4]. While a universally accepted and unifying etiological model does not yet exist, several risk factors have been identified. Management of PNES should be based on multidisciplinary collaboration, focusing on modifiable risk factors. The first priority in the management of PNES is patient engagement that is challenging given the demonstrated low rates of treatment retention [4]. The differential diagnosis of PNES firstly involves ruling out epilepsy as the cause of the seizure episodes, along with other organic causes of nonepileptic seizures, such as syncope, migraine, vertigo, stroke, faking ES, and malingering.

Are psychogenic nonepileptic seizures just another symptom of conversion disorder?

Some authors argue that the etiological and mechanistic distinctions they support, particularly when bolstered by additional data, give reason to sustain a separation between these conditions [5].

In 2003, an international consensus group of clinician-researchers in epilepsy, neurology, neuropsychology, and neuropsychiatry from the International League Against Epilepsy Nonepileptic Seizure Task Group collaborated with the aim of developing clear guidance on standards for the diagnosis of PNES. Because the gold standard of vEEG is not available in many countries, and for every patient, the group delineated a staged approach to PNES diagnosis. Using a consensus review of the literature, this group evaluated key diagnostic approaches. These included history, EEG, ambulatory EEG, vEEG/monitoring, neurophysiologic, neurohumoral, neuroimaging, neuropsychological testing, hypnosis, and conversation analysis. Levels of diagnostic certainty are developed including possible, probable, clinically established, and documented diagnosis, based on the availability of history, witnessed event, and investigations, including vEEG. The aim and hope of this report are to provide greater clarity about the process and certainty of the diagnosis of PNES, with the intent to improve the care for people with epilepsy and PNES [6].

There is no general scientific consensus as to what causes PNES. However, some physicians [7] *believe that the condition may be triggered by psychological problems (irrespective of whether the patient shows any obvious psychological distress or pathology). It is estimated that 20% of seizure patients seen at specialist epilepsy clinics have PNES.*

Other author [8] *believes that PNES can significantly affect an individual's quality of life, the health care system, and even society. The first decade of the new millennium has seen renewed interest in this condition, but etiological understanding and evidence-based treatment availability remain limited. After the diagnosis of PNES is established, the first therapeutic step includes a presentation of the diagnosis that facilitates engagement in treatment.*

To date, only very narrow aspects of ethical dilemmas in PNES have been explored, but without doubt, the most important ethical values at stake include trust, transparency, confidentiality, professionalism, autonomy of all stakeholders, and justice.

Recently, Gul and Ahmad [9] "demonstrated cognitive impairment in terms of the interrupted ability to switch between emotion and non-emotion face categorizations in patients with PNES. In contrast, healthy individuals exhibited efficient switching between these face categorizations. They also found in patients with PNES, an asymmetric relationship between

emotion and age tasks, while this asymmetry was absent in the healthy group. Their results demonstrated that patients with PNES used expressive suppression to regulate their emotions more frequently than the control group and on the other hand, patients with PNES less frequently reappraised their cognitions than healthy individuals. This is the first study demonstrating the presence of switching deficits in terms of inferior cognitive control of emotion in patients with PNES as compared to healthy individuals”.

PNESs are relatively common, accounting for 5–40% of visits to tertiary epilepsy centers. Inpatient vEEG monitoring is the gold standard for diagnosis as mentioned before, but additional positive predictive tools are necessary given vEEG’s relatively scarce availability. Robbins et al. [10] investigated if the number of patient-reported allergies distinguishes between PNES and epilepsy, using electronic medical records, ICD-9 codes, and text-identification algorithms to search EEG reports, and they identified 905 cases of confirmed PNES and 5187 controls with epilepsy but no PNES. Patients with PNES averaged more self-reported allergies than patients with epilepsy alone (1.93 vs. 1.00, $p < 0.001$). They concluded that “long allergy lists may help identify patients with PNES and hypothesize that a tendency to inaccurately self-report allergies reflects a maladaptive externalization of psychologic distress and that a similar mechanism may be responsible for PNES in some patients with somatic symptom disorder”.

Many patients with PNES dismiss the idea that their seizures are psychogenic, especially if the correct diagnosis comes after many years of treatment for epilepsy [11].

Outcomes in PNES are generally poor: 71% of PNES patients continue to have seizures 4 years after diagnosis and 56% are dependent on Social Security assistance. Neurologic and psychiatric factors associated with poor outcome include:

- history of epilepsy
- abnormal MRI
- presence of a psychiatric diagnosis
- age > 30
- duration of illness (the longer the patient has been treated for epilepsy, the worse the prognosis) [11].

In Diagnostic and Statistical Manual of Mental Disorders, fifth edition, “PNES do not have a unique classification as they can be found within different categories: conversion, dissociative, and somatization disorders. The ICD-10, instead, considers PNES within dissociative disorders, merging the dissociative disorders and conversion disorders, although the underlying defense mechanisms are different” [12].

Last year, some authors conducted 140 empirical studies on the following aspects of PNES: life adversity, dissociation, anxiety, suggestibility, attention dysfunction, family/relationship problems, insecure attachment, defense mechanisms, somatization/conversion, coping, emotion regulation, alexithymia, emotional processing, symptom modeling, learning, and expectancy, and they concluded that:

“physical symptom reporting is elevated in patients with PNES; trait dissociation and exposure to traumatic events are common but not inevitable correlates of PNES; also, concluded that there is a mismatch between subjective reports of anxiety and physical arousal during PNES; and inconsistent findings in this area are likely to be attributable to the heterogeneity of patients with PNES” [4].

The main goal of this chapter is to compare our finding from 2003 with recent investigation on PNES to identify new knowledge and challenges.

1.1. Our study

In 2003, we studied 32 rural patients from the poorest regions in Mthatha (South Africa), diagnosed as epilepsy due to NCC presenting PNES. We found that the common clinical characteristics of this series and its psychological profile were duration of events, history of sexual abuse in females, absent of focal neurological signs, vocalization in the middle of the seizures, and lack of postictal symptoms were very useful for its differential diagnosis and the possible difference between the clinical features and psychological profile of those patients and others without PNES. Finally, some advices for the management of this condition by family doctors were delivered [13].

As mentioned [14–16], PNES are sudden changes in behavior that resemble epileptic attack but lack organic cause and are also known by conversion seizures, dissociative seizures, hysterical seizures, psychogenic seizures, and nonepileptic seizures. They are quite often misdiagnosed and represent the opposite end of the spectrum from seizures that mimic psychiatric disorders without organic cause and an expected EEG changes. Accurately distinguishing PNES from EP and other illnesses is difficult because of the breadth and overlap of symptoms seen in each condition and the frequent co-occurrence of PNES and epilepsy [14].

There is a general consensus about subjects with PNES that exhibited trauma-related profiles which differed significantly from those of epileptic comparison subjects and closely resembled those of individuals with a past medical history of traumatic experiences [15–17]. As we published, PNES patients frequently report a history of physical and sexual abuse, and traumatic experience is considered part of the mechanism for producing dissociation and may be a manifestation of dissociative disorders, especially when a history of sexual or physical abuse is documented [18]. In our region, sexual abuse is more frequently seen among members of the same family.

At the present moment, there exists a controversy regarding the significance of dissociation and conversion in the pathogenesis of PNES. Soon after the elimination of the term “hysterical neurosis” from the current diagnostic systems, these kinds of seizures were diagnosed as either Dissociative Disorders (ICD-10) or in the DSM IV as Somatoform disorder, most often conversion type.

“The significantly higher incidence of dissociation in the patients with PNES suggests dissociation in the pathogenesis of these seizures” [13].

Significant advances have been made in the diagnosis and treatment of epilepsy before 2003. With the introduction of vEEG monitoring, physicians are now able to reliably differentiate epilepsy from other conditions that can mimic it, including PNES. Many new AEDs have become available in recent years. The ketogenic diet is another treatment option in certain types of epilepsy and the vagus nerve stimulator, approved in 1997, represents another treatment modality for refractory epilepsy, and finally epilepsy surgery is an effective treatment for those patients with uncontrolled epilepsy.

Our study was performed at the former Transkei which was one of the three administrative authorities of the so-called independent South African homelands (Ciskei, Transkei, and the Cape Provincial Administration under different apartheid governments). It is currently named as region D and E of Eastern Cape Province, and it is also one of the poorest region of the country. That region serves as a labor reservoir for other wealthier provinces, with men leaving behind women and children, while they seek and find employment elsewhere. Our region has the most elevate indices of poverty and underdevelopment and shows a remarkable limited access to employment, cash income, primary education, safe and clean water, proper toilet facilities, proper refuse disposal, electricity, and telecommunication. Some communities still do not have easy access to any health care facility.

The aim of this study was to identify a psychological profile of a group of patients with epilepsy NCC-related presenting PNES and to detect the possible difference between the clinical features and psychological profile of patients affected by PNES and ES NCC-related and those patients in whom EPs are associated with NCC only and have been reported earlier [19–25].

We included female and male patients [13]. In this region, people beyond age of 13 are considered as adults. Therefore, people aged 13 years and older who had all developed EP fulfilling the International League Against Epilepsy criteria for epilepsy and the radiological criteria for calcified NCC (considering multiples intraparenchymal calcifications measuring between 2 and 10 mm in patients from endemic regions as pathognomonic) were selected, and others experienced more than one attack of PNES per month. Patients were excluded due to the following reasons: seizures caused by clear precipitants such as alcohol or hypoglycemia; we also excluded patients with previous medical history of head injury, syncope, stroke, brain tumor, cortical dysplasia, hyponatremia, hypomagnesaemia, hyperparathyroidism, cardiac arrhythmias, heart failure, and history of medication taken on the past 6 months such as theophylline, meperidine hydrochloride, isoniazid, antipsychotic drugs, alkylating agent, beta-lactam antibiotics, tricycle antidepressants, acyclovir, beta-blockers, and decongestants; also pregnant or breastfeeding women and patients with any medical condition that might interfere with the interpretation of the results of this study. At screening, all patients had a physical examination, including a detailed neurological examination done by one of us (FSH), routine laboratory test including hematology, urinalysis, urea, and electrolytes, glucose, plain skull X-rays, CT scan of the head, and a 32-channel digital EEG (Nihon Khoden) for 30 minutes recording using opening and closing the eyes and 3 minutes hyperventilation as activating maneuver.

Seven patients presented PNES that we could not distinguish clinically from EP; therefore, their anticonvulsant medication was rapidly tapered to provoke seizure; if the seizure did not develop, other serial maneuvers including 24 hours' sleep deprivation followed by

hyperventilation and suggestion with intravenous saline injection were done. Diagnosis of PNES was considered when their seizures did not change the background EEG activity under observation plus others clinical features of PNES. All patients granted written informed consent before entering the study [13].

All patients presented radiographic signs of active and/or calcified NCC on CT scan (**Figure 1**), and signs of other stage of the parasite were also observed but the predominant finding was no less than five calcified lesions fulfilling the radiographic criteria for calcified NCC at the brain parenchyma. In this series, 37% of patients (all women) were on disability grant program for epilepsy, and that cash income was the only way for alleviating their requirements and poverty; however, evidence of malingering on this group was not be identified [13].

About 85% of the studied female patients were single mothers or married women living alone with their children, while their husband was working in gold mines very far away from home and only contact between them happened on December every year.

A total of 17 female patients from our series complained of a previous history of sexual abuse, and 14 of them physical abuse as well. Members of their own family raped 10 women, and 11 mentioned other members of their families that have had been raped during their early youth. According to information obtained from this group, some families suffered deeply when one of their members was raped and six people (not included in this series) were also murdered. Usually their father or the mother became chronically depressed, alcoholic, and their socio-economic situation became remarkably deteriorated; for five patients to talk about this topic was rejected, and each refused to accept psychiatry or psychological referral because of financial or

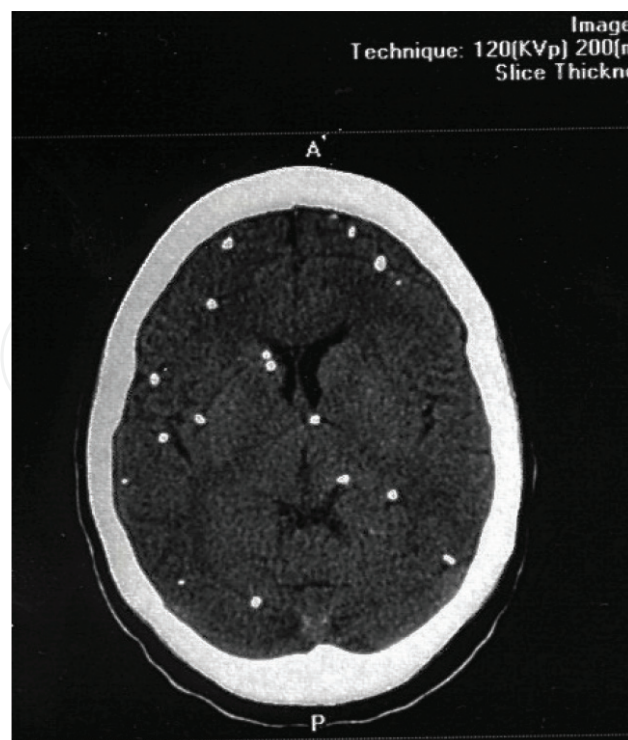


Figure 1. Bilateral calcified NCC lesions on CT scan of the brain.

transportation’s problems (25%) because they did not consider it necessary (18%) or for other reasons. About 38% got injuries on both group including tongue biting [13].

Maximal duration of tonic-clonic ES was 95 seconds and for PNES was 904 seconds, and minimal duration was 45 seconds for EP and 18 seconds for PNES. See **Table 1**.

Psychic manifestations were present in different group: frontal lobe epilepsy (FLE), tonic-clonic generalized (TCG), partial complex motor seizure (PCS), and PNES: Rocking: PNES = 47, FLE = 63; PCS = 18, TCG = 5; Kicking: PNES = 60, FLE = 75, PCS = 21, TCG = 0; Cursing PNES = 54, FLE = 35, PCS = 47, TCG = 0; Babinski: PNES = 0, FLE = 65, PCS = 76, TCG = 83; Pelvic thrusting: PNES = 57, FLE = 0, PCS = 63, and TCG = 5; and other dissociative symptoms of depersonalization and deserialization were present only in patients with PCS/PNES (see **Tables 2** and **3**).

No changes of the background activity on the EEG during provocative saline infusion and the occurrence of PNES were seen.

In general, patients complained of PNES revealed higher percentage of Somatoform Disorders and Cluster B Personality Disorders. The occurrence of PNES mimicking generalized tonic-clonic ES was documented only on illiterate peoples.

Three patients complained of auditory hallucinations, two had focal complex motor seizures as well, and the third one presented TCG seizures and paranoid schizophrenia; all presented calcified NCC on the basal ganglia without active or calcified lesion of NCC on the temporal lobe. EEG under provocative saline solution done in two patients did not show changes on the background activity during the test (**Figure 2**).

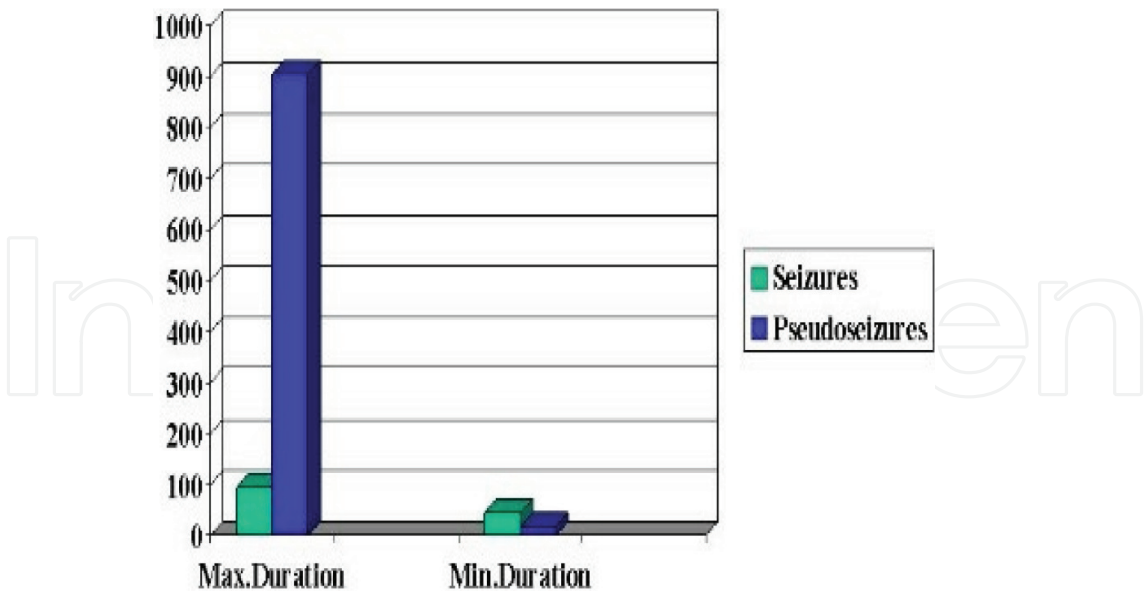


Table 1. Duration of the events in seconds.

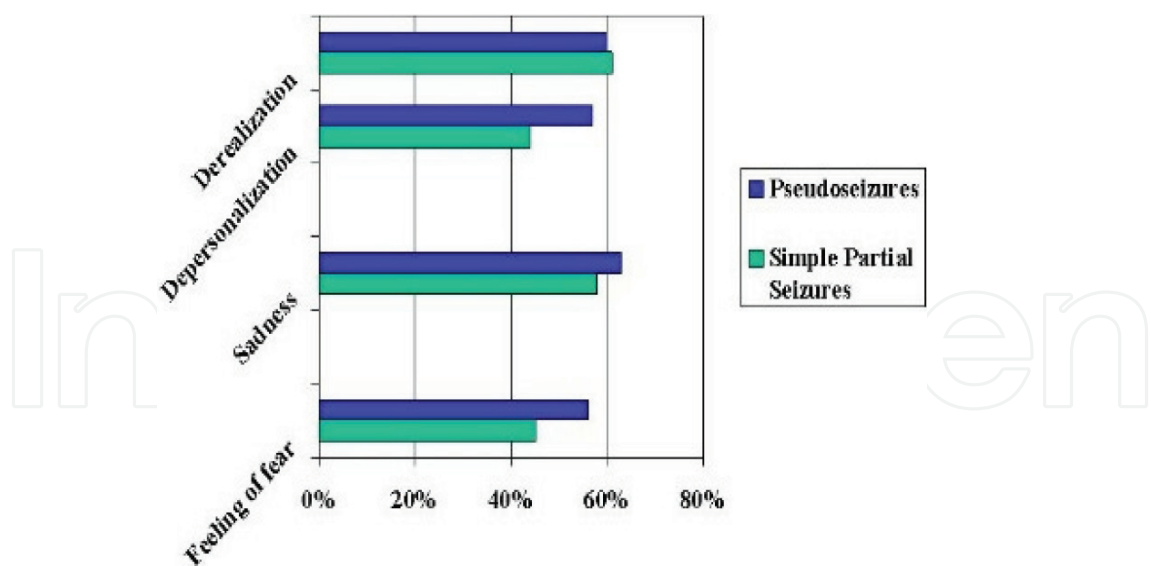


Table 2. Psychic manifestations in both groups.

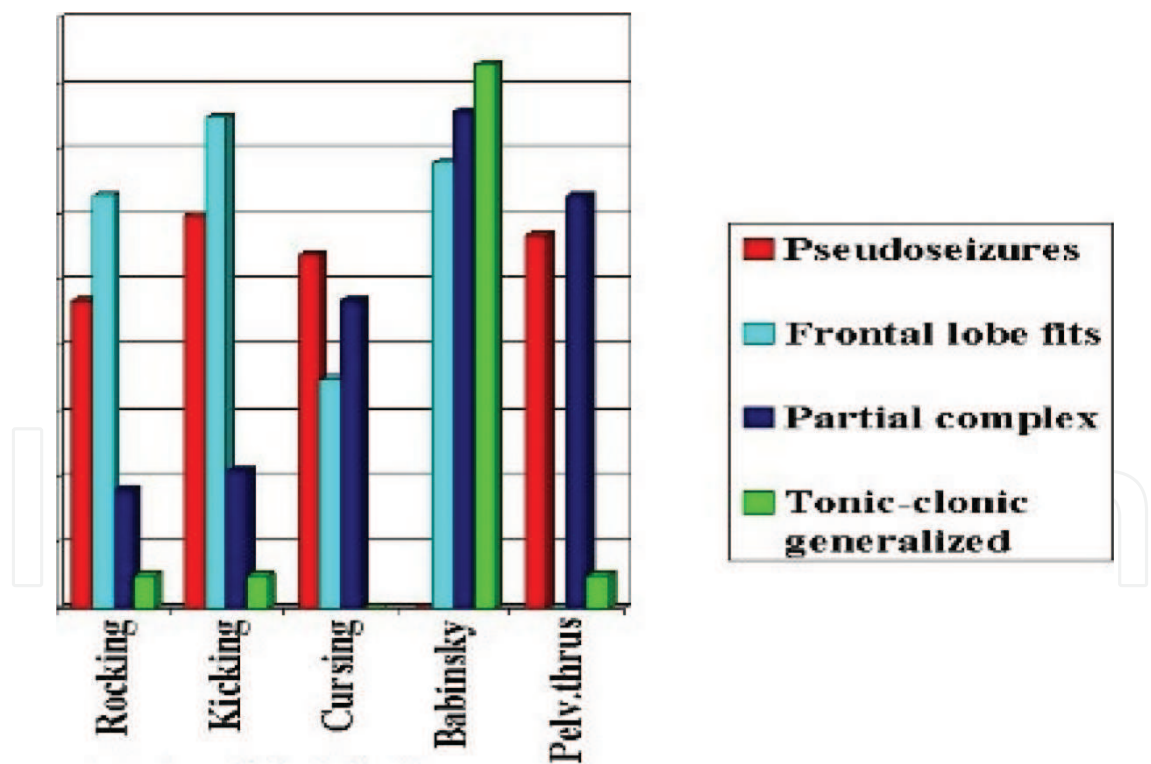


Table 3. Frequency of clinical signs during the event.

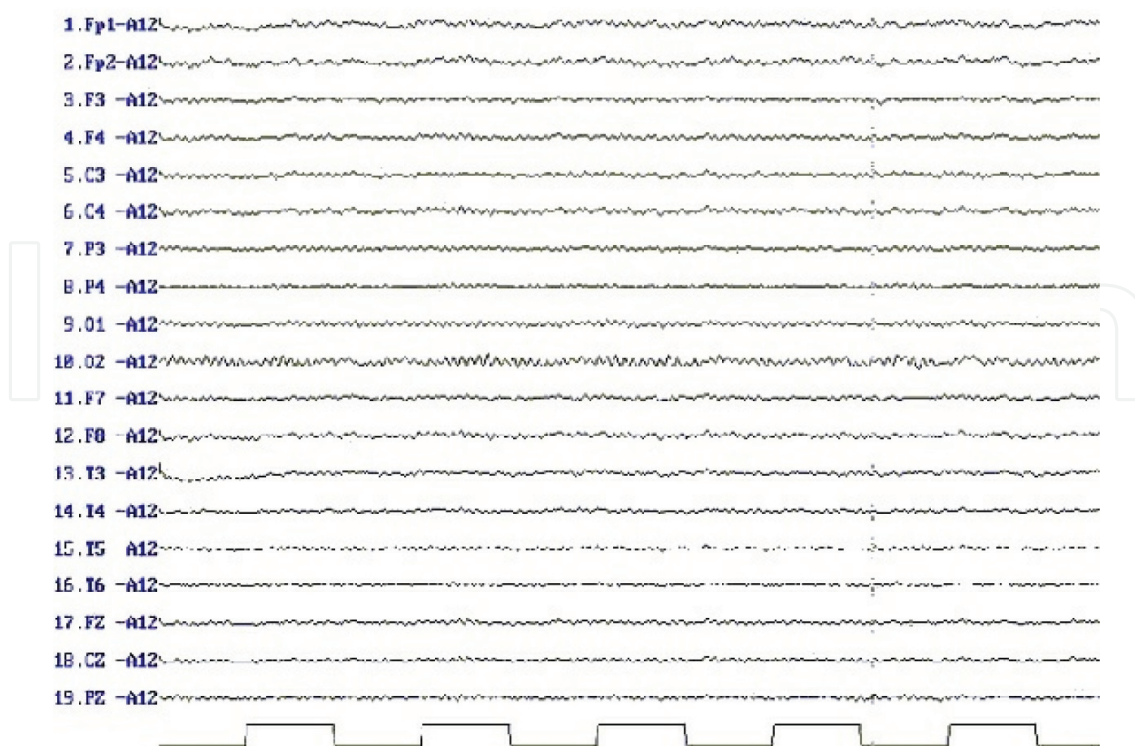


Figure 2. No changes of the background activity on the EEG during provocative saline infusion and the occurrence of PNES.

In Transkei, ES are the commonest clinical expression of calcified NCC followed by headache as it had been reported by us previously [19–40], but the associated PNES is related with other functional disturbances which were not usually present in patients with epilepsy and NCC alone, although some cases have been reported [41–43].

In temporal lobe epilepsy, some symptoms such as reactive automatisms and subjective abnormal sensations are difficult to differentiate from dissociative symptoms of depersonalization, derealisation, and alteration of consciousness, which can be misinterpreted as symptoms of ES; for the other hand, some nonspecific EEG abnormalities and possibly structural NCC findings can contribute to reinforce this diagnostic impression; therefore, when they are present, despite the absent of other reliable diagnostic tools, both “organic” and “functional” disturbances should be treated at the same time [13].

“Bilateral motor seizures with retained consciousness are rare and often mistaken for PNES [42]. When a realistic threat of physical or sexual assault to a member of their family involved in the problem is revealed, is important the role for family therapy skills in the evaluation and treatment of PNES” [43].

Some patients did not improve from the occurrence of PNES probably because of lack of more specialized treatment, and others did not discontinue their treatment including AED, in spite of our personal agreement, probable because of fear to loss their disability grant among other reasons and also because of ignorance, superstitions, and poor health education. Many patients

found solace in becoming and remaining neurological ill; thus, defense mechanism of denial, dissociation, introjections, identification, and symbolization contributed to the patient's symptom picture and to their adaptation to traumatic life events.

"Bringing the unconscious psychotic elements into conscious awareness is an important aspect of the treatment of dissociative disorders [44] and may be assayed by family physician if there is no other choice".

Using AED in patients with PNES before its confirmation was a common problem in other series [45] but not for us because all patients from our series also presented ES and then were treated accordingly.

"Auditory hallucinations, are paradigmatic symptoms of the schizophrenic patients, and can be present in disorders such as: Alzheimer's disease, epilepsy, deafness, tumors of the temporal lobe, and toxic psychosis, usually due to disturbances of the left temporal lobe, limbic, and paralimbic areas. We could not have demonstrated the source of the hallucinations in our series but based on our observations we have hypothesized that hallucinations could be secondary to hyperactivity of the basal ganglia (thalamus and striatum) since that mechanism was before-published" [46].

Malingering is an accusation, and the people have intentional and obvious goals, such as to get financial benefits or avoidance of duty or school, to reach better position in penitentiary, evasion of criminal prosecution, obtaining of drugs or compaction among other. These goals may resemble secondary gain in conversion symptoms but with the distinguishing feature being the conscious intent in the production of the symptoms.

Why more ladies than gentlemen in our series? Because there are more females than males living in Transkei (due to temporal migratory reasons) and also because women are more susceptible than men to develop this kind of somatoform disorder therefore increased incidence and prevalence of PNES is expected. Charcot and Freud [47] *emphasized the sexual aspects of the seizure as has the current interest in childhood sexual abuse*. Major mood disorders and severe environmental stress, especially sexual abuse, were common problems among our patients and they were considered in every case. From case studies and review of the medical literature, we believe that PNES in women express rage, fear, and helplessness against the dominant and abusive male rather than sexual conflicts. *Emphasizing the aggressive component of seizures does not minimize the traumatic effects of sexual abuse but rather includes it as leading to rage and helplessness [13].*

We performed EEG under provocative suggestion and intravenous (IV) normal saline solution in a small number of patients only because we consider that deceptive diagnostic tests are justified only in exceptional situations [13]. The use of provocative IV normal saline solution in that way is fundamentally deceptive, requiring the physician to intentionally and directly lie to the patient and causing the patient to believe that the administered solution caused his seizures, provocative saline infusion compromises the fiduciary obligation of truthfulness, is inimical to patient autonomy, is undignified, and risks grave harm to patient trust in physicians; however, if no deceptive alternatives are not available and the difficulty of distinguishing malingerers cannot be solved,

then we have not choice and deceptive diagnostic testing should be implemented. Without such deception, the test might be useless [48].

From our personal experience, sometimes those patients have to be treated by family physicians. Under those circumstances, we strongly recommended being very patient, very kind, and also very gentle, we advise do not accuse anybody of malingering or deliberately faking the seizures under any circumstances and always advised to get counseling. We suggest do not forget they inability for controlling their PNES and for proper socialization and its impact on their families, friends, and other members of the community. We learned that it is a good practice to understand their disabilities and frustrations and to identify their hopes. It is very important to define the underlying causes and the triggering factors for PNES such as rage, fear, and panic among others and to contribute in the healing process of emotional hurts and their emotional control; to provide an ideal psychological support and to address an adequate management of stress, emotional upset, or physical illness are also recommended; do not named those patient as hypochondriac and to explain clearly why they are unaware of the source contributing to the events, when it will be appropriated [13].

“When patients are having PNES to keep them safe, just as would be done when they are having ES is strong recommended, if the diagnosis of PNES is clear-cut then leaving the patient alone until it is over, keeping the environment calmed and free of startling noises is the best choice”.

When the clinical event of PNES is over, try to elicit some kind of respond from the patient. Never use suggestions by hypnotic procedures if you have not enough expertise.

Physical abuse on patients having PNES must be damned forever. It is very successful to encourage patients for exploring their own feelings and assisted in learning to cope with the feelings in new ways. Patients with history of attend to suicide were not suitable for this group. If there is not a good response in a due time, the diagnosis must be revised.

The clinical differentiation of PNES from epileptic attacks in patients with NCC is particularly difficult and sometimes almost impossible, if 24-hour video-EEG monitoring techniques are not available, but duration of events, history of sexual abuse in females, focal neurological signs, vocalization in the middle of the seizures, and lack of postictal symptoms can be very useful for its differential diagnosis. However, if the patient presents PNES, temporal lobe epilepsy, other types of epileptic seizures because of NCC, and some associated conditions such as factitious disorder and malingering, then confirmation PNES cannot be reached. *Under exceptional circumstances those patients can be treated by their family physician if some specialized advices are adjusted.*

In summary, we review the commonest clinical features in PLNCC presenting PNES and epileptic seizures in our series of patients. To differentiate ES from PNES or vice versa, clinical psychiatric and neurological knowledge are mandatory; however, if both manifestations are present on the same patient other diagnostic tool should be required. We conclude that:

“Some features are more or less likely to suggest PNES but they are not conclusive and should be considered within the broader clinical picture. Features that are common in PNES but rare

in epilepsy include: biting the tip of the tongue, seizures lasting more than 2 minutes (easiest factor to distinguish), seizures having a gradual onset, a fluctuating course of disease severity, the eyes being closed during a seizure, and side to side head movements. Features that are uncommon in PNES include automatisms (automatic complex movements during the seizure), severe tongue biting, biting the inside of the mouth, and incontinence. If a patient with suspected PNES has an episode during a clinical examination, there are a number of signs that can be elicited to help support or refute the diagnosis of PNES such as: normal size of the pupils, pupillary reflexes, cutaneous plantar reflexes, and caloric test” [13].

2. PNES at the present moment

2.1. Definition

Despite the terminology of “*pseudo seizures*” is obsolete, some authors still using that at the present moment and define PNES, as paroxysmal episodes that can be similar to ES and can be misdiagnosed very often by general physician and medical officers. It is important to highlight that PNES are psychological disorders such as emotional or stress-related events

“Paroxysmal nonepileptic episodes can be either organic or psychogenic. Good examples of organic nonepileptic paroxysmal symptoms are migraine, syncope and transient ischemic attack (TIA). The terminology on the topic has been variable and, at times, confusing. Various terms are used, and apart from pseudo seizures, another such as: nonepileptic seizures, nonepileptic events, and psychogenic seizures” [49],

and PNES, followed by nonepileptic event(s), psychogenic attack(s), nonepileptic attack(s), and psychogenic nonepileptic attack(s) in Google and PubMed Google and in PubMed using multiple search terms (<https://www.google.com> and <http://www.ncbi.nlm.nih.gov/pubmed>). The broad spectrum of synonyms used to refer to PNES in the medical literature reflects a lack of internationally accepted and uniform terminology for PNES. In addition to “seizure(s),” lay people use the word “attack(s)” to describe PNES [49, 50].

PNES has been the preferred term in the literature, but in practice, the term “seizures” is confusing to patients and families [49]. Other authors consider that PNESs are the most common paroxysmal event misdiagnosed as epilepsy, and they significantly affect quality of life, functional status and use of medical resources [51, 52].

By definition, PNES is a psychiatric disorder; more specifically, it is a conversion disorder, which falls under the diagnostic category of somatic symptom disorders in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). The specific DSM-5 criteria for conversion disorder are:

One or more symptoms of altered voluntary motor or sensory function:

- Clinical findings provide evidence of incompatibility between the symptom and recognized neurological or medical conditions.

- The symptom or deficit is not better explained by another medical or mental disorder.
- The symptom or deficit causes clinically significant distress or impairment in social, occupational, or other important areas of functioning or warrants medical evaluation.

According to the *DSM-5* classification, neurological symptoms that are found, after appropriate neurological assessment, to be incompatible with neurological pathophysiology can fall under conversion disorder, factitious disorder, or malingering [49].

The immobility, loss of independence, and anxiety that occurs during the monitoring process using vEEG can be difficult for older adults [53]. PNES is also a remarkably challenging and complex medical condition that gives rise to a number of ethical issues with which even the most skilled clinician struggles [54].

“Seizures can be divided into three major categories: epileptic seizures (ES), PNES, or physiologic nonepileptic events” [55].

Like epileptic seizures, PNES present as paroxysmal time-limited, alterations in motor, sensory, autonomic, and/or cognitive signs and symptoms, but unlike epilepsy, PNES are not caused by ictal epileptiform activity. In contrast to ES, which are a manifestation of excessive and hypersynchronous discharges in the brain, PNES have psychologic underpinnings and causes. Physiologic non-epileptic evoked seizures are neither epileptic nor psychogenic, rather they are events associated with systemic alterations that produce an ictus (e.g., convulsive syncope or hypoglycemic seizure) [56, 57]. PNES occur across cultures worldwide. Events described as PNES and occurring in a similar context to PNES seen in industrially developed countries are reported from threshold or developing countries, as well. PNES therefore seem to represent a fairly universal human condition. The semiology is described similarly across ethnicities and cultures [57].

As is very well known, functional neurological disorder (conversion disorder) is a neurobehavioral condition frequently encountered by epileptologist, neurologists, and family physicians.

Observational research studies “suggest that PNES and Functional Movement Disorders may represent variants of similar (or the same) conditions given that both groups exhibit a female predominance, have increased prevalence of mood-anxiety disorders, frequently endorse prior abuse, and share phenotypic characteristics” [55].

Physical and neurologic findings are usually normal, but the examination can also uncover suggestive features. For example, overly dramatic behaviors, give-way weakness, and a weak voice or stuttering can be useful predictors. Psychological features suggestive of psychogenic episodes include anxiety, depression, inappropriate affect or lack of concern (*la belle indifférence*), and multiple and vague somatic complaints suggestive of somatization disorder, and abnormal interaction with family members [49].

2.2. Gender

PNES are more prevalent among women worldwide and we also find similar results in our series. However, Asadi-Pooya et al. [57] investigated the potential differences in demographic

and clinical characteristics of PNES between women and men from Iran in 2013 and they did not observe any significant differences between women and men with PNES with regard to demographic, clinical, and semiological characteristics. Likewise, seizure characteristics and semiology were very similar in both genders. It appears that an Islamic lifestyle (in Iran) has little influence on the sex ratio and clinical manifestations of PNES compared with the Western studies. For the other hand,

Gale et al. [58] compare males with PNES to females with PNES and to males with epilepsy and they concluded that gender difference in PNES seizure semiology was associated with whether or not clinically significant somatic symptoms were present; males with elevated somatic symptoms were much more likely to have motor PNES.

However, they did not find evidence of greater psychopathology in males with PNES compared to females. Gender differences in the behavioral manifestation of PNES in the context of presence or absence of somatization may have implications for diagnosis and treatment.

2.3. Epidemiology

PNES is by far the most frequent nonepileptic condition seen in general hospital, neurological institutions, and epilepsy clinic, where they represent 20–30% of referrals. About 50–70% of patients become seizure free after diagnosis, and about 15% also have epilepsy [49]. Similar to conversion disorders, PNES typically begin in young adulthood and occur more frequently in women (approximately 70% of cases) than in men as we found in our study. Although very rare, PNES can also occur in elderly peoples. According to most authors (ourselves included), the combination of ES and PNES occurs in around 10% of patients with PNES. Some cautious should be taken in diagnosing PNES when the onset is in early childhood or elderly peoples. In young age groups, nonepileptic physiologic events may be more common than other organic conditions. Recurrent hospital admissions with apparent seizure status or daily convulsive events suggest PNES, especially when reported by a well and fully conscious patient [59].

Studies on the prevalence of PNES show variable but clinically significant results, from 5 to 33% of outpatients receiving treatment for epilepsy, and from 10 to 58% of inpatients treated for refractory epilepsy present PNES [60].

According to Gates [55] such a significant difference in results may be explained by differences in diagnostic criteria for PNES. A female preponderance of up to 80% has been observed in studies of patients with PNES [50–62]. PNES is present in children and elderly people, but many patients' ages range between the 1920s and 1930s [62–64].

The incidence of PNES in our population was 6.45/100,000/year higher than in previous studies.

Duncan et al. [65] found an incidence of 4.90/100,000/year which is also high and the median diagnostic delay was 0.6 ± 0.2 year. About 50% of their patients diagnosed early became spell free immediately or soon after diagnosis. There were high rates of psychological morbidity, medically unexplained symptoms, and economic dependence before or at the time of onset, and the early outcome was predicted by employment status. Other authors consider that

PNESs are diagnosed in at least 10–40% of the patients seen for long-term monitoring of epilepsy, and it is no surprise that patients with PNES are often treated for epilepsy [66].

PNES and psychogenic movement disorders (PMD) are among the most common psychogenic neurologic disorders.

PNES are common at neurological institutions and epilepsy clinics, where they are seen in 20–30% of patients referred for refractory seizures. PNES are probably also common in the general population, with an estimated prevalence of 2–33 cases per 100,000 population, which makes PNES nearly as prevalent as multiple sclerosis or trigeminal neuralgia [49].

2.4. Sexual abuse

Chen et al. [67] performed a systematic review and meta-analysis in some series of patients about sexual abuse and lifetime diagnosis of psychiatric disorders.

The search yielded 37 eligible studies, 17 case-controls, and 20 cohorts, with 3,162,318 participants. There was a statistically significant association between sexual abuse and a lifetime diagnosis of anxiety disorder (OR, 3.09; 95% CI, 2.43–3.94), depression (OR, 2.66; 95% CI, 2.14–3.30), eating disorders (OR, 2.72; 95% CI, 2.04–3.63), posttraumatic stress disorder (OR, 2.34; 95% CI, 1.59–3.43), sleep disorders (OR, 16.17; 95% CI, 2.06–126.76), and suicide attempts (OR, 4.14; 95% CI, 2.98–5.76).

Therefore, a history of sexual abuse is associated with an increased risk of a lifetime diagnosis of multiple psychiatric disorders [67]. Patients having PNES present a high prevalence of traumatic life events; therefore, psychosocial factors are thought to play an important role in the etiology. Neurobiological factors may also contribute to the development of seizures, as a subgroup of patients is characterized by cognitive impairment and subtle structural and functional brain abnormalities [68].

Antecedent sexual trauma or abuse is thought to be important in the psychopathology of psychogenic seizures and psychogenic symptoms in general. A history of abuse may be more frequent in convulsive rather than limp type of PNES [49].

2.5. Psychogenic nonsyncopal collapse vs. PNESs

Heyer et al. [69] characterized the clinical features of tilt-induced psychogenic non-syncopal collapse (PNSC) from a cohort of young patients and to compare the semiology between PNSC and EEG-confirmed PNES and concluded that PNSC events were briefer than PNES events (median: 45 versus 201.5s, $p < .001$). Negative motor signs (head drop, body limpness) predominated in PNSC (85% versus 20%, $p < .001$), while the positive motor signs of convulsion occurred more often with PNES (90% versus 30%, $p < .001$). Behavioral arrest (25% versus 32.5%, $p = .46$) and eye closure (85% versus 72.5%, $p = .21$) did not differ between PNSC and PNES. Patients with PNSC were more likely to be tearful before (30% versus 7.5%, $p = .02$) and after (62.5% versus 7.5%, $p < .001$) an event.

In spite of overlap exists, the features of PNSC generally appear similar to neutrally mediated syncope, while the features of PNES generally appear similar to ES.

2.6. Diagnosis

The patient's history may suggest the diagnosis. Several clues are useful in clinical practice and should raise the suspicion that seizures may be psychogenic rather than epileptic. Misdiagnosis of epilepsy is frequent and occurs in approximately 25% of patients with a previous diagnosis that does not respond to AED. Therefore, many cases of misdiagnosed epilepsy are eventually shown to be PNES.

Other paroxysmal conditions are occasionally misdiagnosed as epilepsy, but PNES is by far the most commonly misdiagnosed condition, accounting for >90% of misdiagnoses at epilepsy centers [49].

Despite the ability to diagnose PNES with near certainty by using vEEG monitoring, the time to diagnosis is long, about 7–10 years. This delay indicates that neurologists may have an insufficiently high enough index of suspicion for PNES [49, 70].

Approximately 80% of patients with PNES have been treated with AEDs before the correct diagnosis is made. A psychogenic etiology should be considered when AEDs have no effect whatsoever on the reported frequency of seizures [49].

Given the substantial economic costs and mental health burden of misdiagnosis, it is imperative to establish early identification, correct diagnosis, and effective treatment of PNES in order to provide the greatest opportunity for remission of events, improved psychological functioning, and social-vocational outcome [65].

The great majority of PNES are classified as mental disorders in the current medical nosologies (only malingered seizures are not considered a mental disorder).

The average delay from first seizure to diagnosis of psychogenic non-epileptic seizures (PNES) is over 7 years. The reason for this delay is not well understood. We hypothesized that a perceived decrease in seizure frequency after starting an anti-seizure medication (ASM) may contribute to longer delays, but the frequency of such a response has not been well established [3].

Earlier diagnosis also reduces unnecessary doctor's visits and missed school/working days. The implementation of continuous education programmers for healthcare providers in particular could contribute positively to the diagnostic process of PNES for patients [71, 72].

In 2014 Elliot and Chariton [73] studied 689 patients presenting some events leading to a diagnosis, 47% (n=324) with PNES only, 12% (n=84) with PNES & Epilepsy and 41% (n=281) with Epilepsy only. Five biological predictors of a PNES only diagnosis was found; number of years with events (OR=1.10), history of head injury (OR=1.91), asthma (OR=2.94), gastro-esophageal reflux disease (OR=1.72) and pain (OR=2.25). One psychological predictor; anxiety (OR=1.72) and two social predictors; being married (OR=1.81) and history of physical/

sexual abuse (OR=3.35). Two significant biological predictors of a PNES & Epilepsy diagnosis were found; migraine (OR=1.83) and gastro-esophageal reflux disease (OR=2.17).

The importance of considering the biopsychosocial model for the diagnosis and treatment of PNES or PNES with concomitant epilepsy based on these finding is certain.

Clinicians need to take a detailed time-consuming history from parents and when possible from the patient to identify warning signs suggestive of PNES. Such as: *an inconsistent seizure history, gradual and slow onset, as well as long duration of seizures and lack of seizure occurrence when the patient is alone. Recognizing signs suggestive of PNES is particularly difficult in the 35–44% of patients that have comorbid epilepsy* [73, 74]. The diagnosis and management of PNES is often challenging and fraught with discord and disagreement between patients, parents, and physicians [70].

In neuropsychiatric diseases, disturbances of the autonomic nervous system (ANS) are common. Heart rate variability (HRV) is useful to assess for disturbances of both sympathetic and parasympathetic activity, whereas electrodermal activity (EDA) can assess sympathetic activity. Parasympathetic HRV parameters are typically decreased in posttraumatic stress disorder (PTSD), while EDA is increased. Nevertheless, in major depressive disorder (MDD) and dissociation, both parasympathetic and sympathetic markers are decreased. Using HRV, ANS abnormalities have also been identified in PNES, indicating lower parasympathetic activity at baseline [75]. Other authors also use HRV in order to compare maximum autonomic activity of ES and PNES as biomarkers for distinguishing these types of clinical episodes. However, the great variation of autonomic response within both groups makes it difficult to use these HRV measures as a sole measurement in distinguishing epileptic seizures from PNES [76].

PNES can be suspected in patients with a psychosocial history with evidence of maladaptive behaviors or associated psychiatric diagnoses. To pay special attention during mental status assessment, especially to the patient's general demeanor, the appropriateness of his or her level of concern, over dramatization, and hysterical features is strongly recommended. Certain symptoms and signs suggest ES. These include significant physical injuries, in particular, tongue biting on the lateral side, the duration of the seizures, and an ictal cry are highly specific to generalized tonic-clonic seizures and are helpful signs when present [49].

Once the PNES diagnosis and underlying psychological problems have been ascertained by the neurologist and mental health professional, a communication process relaying the diagnosis in a manner that promotes early acceptance of PNES and the treatment plan is imperative to preserve the best outcome possible for the patient [72].

Conducting the vEEG and mental health evaluation during the current hospitalization prevents additional delays in diagnosis. In areas where EEG video monitoring is not available, clinicians can be used a staged approach for diagnosis developed by the task force of the International League Against Epilepsy, these included: history, EEG, ambulatory EEG, vEEG/monitoring, neurophysiologic, neurohumoral, neuroimaging, neuropsychological testing, hypnosis, and conversation analysis [6, 77]. The task force proposed the following four categories of certainty for PNES diagnosis:

- Documented PNES – confirmed by clinical history plus EEG video monitoring.
- Clinically established PNES – defined by clinical history, clinician witness, and EEG recording of habitual events without video.
- Probable PNES – determined by clinical history, clinician witness of video or live events, and a normal EEG.
- Possible PNES – relies on patient's self-report of clinical events and a normal EEG.

As is done with PMD diagnosis, levels of diagnostic certainty are ranked based on what data are available from history, witnessed event, and diagnostic testing, with levels of Possible, Probable, Clinically Established, and Documented diagnosis.

The roles of the specialists involved in the patient's care, how the information is communicated, and subsequent follow-up needs to be carefully considered in the values trade-offs that occur [72]. The issues of communicating the diagnosis to the patient and making treatment recommendations which should ideally be coordinated using a multidisciplinary team approach, involving the disciplines of neurology, psychiatry, psychology, social work, nursing, and anyone else necessary for this process [65]. The language to be used in this communication requires special attention and dedication, selecting the best descriptor for patients and families that highlights transparency and honesty, with avoidance of stigma and negative emotional response. We argue for providing parents and the patient initial diagnostic feedback separately. We also recommend that after communicating a diagnosis of PNES, neurologist/epileptologist with independent prescriptive authority, in addition to physicians, and families may struggle with the choice of withdrawing AEDs for the treatment of young patients for whom the AEDs have been taken for a long time.

Although the DSM-5 classification is simple in theory, knowing whether a given patient is faking it is nearly impossible. In some circumstances, intentional faking can be diagnosed only by catching a person in the act of faking (e.g., self-inflicting injuries, ingesting medications or eye drops to cause signs, putting blood in the urine to simulate hematuria) [49].

When the patient is purposely deceiving the physician (i.e., faking the symptoms), factitious disorder and malingering must to be taken into account. To distinguish factitious disorder and malingering from PNES just consider that, in malingering, the reason for the deception is tangible and rationally understandable (albeit possibly reprehensible) such as avoiding military duty, avoiding work, obtaining financial compensation, evading criminal prosecution, or obtaining drugs. In factitious disorder, the motivation is a pathologic need for the sick role [49].

An important corollary is that malingering is not considered a mental illness, whereas factitious disorder is. As such there are no specific diagnostic criteria for malingering. A generally accepted view is that most patients with PNES have conversion disorder, rather than malingering or factitious disorder [49].

Dacrystic seizures are rare clinical occurrences characterized by sudden lacrimation, grimacing, sobbing, sad facial expression, and yelling, with a special challenging differential diagnosis with PNES. To differentiate dacrystic seizures from PNES can be very difficult from

the point of view of symptomatology of psychiatric symptoms but if vEEG monitoring captures a prolonged seizure compatible with a dacrystic seizure its final diagnosis. The presentation of dacrystic seizures has common elements with PNES, and it is possible that the patient has both types of crisis. Apart from that there are a few medical reports in the literature about this matter [6, 78–80].

Laboratory studies are useful in excluding metabolic or toxic causes of seizures (e.g., hyponatremia, hypoglycemia, drugs). Prolactin and creatine kinase (CK) levels rise after generalized tonic-clonic seizures and not after other types of episodes. However, sensitivity is too low to be of any practical value (i.e., lack of elevation does not exclude epileptic seizures) [49].

2.6.1. Electroencephalogram and provocative techniques, activation or inductions

The “gold standard” for proper diagnosis of PNES is vEEG [77]. During vEEG assessment, behavior and EEG activity are registered at the same time. A spontaneous or elicited event is defined as a PNES, when there is no spike/slow waves EEG activity, during or after the ictus, and semiology is consistent with PNES and not ES.

Jedrzejczak et al. [81] reported a clinical and electrophysiological analysis of type and duration of seizures recorded by means of long-term vEEG monitoring, a method which enables accurate diagnosis of PNES occurring with or without ES. Analysis is based on 1083 patients, hospitalized at their department between 1990 and 1997, with a preliminary diagnosis of epilepsy. A total of 85 patients (7.8%) were diagnosed as PNES. Long-term video-EEG monitoring was performed in 70 patients. In 55 (79%) of these patients, 230 seizures (221 pseudo epilepsy and nine epileptic) were recorded. In 30 patients (32%), the diagnosis was based on clinical observation of the seizures and on the number of EEG recordings, including activating procedures such as sleep deprivation, photo stimulation, hyperventilation, and AED withdrawal. The authors proved the difficulties involved in the diagnosis of psychogenic pseudoepileptic seizures and the negligible value of neuroimaging techniques and interictal EEG recordings in the differential diagnosis of epileptic versus nonepileptic seizures.

We review the influence of gender on psychogenic nonepileptic seizures (PNES) diagnosis and another author did the same.

Noe KH et al. [80] in 439 subjects undergoing video-EEG (vEEG) for spell classification, of which 142 women and 42 men had confirmed PNES. The epileptologist predicted diagnosis was correct in 72% overall. Confirmed epilepsy was correctly predicted in 94% men and 88% women. In contrast, confirmed PNES was accurately predicted in 86% women versus 61% men ($p=0.003$). Sex-based differences in likelihood of an indeterminate admission were not observed for predicted epilepsy or physiologic events, but were for predicted PNES (39% men, 12% women, $p=0.0002$).

vEEG monitoring refers to continuous EEG recorded for a more or less prolonged period with simultaneous video recording of the clinical manifestations. Having a correlation of the recorded behavior (video) and the EEG cortical activity, the diagnosis of ES or PNES attacks can be made definitely in nearly all cases [81, 82].

Using vEEG of patients, Hubsch et al. [83] conducted multiple correspondence analysis and hierarchical cluster analysis to construct a practical and useful semiological classification of PNES, which identified five clusters of signs: dystonic attack with primitive gestural activity, pauci-kinetic attack with preserved responsiveness, pseudo syncope, hyperkinetic prolonged attack with hyperventilation and auras, and axial dystonic prolonged attack.

The ability to diagnose PNES when vEEG is not available may open opportunities to lower and middle income countries, where monitoring is not available.

Provocative procedures, such as saline provocation, hypnosis, simple suggestions, suggestive interview, or a mixture of them, have been used to obtain a typical event; however, the ethics of provocative procedures has been raised.

Activation maneuver, inductions, or provocative techniques can be remarkably useful for the diagnosis of PNES, mainly when the diagnosis is uncertain and no spontaneous episodes occur during assessment. In many epilepsy centers, to use a provocative technique to aid in the diagnosis of PNES is allowed. For example, an intravenous injection of normal saline is traditionally and most commonly used, but other techniques such as hypnosis, among others, can be used. The use of suggestion techniques ranging from simple verbal suggestion to injection of saline may improve rate of seizure capture; at the present moment, an important number of authors are in favor [6, 77, 84–89], while others do not approve these procedures [90, 91]. Some authors support use of simple suggestion techniques, if the patient is clearly informed of what is being done and why (this does not seem to prevent patients from having events during recording) [92].

The recent use of hypnosis in the diagnostic process of PNES includes its use in seizure provocation, which was tested in samples in the recent literature.

2.6.2. Neuroimaging

Excepting lesions with epileptogenic potential (such as mesial temporal sclerosis) neuroimaging findings are of modest differential diagnostic value for ES and PNES at present, but it is diagnostic for patients PLNCC.

All patients presenting epileptic seizures secondary to NCC have abnormalities on CT scan or magnetic resonance imaging (MRI) scan of the brain characterized by calcified edema surrounding or not by perilesional edema and or active cysticerci at different stage [1, 2, 13, 19–40]. However, most patients with idiopathic epilepsy have normal MRI studies [62], and a significant number of patients with lone PNES have abnormalities [61, 77]. More recently, structural and functional imaging studies in patients with PNES have documented changes in cortical and cerebellar regions at group level [92]; in functional connectivity between emotional, cognitive, and motor regions [93–95] and between structural and functional connectivity network coupling [95]. More studies are needed to determine whether there are actual conversion/dissociation networks [93].

Lesions with epileptogenic potential (such as mesial temporal sclerosis) are more commonly found in patients with epilepsy but have also been described in patients with PNES and are clearly not sufficient for a diagnosis of epilepsy.

Convergent neuroimaging findings implicate alterations in brain circuits mediating emotional expression, regulation and awareness (anterior cingulate and ventromedial prefrontal cortices, insula, amygdala, vermis), cognitive control and motor inhibition (dorsal anterior cingulate, dorsolateral prefrontal, inferior frontal cortices), self-referential processing and perceptual awareness (posterior parietal cortex, temporoparietal junction), and motor planning and coordination (supplementary motor area, cerebellum). Striatal-thalamic components of prefrontal-parietal networks may also play a role in pathophysiology. Aberrant medial prefrontal and amygdala neuroplastic changes mediated by chronic stress may facilitate the development of functional neurological symptoms in a subset of patients [94–96].

Neuroimaging studies have demonstrated that PNES are characterized by unstable cognitive-emotional and motor system, which is engaged in hyperactivity of limbic regions and sensorimotor area. The insula, which is a part of the limbic system, includes various sub regions with some distinct connectivity patterns separately, whether these insular sub regions show different connectivity patterns respectively in PNES remains largely unknown according with the investigations done by Rong et al. [97].

They investigated the functional connectivity (FC) of insular sub regions in PNES and extend the understanding of the complex pathophysiological mechanisms of this disease. A resting state FC based on the insular sub regions was conducted in 18 patients and 20 healthy controls. They examined the differences in FC values between PNES patients and controls using two sample t tests, and their results showed that patients had significantly stronger FC between insular sub regions and sensorimotor network, lingual gyrus, superior parietal gyrus and putamen, which suggested a hyperlink pattern of insular sub regions involved in abnormal emotion regulation, cognitive processes, and motor function in PNES. Pearson correlation analysis between the mean FC values within abnormal regions and the frequency of PNES further indicated that PNES exhibited abnormal functional organization whose stressful emotion of patients has great direct influence on their motor functions.

They concluded that differentially impaired functional connectivity patterns of insular sub regions might provide new insights into the complex neurological mechanism of PNES [97].

Functional neuroimaging data in various functional neurological disorders increasingly support specific neurobiological dysfunction. However, to date, only one study has been reported on positron emission tomography (PET) in patients presenting with PNES.

Arthuis et al. [98] reported sixteen patients being evaluated in a specialist epilepsy centre underwent PET with 2-deoxy-2-[fluorine-18] fluoro-d-glucose (18) FDG-PET) because of suspected intractable epileptic seizures. However, in all patients, the diagnosis was subsequently confirmed to be PNES with no coexisting epilepsy. (18) FDG-PET was also performed in 16 healthy controls. A voxel by voxel intergroup analysis was performed to look for significant differences in interictal (resting state) cerebral metabolism. In addition, metabolic connectivity was studied using voxel-wise inter-regional correlation analysis.

They found that patients with PNES exhibited significant PET hypometabolism within the right inferior parietal and central region and within the bilateral anterior cingulate cortex. A significant

increase in metabolic correlation was found in patients with PNES, in comparison to healthy participants, between the right inferior parietal/central region and the bilateral cerebellum and between the bilateral anterior cingulate cortex and the left parahippocampal gyrus. Although they cannot exclude that their data reflect changes due to comorbidities, they may indicate a dysfunction of neural systems in patients with PNES. Hypometabolism regions might relate to two of the pathophysiological mechanisms that may be involved in PNES, that is, emotional dysregulation (anterior cingulate hypometabolism) and dysfunctional processes underlying the consciousness of the self and the environment (right parietal hypometabolism) [97].

2.7. Treatment

The first treatment phase in PNES is patient engagement. Treatment is complex, requiring multidisciplinary care and patients, and their families must understand the diagnosis to comply with the recommendations of the psychiatric caregiver [49]. The next phase of treatment is acute interventions, and most research studies focus on short-term evidence-based interventions. It seems to be that the cognitive-behavioral therapy is supported by most of randomized controlled pilot trials. However, psychotherapeutic and psychopharmacological interventions have been less well-studied using controlled and uncontrolled trials [98].

Treatment of PNES varies and can include psychotherapy and use of adjunctive medications to treat coexisting anxiety or depression. Psychogenic symptoms are, by definition, a psychiatric disease, and a mental health professional should manage them. The main obstacle to effective treatment is effective delivery of the diagnosis. The physician delivering the diagnosis must be compassionate, remembering that most patients are not faking, but also firm and confident to avoid the use of ambiguous and confusing terms. Patients who accept their diagnosis and follow through with therapy are more likely to experience a successful outcome; therefore, patient education is critical and is the first step in treatment [49].

LaFrance Jr et al. [6] found that a cognitive behavior therapy-informed psychotherapy significantly reduces the seizures in patients with PNES.

“Cognitive behavioral therapy has evidence of efficacy, including one pilot randomized, controlled trial where cognitive behavioral therapy was compared with standard medical care. The antidepressant sertraline did not show a significant difference in event frequency change when compared to placebo in a pilot randomized, double-blind, controlled trial, but it did show a significant pre- versus post treatment decrease in the active arm.”

“Other interventions that have shown efficacy in uncontrolled trials include augmented psychodynamic interpersonal psychotherapy, group psychodynamic psychotherapy, group psycho education, and the antidepressant venlafaxine” [6].

Some investigations done in 2010 and 2013 suggested serotonin selective reuptake inhibitors (SSRIs) and sertraline may be helpful in reducing seizures in PNES, respectively [49].

Carlson and Nicholson Perry [99] “evaluated and synthesized the available evidence from the previous 20 years regarding the utility of psychological interventions in the management of

psychogenic non-epileptic seizures (PNES) and found that 82% of people with PNES who complete psychological treatment experience a reduction in seizures of at least 50%."

Hilmarsdóttir et al. [100] "addressed the current research on psychotherapeutic treatment for PNES by discussing recent reviews and six randomized controlled trials (RCTs) on the subject and concluded that, larger well-designed randomized controlled trials are needed in order to support the evidence of psychological interventions for their patient group".

Duncan et al. [101] "reported that half of their patients informed being free of seizures following intervention. Being employed predicted good outcome, but the best predictor of being seizure free at 6 months was having an internal locus of control. This may be useful practically and requires further study".

"No good predictors of long-term outcome were found, possibly because of loss to follow up. PNES may manifest themselves in very different ways and usually have complex root causes". Optimal treatment of persons experiencing PNES requires close cooperation between the neurologist and the psychiatrist [102].

The delivery of brief manualized psycho-educational intervention for PNES by health professionals with minimal training in psychological treatment was feasible. The intervention was associated with higher rates of PNES cessation than those observed in previous studies [103].

Some authors investigated whether initial adherence to treatment in PNES differed on the basis of mental health treatment modality and which subject characteristics were predictive of adherence. Initial adherence rates were 54% for combined treatment conducted in the same institution (integrated intervention) and 31% for psychotherapy and psychiatric management offered in different settings (divided intervention). Cognitive complaints and current exposure to antiepileptic drugs (AEDs) were more common among nonadherent patients, and being married (or having a live-in partner) was more common among adherent patients. A predictive model using the mentioned variables (intervention type, marital status, cognitive complaints, and concurrent use of AEDs) showed that this set of variables was predictive of adherence [104].

While PNES is treated by mental health professionals, continued involvement by a neurologist or epileptologist is associated with better outcomes, regardless of the limited direct care provided. Moreover, parents of children with PNES are expected to discuss the diagnosis with the pediatric epileptologist/neurologist, and this expectation should be respected [72].

Plioplys [105] suggests that "professionals in epilepsy care that lack sufficient knowledge about PNES may be more likely to continue AEDs at a parent's request. These professionals may also be more likely to continue AEDs in order to facilitate acceptance of the diagnosis and/or to prevent a delay in psychological treatment. A clinician may be concerned that refusing a request to continue AED treatment will result in the family seeking out a clinician who would unquestioningly supply them with requested medicines, i.e. "doctor-shopping." This risk may be heightened if parents observe their child's non-epileptic episodes becoming worse. Parents may also wish to continue AEDs as a means to avoid social stigma associated with PNES, particularly at school".

It is clear-cut defined that clinicians are under obligation to provide medical treatment deemed to be inappropriate or ineffective [106, 107]. Instead of continuing to prescribe AEDs, exploring the underlying reasons for why the parents want to continue AEDs despite the PNES diagnosis allows the physician to directly address parents' concerns regarding discontinuation. PNES patient and their relatives may turn to clinicians for advice regarding disclosure of PNES diagnosis to third-parties, including school nurses, school administrators, teachers, classmate, day care providers, and peers. The clinicians' obligation is to counsel patients and their parents on the conflicting values that are at stake: preserving the patient's and family's privacy, protecting the patient from social stigma and physical harms, and promoting continuity of therapeutic care.

Neurologist and epileptologist should educate the patient and their relatives that these values are not easily reconcilable and deciding whether to disclose the diagnosis involves an inherent trade-off, and the prognosis of these patients is still relatively poor, and a good outcome seems dependent on a young age at diagnosis, early diagnosis, less severe psychological comorbidities, and continued follow-up and management by the diagnosing neurologist, epileptologist, or clinician [8, 49, 105, 108–116].

The arguments for disclosing with both parents and child together would be primarily based on cultivating trust with patient and parents and between patient and parents through maximal transparency [72].

2.8. PNES vs. epileptic seizures

Impairment of consciousness and reduced self-control are key features of most psychogenic nonepileptic seizures (PNESs), although, compared with patients with epilepsy, those with PNESs demonstrate greater conscious awareness during their seizures.

Some authors [117, 118] “suggest that an understanding of conscious experiences and discrepancies between subjective impairment of consciousness and the lack of objectifiable neurobiological changes in PNESs may benefit from an examination of emotion processing, including understanding sensory, situational, and emotional triggers of PNESs; emotional and physiological changes during the attacks; and styles of emotional reactivity and regulatory capacity [117] reported allergies helps distinguish epilepsy from psychogenic nonepileptic seizures” [118].

Psychopathology levels are elevated in patients with PNES and those with epilepsy. However, patients with PNES report higher rates of trauma and neglect, poorer health-related quality of life (HRQoL), and an increased prevalence of insecure attachment. In this study, patients with PNES reported higher levels of anxiety and depression and lower HRQoL than those with epilepsy. PNES: No significant correlations were found with HRQoL but depression correlated positively with attachment avoidance, attachment anxiety, and relationship conflict. Anxiety correlated positively with attachment avoidance, attachment anxiety, and relationship conflict, and negatively with relationship depth and support. Epilepsy: HRQoL correlated negatively with seizure severity, depression, anxiety, attachment avoidance, and attachment anxiety. Depression correlated positively with attachment avoidance, attachment anxiety, and relationship conflict. Anxiety

correlated positively with seizure severity, attachment avoidance, and attachment anxiety. Correlations between measures of relationship quality and anxiety were stronger in patients with PNES versus those with epilepsy ($z_s = 2.66$ to 2.97 , $p < 0.004$). Attachment style and relationship quality explained larger amounts of variance in depression (45%) and anxiety (60%) in the patients with PNES than those with epilepsy (16 and 13%). In conclusion, levels of anxiety and depression were higher in patients with PNES than those with epilepsy. Interpersonal problems were much more closely associated with anxiety and depression in patients with PNES than those with epilepsy. The findings support the use of therapeutic interventions for PNES focusing on attachment and relationship issues [119].

Some investigations have attempted to compare patients affected by PNES to patients affected by functional motor symptoms from a demographic, clinical, and psychological perspective. Nevertheless, results are quite controversial, and significant conclusions have not been reached. Therefore, some authors evaluated the phenomenology of psychology of the two groups assessing levels of dissociation and its subcomponents, alexithymia and interceptive sensitivity in patients with PNES and in patients with FMS, and the investigation showed different psychological mechanisms underlying patients with PNES and patients with FMS [120].

Some authors [121] “studied eligible patients ($n = 51$) that were divided into those with PNES + ES ($n = 24$) and those with PNES alone ($n = 27$). The follow-up period was 4.8 ± 0.3 and 4.3 ± 0.3 years, respectively. Both groups had similar female predominance and similar age at admission to the vEEG unit. Time from PNES onset to hospitalization was longer in PNES patients compared to those with PNES + ES. The majority of subjects in each group reported a history of at least one major stressful life event. Opisthotonus was significantly more frequently observed in PNES patients, and they had more events during vEEG hospitalization. Psychogenic events ceased during the follow-up period in 22% of the PNES patients and in 58% of the PNES + EPI patients ($P > 0.001$)”.

Their results indicate that following vEEG-based diagnosis of PNES, the long-term outcome of PNES cessation may be more favorable for patients with concomitant epilepsy than for patients without epilepsy.

Neuropsychological tests do not distinguish ES from PNES at the individual level. Clinical features that favor PNES are:

Fluctuating course.

Asynchronous movements (frontal lobe partial seizures excluded).

Pelvic thrusting (frontal lobe partial seizures excluded).

Side to side head or body movement (convulsive events only).

Closed eyes during the episode.

Long duration.

Other signs that can help are gradual onset, no stereotyped events, flailing or thrashing movements, opisthotonus “arc en cercle”, tongue biting, urinary incontinence, and “swoon” type events should raise suspicion of PNES if prolonged over a minute, atonic ESs are much

shorter and typically occur in the epilepsies with other seizure types, for example, Lennox–Gastaut syndrome.

Signs that favor ES.

Occurrence from EEG-confirmed sleep.

Postictal confusion.

Stertorous breathing.

Occurrence during sleep only (*EEG-confirmed sleep*).

2.9. Associated minor or major injuries

Ictal injuries in PNES have been reported previously and history of any minor (e.g., tongue biting, bruises, and lacerations) or major (e.g., burns and fractures) physical injuries associated with their seizures, since their disease started is well known. In our region, one of the most common type of reported injury was burning lesions that happened in patients fitting close to the fire used to heat the room apart from tongue biting, lacerations, bruises, limb fractures, and dental injury. Therefore, PNES is also associated with physical injuries. Despite the shibboleth that injuries rarely occur during PNES, mild injuries commonly happen and even severe injuries such as fractures and burns are not uncommonly reported in these patients. *Patients with more dramatic seizure manifestations (e.g., urinary incontinence) were more likely to report ictal injuries* [121].

Tongue biting (TB) may occur both in seizures and in PNES. A systematic review to determine sensitivity, specificity, and likelihood ratios (LR) of TB was done.

“Five studies (222 epilepsy patients and 181 subjects with PNES) were included. There was a statistically significant higher prevalence of TB (both without further specifications on site of lesions and lateral TB) in patients with seizures. Pooled accuracy measures of TB (no further specifications) were sensitivity 38%, specificity 75%, pLR 1.479 (95% CI 1.117-1.957), and nLR 0.837 (95% CI 0.736-0.951). Pooled measures of lateral TB were sensitivity 22%, specificity 100%, pLR 21.386 (95% CI 1.325-345.169), and nLR 0.785 (95% CI 0.705-0.875). Only a pooled analysis of data demonstrated a statistically significant pLR for lateral TB. Lateral TB but not ‘any’ TB has diagnostic significance in distinguishing seizures from PNES, supporting the diagnosis of seizures. Tongue biting without further specifications has, therefore, no value in the differential diagnosis between seizures and PNES” [122].

3. Ethics

Currently, only a very narrow window of ethical dilemmas in PNES has been explored.

Numerous distinct ethical dilemmas arise in diagnosing and treating pediatric and adolescent patients with PNES. Important ethical values at stake include trust, transparency, confidentiality, professionalism, autonomy of all stakeholders and justice [122].

In 2003, we had not video-EEG facilities and then a procedure to provoke and to distinguish PNES from ES in our setting is introduced. At that time, we got IRB number, an approval by the Ethical Advisory Board (A0;012-2000) and written informed consent from selected patients. However, today, we have no doubt that it was a nonethical procedure, and in spite of that we did not afford any problem, we deeply regret about that procedure.

Confirming a PNES diagnosis and disclosure this information to the child, parents and other interested people build up a special challenge related to the values of justice professionalism, human resource utilization, and trust for health care providers in relation to patients, families, and other colleagues. The preservation of an adequate therapeutic relationship plays strongly in the values at stake. Most of neurologists felt confident about discontinuing the medical treatment when diagnosis of PNES is confirmed, but ethical dilemma arises when the prescribing clinician faces is discontinuing AEDs in a timely manner without losing the trust and confidence of the patient and/or the patient's relatives. Sometimes some patients and relatives decide to seek for a second medical opinion and we have to respect that.

Elements often taken into account during ethical dilemmas include the patient and family's treatment preferences, developmental stage, psychosocial background, quality of life, applicable laws, institutional policies, professional duties, and other practical stakeholder obligations and responsibilities. Even the most skilled attending doctor struggles with ethical dilemmas that arise during diagnosis and management of PNES patients. These relationships coupled with the uncertainty and stigma surrounding PNES result in complex dilemmas for treating clinicians. Significant mental health, social, and community resources are frequently necessary to effectively treat this patient population, but these resources are scarce. To ensure a successful management of PNES, all ethical values should be taken in to consideration from the first clinic [122–126].

Acknowledgements

We would like to thanks to Prof. Olivier Wenker, CEO of Internet Journal of Publications to granted permission for including in this chapter some figures and tables published online by the before-mentioned editorial house.

Parts of this chapter are taken from the authors' former work. In this regards we also want to acknowledge to following sources:

1. Foyaca-Sibat and Ibañez-Valdés [13].
2. Cole et al. [123].
3. Benbadis [49].

One of the article was published by IJN and co-authored by Prof. H Foyaca who is also an Editor-in-Chief of the IJN. The other two sources were properly cited in the body of this chapter and the reference list. We also declare that we have not conflict of interest.

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