Psychogenic nonepileptic seizures

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ABBREVIATIONS

BDNF:	Brain derived neurotropic factor
CBBT:	Cognitive behavioral therapy
CBT-ip:	Cognitive behavioral therapy informed psychotherapy
DD:	Differential Diagnosis
EEG:	Electroencephalography
EKG:	Electrocardiogram
ILAE:	The International League Against Epilepsy
vEEG:	Video Electroencephalography Test
MRI:	Magnetic Resonance Imaging
NSE:	Neuron specific enolase
PMD:	Psychogenic movement disorder
PNES:	Psychogenic non-epileptic seizures
Serum GFAP:	Serum glial fibrillary astrocyte protein
Serum PRL:	Serum prolactin levels

SAŽETAK

PNES su psihogeni ne-epileptički napadaji koji mogu izgledati slično epileptičkim napadajima, ali se smatraju ne-epileptički po naravi, zbog nedostatka epileptiformne aktivnosti na EEG-u. Za razliku od epilepsije, smatra se da su PNES izazvani stresom, s psihološkim porijeklom. Dijagnoza PNES-a počiva na kombinaciji povijesti pacijenata, kliničkih opservacija i video EEG nalaza. Video EEG igra ključnu ulogu u dijagnozi PNES-a i na kraju poboljšava pacijentovo prihvaćanje dijagnoze PNES-a i prihvaćanje terapije. Pogrešna dijagnoza je česta i problematičan izazov u PNES-u, a značajno kašnjenje u dijagnozi se često događa kod bolesnika. To predstavlja ozbiljan problem, ne samo sa strane neliječenja ili pogrešnog liječenja bolesti koje dolaze s pogrešnom dijagnozom / nedostatkom dijagnoze, ali i sa nepraćenjem bolesti što je uobičajeno u PNES-u. Pogrešna dijagnoza PNES-a i dalje dovodi do opterećenja pacijentu i zdravstvenom sustavu, što rezultira nepotrebnim primanjem u bolnice te dijagnostičkim i terapijskim intervencijama.

Ispravna i brza dijagnoza PNES-a omogućuje bolju prognozu i poboljšanu psihološku i društvenu dobrobit pacijenta. Još se uvijek dugoročne prognoze PNES-a nisu pokazale povoljne, jer mnogi bolesnici i dalje pate od napadaja usprkos terapiji. Psihološka terapija, s naglaskom na prepoznavanje uzroka i poučavanja upravljanja stresom, smatra se terapijom prvog reda u upravljanju PNES-om. Svrha ovog rada je dati opći pregled PNES-a, njegovih ko-morbiditeta, stalnih dijagnostičkih izazova povezanih s ovim stanjem, te mogućnosti liječenja, s naglaskom na važnost ranog prepoznavanja i točnu dijagnozu u poboljšanju dugoročnog ishoda bolesnika.

Ključne riječi: Psihogeni ne-epileptički napadaji, EEG, komorbiditet, konverzivni poremećaj

SUMMARY

PNES are psychologically derived paroxysmal events which commonly present in early adulthood, occur more often in woman, and can appear clinically similar to a number of other neurological disorders. Events can include variable and non-stereotypical features, with a duration of seconds to minutes. It is known that certain epilepsy syndromes can present without clear epileptiform changes, and this adds to the difficulty in accurate diagnosis of PNES.

Accurate and timely diagnosis of PNES is paramount to the health and well-being of the patient. Video EEG is important not only as a diagnostic tool in PNES, but also in facilitating patient acceptance of the diagnosis, and compliance towards the recommended therapy. Misdiagnosis remains an important issues in PNES, and serious steps need to be taken to minimize this occurrence in the PNES community. Misdiagnosis leads to burden to both the patient and the health care system, resulting in unnecessary hospital stays, and interventions.
More than half of patients with PNES suffer from one or more comorbidities. Timely and accurate diagnosis of PNES, allows for a treatment plan of the patient's comorbidities, which can improve overall psychological well-being and functioning of the patient. Treatment options of PNES are limited, with psychological therapy being first line treatment.

The purpose of this paper is to give a general overview of PNES, the clinical aspects of the events, the diagnostic and treatment challenges, it's comorbidities, therapy, with emphasis on the importance of early recognition and accurate diagnosis in improving long term outcome in the patient.

Key words: Psychogenic nonepileptic seizures, EEG, comorbidity, conversion disorder

1. Introduction

PNES is considered to be a type of conversion disorder consisting of psychologically derived paroxysmal events which are not considered to be epileptic in origin. (1) A conversion disorder implies that the patient is not aware and is not consciously faking their symptoms or episodes. (6) Although these events can sometimes resemble epileptic events, they lack clear epileptiform activity on an EEG. (1) The true origin of PNES is not yet fully understood, but recent theory suggests they might be a result of neurobiological dysfunctions at specific brain networks and abnormal connectivity of the networks (2) PNES commonly present in early adulthood and are more commonly occurring in woman with a prior history of sexual abuse, physical abuse, neglect, traumatic brain injury . (2)

Misdiagnosis and delayed diagnosis represent a common and persisting issue with PNES, with an average time needed for diagnosis ranging from 1 to 16 years. (1) As well, up to 10% of outpatients in epilepsy clinics and 20-40% of inpatients in epilepsy monitoring units are found to be suffering from PNES as opposed to epileptic seizures. (2) A delay in diagnosis of PNES leads to diminished patient outcome due to uncontrolled PNES events, unaddressed psychiatric comorbidities, and side-effects of anti-epileptic medication. (1) PNES can at times present in a way that can be difficult to immediately distinguish from true epileptic events. It is important for the physician to be aware of some main differences which can help in the initial differentiation of PNES and epileptic event. Unlike epileptic seizures, PNES do not begin abruptly, follow with stereotypical repetitive clinical manifestation, and end with a post ictal period of lingering symptoms such as drowsiness or weakness. (3)

The long term prognosis and morbidity associated with PNES can resemble that of refractory epilepsy, with PNES patients experiencing significant long term disability. In addition, psychiatric comorbidities are experienced by over 90% of patients with PNES,

further complicating the long term function and wellbeing of the patient. (4) Depression, posttraumatic stress disorder, and personality disorders include the most commonly occurring comorbidities found in patients with PNES. (6)

Diagnosis of PNES can be challenging, with no signal clinical data being definitively diagnostic for PNES, but rather a multitude of clinical evaluations must be considered together before a diagnosis can be made. (3) As well, diagnostic tests must be performed during a PNES event in order to be most definitive, as tests which are done in between events will have limited diagnostic value. (5) Patient history, seizure semiology, ictal/peri-ictal physical exam, ictal/interictal EEG data are all important parts of the PNES diagnostic process. (3)
In terms of the single most valuable diagnostic tool in PNES, VEEG remains to be the gold standard, providing a sensitivity of (93%) and specificity of (94%) to the diagnosis of PNES (3), and playing an important part in treatment effectiveness and patient compliance.

When considering differential diagnosis of PNES it is important to take into account the three main forms in which PNES may present; notably, convulsive, swoon and pseudoabsence PNES patterns. (5) The differential diagnosis of convulsive PNES is tonic clonic seizure, the DD of swoon PNES is syncope, (vasovagal or cardiac) and the DD of pseudoabsence PNES is absence seizure type. (5)
While cardiac syncope can be easily excluded with ECG monitoring during an event; it can be more challenging to differentiate between vasovagal syncope and PNES as both events usually have similar EEG slowing or flattening. One of the only main differences between swoon-type PNES and vasovagal syncope is the duration of time of the event with swoon-type PNES typically lasting much longer than typical vasovagal syncope. (5) As well, it is known that certain seizure types, such as simple partial seizures, usually do not contain evidence of ictal epileptiform activity on the scalp EEG, therefore a normal

EEG alone, does not necessary preclude PNES. (3)

Once a diagnosis of PNES has been made, the next set of challenges is facilitating patient acceptance of their PNES diagnosis. It is common for patients to struggle with both accepting and understanding their diagnosis of PNES. This can further confound treatment effectiveness and reduce patient compliance. (5) As well, it is important to emphasize to the patient that while their illness is not epileptic in nature, it is not any less significant than a diagnosis of epilepsy. (3) Video EEG evidence has been shown to facilitate patient acceptance of diagnosis and has been associated with improved long-term outcome. (5)

Early and correct diagnosis of PNES improves psychological functioning of the patient as well as their social vocational outcome. (1)
There are currently no definitive studies comparing the effectiveness of one PNES treatment over another. (1) Focus relies on addressing underlying psychological stressors, comorbidities and maladaptive emotional/cognitive functioning. Some PNES therapies available include, cognitive behavioral therapy, psychodynamic, family system, and learning theory. (1)

2. Review of Literature

2.1 Overview of Psychogenic Non-epileptic Seizures

Psychogenic non-epileptic seizures (PNES) refer to episodic convulsive body movements of biopsychological origin. Although PNES may appear similar to an convulsive seizure, they are not associated with electrical discharges. (1)

2.2 Aetiology

A PNES is a psychologically derived paroxysmal event which might sometimes appear clinically similar to an epileptic event; however, lacks clear epileptiform activity on an EEG. (1)

The diagnostic label of "PNES" postulates that the seizure has a psychological cause as opposed to an epileptic cause. (1, 8) A recent popular theory on PNES suggests that the episodes might be conditioned through a patient's individual experiences to become reflex-like behaviors as a response to certain emotional stressors. Evidence of this theory lies in the stereotypical yet malleable characteristic specific to PNES. (8)

2.3 Epidemiology

Roughly 5 to 10% of outpatients in epilepsy clinics and 20 – 40% of inpatients in epilepsy monitoring units do not suffer from epilepsy but in actuality have PNES. (2) PNES is relatively uncommon, with an occurrence rate of approximately 1.4-4.9 cases per 100,000 people per year. PNES usually begins in early adulthood and occurs more often in females than males. (2)

There are certain known factors which are believed to increase the risk of developing PNES, some of which include: sexual abuse, physical abuse neglect, traumatic brain injury. (2)

2.4 Clinical Manifestations

In order to correctly diagnose PNES it is important to begin with a thorough neurological and psychiatric history and examination.

A few of the most commonly occurring physical PNES features include: excessive movement of limbs, trunk and head. Some other frequent manifestations of a PNES episode includes: long duration, occurrence from apparent sleep with EEG verified wakefulness, fluctuating course, asynchronous movements, pelvic thrusting, panic symptoms, side-to-side head or body movement, closed eyes during the episode, ictal crying, memory recall, and absence of postictal confusion. (8) These specific features allow for a PNES diagnosis to be made with high confidence, however very rarely these manifestations can also occur during an epileptic seizure. This can unfortunately make clinical differentiation between the two disorders, sometimes difficult. (8) Current findings on PNES imply not only the seizures episodes to be problematic to the patient, but also the varying psychological comorbidities associated with the disorder, which may affect the patient's long-term mental health and social functioning. (8)

Historical factors which imply a likely diagnosis of PNES include: treatment resistance to more than 2 AEDs, seizures which are nonresponsive to AED therapy, clear environmental or emotional triggers, presence of witnesses during event, history of chronic pain, fibromyalgia, chronic fatigue syndromes, history of comorbid psychiatric illness, personality disorder or substance abuse, history of remote or current abuse or trauma, presence of repeatedly normal EEG in the presence of recurrent seizures. (10)

Some common semiological factors of events associated with PNES include: gradual onset, rapid post-ictal re-orientation, undulating motor activity, side-side head shaking, closed eye-lids during events, event lasting > 2 minutes, resisted eyelid opening, lack of cyanosis, partial responsiveness during ictus. (5, 10)

Clinical signs and symptoms can be helpful in diagnosis when vEEG is not available or practical. VEEG is considered to be the gold standard in PNES diagnosis. (5)

Psychiatric diagnostic evaluation with psychosocial assessment needed to gain understanding of patients developmental history, family/social information, educational/occupational history, mental health/treatment, substance abuse/ dependence, abuse/trauma/ neglect history. (5)

2.5 Comorbidities

Depression, posttraumatic stress disorder, and personality disorders all common comorbidities found in patients with PNES. (8) It is important to note that 62% of PNES patients have personality disorder, 49% have posttraumatic stress disorder, 47% have anxiety disorder, 47% also suffer from major depressive disorder. (3)

Patients with PNES have significant long-term disability and reduced quality of life which can similar to those with refractory seizures. As over 90% of patients with PNES have psychiatric comorbidities, it is of utmost importance to treat the entire patient clinical picture and to not only focus on the seizures. (4) One recent study demonstrated that sleep is more commonly reported as a problem in PNES than in people with epilepsy. (4) Research has shown that 30% of patients with PNES also suffer from one or more sleep disorders, and that the poor sleep patterns have been directly linked to reduced quality of life and negatively affected mental health in the PNES patient. (4)

Hyperventilation is an effective inducer of PNES events, with consistent rates of induction across studies. (7) PNES are a form of conversion disorder, which psychiatric orthodoxy holds results from the “conversion” of intrapsychic stress into neurological symptoms, though the aetiology and mechanism of this are unclear. Psychological states are thought to play a role. As well as a history of trauma and abuse. (7) Anxiety and stress is believed to have an etiological role in PNES, with panic symptoms often reported in PNES patients. (7)

3. Differential Diagnosis

Misdiagnosis and delayed identification of PNES is unfortunately a common challenge with 10-40% of patients in the epilepsy monitoring unit being diagnosed with PNES following long-term monitoring. (11) The average time needed for diagnosis of PNES following onset of symptoms ranges from 1 to 16 years. This profound delay inevitably leads to critical issues in regards to mental health of the patient due to unaddressed psychiatric comorbidities and other complications.

Correct and timely diagnostic testing of the patient with PNES is key for successful diagnosis and improved patient outcome. (1) With early and correct diagnosis of PNES, psychological functioning of the patient and social vocational outcome is improved. (1, 11)

Iatrogenic harm is a common and important potential issue in misdiagnosis of the PNES patient. In such cases, a patient with PNES can receive unnecessary and potentially harmful medications such as AEDs which can further lead to increased morbidity and decreased quality of life in this population. (2) The differential diagnosis of convulsive PNES is tonic clonic seizure, the DD of swoon PNES is syncope, (vasovagal or cardiac) and the DD of pseudoabsence PNES is absence seizure type. (2) Cardiac syncope can be easily excluded with ECG monitoring during an event; however, it can be more challenging to differentiate between vasovagal syncope and PNES as both events usually have similar EEG slowing or flattening. (2)

3.1 Vasovagal Syncope

One of the only main differences between swoon-type PNES and vasovagal syncope is the duration of time of the event with swoon-type PNES typically lasting much longer than typical vasovagal syncope. (5)

3.2 Epileptic Seizures

Another serious consequence of misdiagnosis of PNES is unnecessary over-reliance of AEDs, which are not shown to effectively treat symptoms of PNES and carry their own side effects and morbidity risk factors. Misdiagnosis of PNES with epilepsy also leads to unnecessary hospitalizations, and infrequently invasive tests, intubation and other medical interventions. (1) This can cause unnecessary psychological stress to the patient and their family, and can perhaps further exacerbate their PNES. (1, 11) Although the clinical appearance of a PNES event is considered to be remarkably different than that of an epileptic seizure, none of the stereotypical movement patterns of PNES are specifically pathognomonic to PNES. Some examples of typical movement patterns during PNES which differ from epileptic events include: asynchronous limb movements, intermittent shaking movements combined with periods of inactivity, side-side head movements, dystonic body posturing, pelvic movements, keeping eyes closed shut during an event, and other non-stereotypical seizure patterns. (2) Other characteristics of an epileptic seizure such as urinary incontinence, ictal injury and nocturnal occurrence are not features of PNES. (2)

Another notable difference between PNES and epileptic seizures is that ictal impairment is much less pronounced in PNES than in epileptic seizure. (9) Although PNES can sometimes appear similar to a seizure it lacks excessive synchronous cortical activity and cannot therefore be labeled as an epileptic seizure. Most patients will keep their eyes open during an epileptic seizure. Tightly closed eyes which are resistant to eye-opening during an episode are highly indicative of an PNES event as opposed to an epileptic event. (8) If a clinician is unsure of whether to start emergency AED therapy in a patient who is suffering from an unusual seizure-like event while at the clinic, it can be helpful to try and stimulate a startle response from the patient, with a loud noise. A patient who is suffering from a generalized epileptic seizure would not respond to the stimulus, but a patient experiencing PNES will. (8) Frontal lobe seizures: Due to weak EEG signs for frontal lobe epilepsy, ictal semiologic features are vital for diagnosis. (3) Frontal lobe seizures are short in duration (<30s), emerge during physiological sleep, occur in clusters,

only brief post-ictal confusion, all features which differ this seizure type with PNES. (3) There are some notable physical differences between convulsive PNES and generalized tonic clonic seizures. Unlike tonic clonic seizures, PNES events do not include incontinence, tongue biting , impaired corneal reflex, extensor plantar response, and post-ictal stertorous breathing. (3) Epileptic seizures have a characteristic development, usually starting abruptly, followed by a consistent repetitive clinical manifestation, and ending with a post-ictal period of drowsiness or other manifestations. (3) "Generalized tonic clonic seizure evolve through a stereotyped, organized progression, typically beginning with an ictal vocalization. Bilateral adduction and external rotations of the limbs ensue, followed by tonic extension of all four limbs, and then diffuse clonic jerking movements prior to ictal offset and lack of awareness throughout the seizure. (3) "In contrast with convulsive PNES: episode with begin with vocalization which can fluctuate or be persistent throughout the entire event, with more simplified, dysrhythmic asynchronous movements with varying amplitude throughout seizure, and awareness and near immediate post ictal recovery of mental capacity post seizure." (3)

3.3 Panic Attacks

Panic attacks commonly have characteristic features such as palpitations, abdominal distress, derealization/depersonalization, tremulousness, fear of losing control which are –unusual, but still possible in PNES. (3) One key difference between panic and PNES is that -panic episodes peak within 10 min, and end within 20 to 30 min. (3)

3.4 Conversion Disorder

A conversion disorder implies that the patient is not aware and is not consciously faking their symptoms or episodes. Conversion disorder is believed to be involved in most patients with PNES. (8)

3.5 Malingering

In fewer than 5% of cases, the clinical picture can resemble PNES but the patient will in fact be producing their symptoms intentionally as a result of either malingering disorder or factitious disorder. This is a rare but possible differential from PNES that should be considered. (5)

3.6 Psychogenic Movement Disorder

PMDs are a group of disorders which include abnormal movements which are not attributed to any known underlying neurological disorders. (2) They are an uncommon but important differential to consider when diagnosing PNES.

4. Diagnostic Tests and Procedures

One of the main challenges of diagnosing PNES is that tests must be done during an event in order to be most definitive, as tests which are performed between events are of limited diagnostic value. Often in PNES, events are a rare occurrence, and this further complicates the diagnosis process as, obtaining an EEG during an event can be challenging.

Based on a combination of patient history, witness reports, clinician observations, ictal and interictal EEG and ictal video. (2) Home video recordings along with a patient journal documenting description of triggers and event details are easily obtained and can aid in providing the clinician with a more objective and well-rounded picture of the patient's PNES.

Seizure induction procedures have been shown to provide sensitivity as well as high specificity for PNES and can also aid in the diagnosis of the disorder. (2) It is important for the physician to understand that no single clinical data is definitively diagnostic for PNES. (3) A thorough review of a number of clinical diagnostic evaluations and tests are necessary for a confident diagnosis of PNES. Patient history, seizure semiology, ictal/peri-ictal physical exam, ictal/interictal EEG data are all vital parts of the PNES diagnostic process. (3)

4.1 DSM/V Criteria

"DSM-5 conversion disorder criteria have now been modified to incorporate a criterion specifying the presence of signs that are not consistent with neurological disorders, making conversion disorder a "rule-in" diagnosis, rather than a diagnosis of exclusion." (12)

"Three clinical criteria yield a positive diagnostic predictive value of 85% in patients with PNES. 1) At least 2 PNES episodes per week. 2) Refractory to at least 2 AEDs 3) at least 2 routine EEGs without epileptiform activity despite ongoing seizure like episodes." (9)

4.2 ECG

The first studies which discussed electrocardiographic (ECG) changes in PNES were published approximately 25 years ago. (8) Ictal sinus tachycardia has been shown to be a common finding in PNES. The tachycardia which occurs during PNES is more gradual in onset, less pronounced and less persistent once the PNES ceases than the tachycardia which can occur during an epileptic seizure. If tachycardia occurs abruptly, then the episode is much more likely to be an epileptic seizure, than PNES. (8)

4.3 EEG

As well, PNES can sometimes resemble actual epileptic seizures. It is also common for patients to struggle with the acceptance of their PNES diagnosis. For this reason, gaining additional video EEG/ECG recordings, can facilitate patient understanding and acceptance of their disorder. Video EEG/ECG offer objective data which is straightforward and simple to interpret to the patient. Patient acceptance and understanding of their PNES diagnosis is important in assuring successful management of symptoms and compliance. (8, 12)

It is important to take into account some epilepsy patterns, such as simple partial seizures or hypermotor frontal lobe seizures which can exist without clear EEG changes. In these cases it is important to determine when the clinical picture of the PNES event resembles either a simple partial seizure (small jerking movement) or a hypermotor seizure (semi coordinated kicking movements occurring during sleep). Roughly 10 to 15% of patients with PNES, also suffer from additional epilepsy. If a patient with PNES happens to have a learning disability, then their risk of additional epilepsy further increases to approximately 30% As PNES events are often much difference in appearance and longer lasting than true epileptic events, it is always important to consider clinical characteristics of the event, along with EEG findings and adjunctive studies. (12)

In order to diagnose PNES with high sensitivity, it is crucial to capture the event by video-electroencephalogram (EEG). When distinguishing between an epileptic or

nonepileptic event, the presence or absence of epileptiform activity is key. It is not enough to capture one single event by video electroencephalogram (EEG) for a diagnosis of PNES; on the contrary, multiple, prolonged EEG recordings are needed to increase specificity and sensitivity of the diagnosis. As well; results of the EEG must always be interpreted in the appropriate clinical context. (12)

A diagnosis of PNES is made by a EEG recording which shows: an absence of ictal EEG changes, a normal awake EEG rhythm, prior to, during and subsequent to an event (with exception to sinus tachycardia). Although PNES events can be infrequent, up to 30% of patients with PNES will experience an event within a few hours of video recording; furthermore, photic hyperstimulation and hyperventilation can often stimulate PNES. (5)

There are a few adjunctive studies, which, in combination with video EEG monitoring, can aid in producing an accurate diagnosis of PNES. Examples of adjunctive studies in PNES diagnosis include: serum prolactin (PRL) level and postictal EEG monitoring. It is important to understand that these two additional studies are not able to diagnosis PNES accurately without the added information of video EEG monitoring. (5)

Serum PRL is usually elevated following a tonic clonic seizure, therefore a normal postictal PRL is a highly sensitive method of eliminating tonic clonic seizure from the differential diagnosis. (5) Possible false positive serum PRL can occur due to a number of different methods such as a response to dopamine agonists or tricyclic antidepressants. It is important to rule out other possible sources of increased serum PRL when diagnosing PNES. (5) Diagnosis of PNES cannot rely on video EEG alone. (8)

The EEG during syncope usually contains a predictable pattern changing from theta slowing, to delta slowing, ending with a background suppression. (3) VEEG offers the diagnostic gold standard in PNES diagnosis. Evidence has shown that video data alone, without EEG viewed by experienced epileptologist provides a sensitivity of (93%) and specificity of (94%) in diagnosis of PNES. (3) It has been shown that 79% of simple partial seizures do not show ictal epileptiform evidence on scalp EEG. Therefore it is important for the physician to understand that seizure with preserved consciousness,

small motor movement, and lack of epileptiform activity on EEG can still be epileptic despite normal EEG. (3)

4.4 Neuroimaging

As of yet there has been no clear association between PNES and structural or functional brain lesions. (8)

4.5 ILAE Diagnostic Criteria

The international League against Epilepsy has laid down specific criteria to aide in the diagnosis of PNES with greater probability. The ILAE criteria for PNES diagnosis separates diagnostic certainty in four separate levels, those of which include: Possible, Probable, Clinically Established, and Documented. (13) A positive event history with or without a witness, and a negative EEG suggest a possible PNES diagnosis. If the event was witnessed directly by a clinician and the EEG is negative then the diagnosis of PNES becomes probable. If the event appears clinically similar to PNES, and is witnessed by a clinical, with no epileptiform activity during the actual event then the diagnosis has become clinically established. If the event occurs during a video EEG, in the presence of a clinician with experience in seizure disorders, and no epileptiform activity is captured, then the diagnosis is Documented. (13)

4.6 Neurobiological Origin and biomarkers

The neurobiological origin of PNES is considered to be the result of neurobiological dysfunctions at specific brain networks and abnormal connectivity of the networks. Functional MRI studies have shown conflicting findings towards PNES to be hyperlinked with dissociation and emotional dysregulation centers in the brain. As of yet, biomarkers have been generally nonspecific. (2) In a recent study, serum glial fibrillary astrocyte protein (GFAP) levels were measured in patients presenting with either PNES or

Epileptic seizures. (14) Serum GFAP levels were found to be significantly higher in patients who suffered from epileptic seizures as opposed to patients who had PNES. A cut off point of 2.71 ng/ml was found to best differentiate ES from PNES with a sensitivity of 72% and specificity of 59%. (14) The results of the study concluded that serum GFAP levels could eventually be used as an additional diagnostic test to differentiate between epileptic seizures and PNES. (14)

5. Review of Therapy

Once a diagnosis of PNES has been confidently reached, method of conveying the diagnosis to the patient is of utmost importance and is considered to be the first step in treatment of the patient with PNES. (1) It is important to explain the diagnosis of PNES in a non-judgmental, clear, objective way and to avoid the use of pejorative labels such as "pseudo-seizure" whenever possible. Providing the patient with background material on the subject can also be helpful in achieving patient comprehension and understanding of their disorder. (1) It is considered to also be helpful to assure the patient that their symptoms are in fact real, despite lack of EEG findings, and thus must be treated with appropriate therapy. Psychological counselling is considered to be the most effective treatment in PNES and should be recommended to the patient. (1) Since PNES is considered to be a maladaptive response to psychological stress, treatment of PNES consists of identifying and managing the underlying stress; as well, treating possible comorbidities and maladaptive emotional functioning. (1) Psychological therapy is considered the first line treatment in managing PNES. Psychological therapy focuses mainly on teaching the patient to identify their triggers, and manage emotional stress in a healthy way.

Specific examples of PNES therapies include: cognitive behavioral therapy, psychodynamic, family system, learning theory, with neither therapy showing more promising results than another. (1) Currently, there are no universally accepted guidelines on the specific type treatment for PNES. PNES therapy has been described to occur in four steps.

<u>Phase one:</u>

The delivery of the diagnosis of PNES to the patient has been shown to be a very important step and is considered the first step of treatment. If possible, it can be beneficial to have some family members present for this step as this will improve the emotional support of the patient. (2)

Phase Two:

Phase two primarily consists of patient acceptance of diagnosis and subsequent active engagement in the prescribed therapy. Some patients have been shown to need some time after receiving their diagnosis in order to ultimately accept their diagnosis and begin to engage in the recommended therapy or referrals.

Some signs that a patient has successfully entered phase two of their PNES treatment include not seeking second opinions and beginning to actively participate in treatment. (2)

Phase Three:

Phase three of PNES treatment includes acute intervention. It is during this phase that predisposing, precipitating, perpetuating factors are further identified and investigated. Once these factors have been identified, individualized psychotherapeutic and psychopharmacological treatment plans can then be formulated for the patient. Phase three ultimately aims to reduce seizure occurrence, treat psychiatric comorbidities and improve overall quality of life. (2)

In one pilot randomized clinical trial with 34 patients, a combination of cognitive behavioral therapy informed psychotherapy (CBT-ip) with medication (sertraline) was shown to be the most effective treatment option with a 59.3% seizure reduction compared to less favourable results in patients who were treated with medication alone or CBT-ip alone. (2)

Pharmacological treatment plan should include early tapering and discontinuation of AEDs. Psychopharmacologic agents (e.g sertraline, venlafaxine) should be used to treat comorbid mood, anxiety or psychotic disorders.

Phase 4:

Phase four is the last phase for PNES treatment and is particularly important for patients who continue to suffer from seizures. This phase includes all longterm PNES therapy, including long-term psychotherapy, case management and ongoing psychotropic management of psychiatric comorbidities. (2)

Conveying diagnosis to the patient is considered to be a vital step in successful management of the disorder. When explaining the non-epileptic nature of PNES to the patient, it is very important to emphasize that the patient's illness experience is not any less significant than epilepsy. (3) A Recent study focusing on multimodality CBT-informed psychotherapy based on a workbook used by therapists and patients, displayed reduction in seizures, comorbid symptoms and also an improvement of functioning in the patient. (3) It is also important to consider that once diagnosis has been established, AEDs should be tapered carefully under the supervision of a neurologist, with follow up management. (3)

6. Prognosis

Long term outcome of PNES:

The long-term outcome in patients with PNES has not been shown to be favorable, with less than 40% of patients achieving seizure freedom within 5 years following diagnosis. (2)

Furthermore patient compliance and acceptance of their disorder remains a common and confounding factor in achieving adequate seizure control and improvement in psychiatric comorbidities associated with their disorder. (2)

Once a formal diagnosis has been delivered to the patient, in which the patient learns that their seizures are not epileptic, it is not uncommon for PNES events to stop for a short period of time. Unfortunately, in the majority of cases, the PNES event will eventually return unless diagnosis acceptance has been achieved, and the patient is actively engaging in their prescribed treatment therapy. (2) Even in the event of achieving seizure freedom, it is still vital to address the patient's potential psychiatric comorbidities, to ensure improved social functioning and quality of life in the long term. (2)

7. Discussion

PNES is a conversion disorder composed mainly of psychologically derived seizures which are rooted as a maladaptive response to psychological stress, with past trauma and abuse possibly playing an etiological role. (3,7) PNES is a serious disorder which can result in significant long-term disability paralleling that of refractory epilepsy. (3, 1, 4) Anxiety and stress are believed to play a significant role in PNES, with panic symptoms being commonly reported in PNES patients. (7)

Common, physical PNES features include: excessive movement of limbs, trunk, head, along with pelvic thrusting, and closed eyes during the episode. (8) PNES events also tend to be long in duration, occur from apparent sleep with EEG verified wakefulness, have a fluctuating course, asynchronous movements, panic symptoms, ictal crying, memory recall, and absence of postictal confusion. (8) All of these features distinguish PNES from epileptic events. Notably, ictal impairment during PNES is much less pronounced than what you would expect to find in an epileptic seizure. (8)

Many different and varying conditions must be considered in the differential diagnosis of PNES, with tonic clonic seizures, syncope and absence seizures being the most likely alternatives. (5) It is important to address and eliminate all other disorders in the differential diagnosis before determining the events to be PNES and making a final diagnosis. An accurate diagnosis of PNES, with care taken in delivering diagnosis to patient is an essential aspect of minimizing complications and unfavorable outcome in PNES. Early, correct diagnosis of PNES results in improved psychological and social vocational outcome of the patient. (1)

Identifying individual stressors, and promoting healthy strategies aimed at reducing emotional stress are paramount to reducing PNES events, improving symptoms of comorbidities, and overall functioning of the patient. (1)

Misdiagnosis and delayed identification of PNES continue to be troublesome with up to

40% of patients in the epilepsy monitoring unit being diagnosed with PNES following long-term monitoring. (1) Misdiagnosis and delayed diagnosis of PNES is known to result in complications such as unnecessary hospital visits, invasive testing, over reliance of AEDs, unaddressed psychiatric comorbidities and more. (1) All of which further exacerbate PNES by adding unnecessary psychological stress to the patient and their family. (1)

Diagnosis of PNES rests on a combination of patient history, witness reports, clinician observations, ictal and interictal EEG and ictal video, with no single clinical data being definitively diagnostic. (2, 3) Home video recordings are easily available and can e of aid in the diagnosis. Seizure induction procedures have decent sensitivity and excellent specificity rates for the diagnosis of PNES. (2) Hyperventilation is a helpful diagnostic tool to consider, as it is an effective inducer of PNES events, with consistent rates of induction across studies. (7)

Video EEG remains the gold standard in diagnosis of PNES, providing objective data which is straightforward and easy to interpret to the patient, and their relatives. (5) Video EEG results aide in patient acceptance of the non-epileptic nature of their illness, and ultimately allows for improved patient compliance and enhanced effectiveness of PNES therapy. (5)

Psychological comorbidities are a significant aspect of PNES as they can occur in over 90% of patients. The most commonly occurring comoridites of PNES include depression, PTSD, and personality disorders. (6) These disorders can further disrupt the functioning and well-being of the patient, and long-term outcome.

Currently there are no universally accepted guidelines on the type or duration of treatment which is best suitable for PNES. (2) Treatment of PNES has been conceptualized to occur in four phases, namely, diagnosis delivery, patient engagement,

and acute intervention, (2) Cognitive behavioral therapy informed psychotherapy (CBT-ip) with medication (sertraline) has been shown to be an effective treatment option in PNES with a 59.3% seizure reduction. (2)

Only 40% of patients with PNES go on to achieve seizure freedom within 5 years of diagnosis. (2) As well, patient compliance and acceptance of their disorder remains a limiting factor in long-term improvement of psychological comorbidities and PNES event control. (2) Psychological comorbidities should be treated and followed in order for best possible PNES outcome to be achieved. (2)

8. Conclusion

In conclusion, PNES is a psychologically derived paroxysmal event with emotional stress, past history of abuse as the main possible triggers. (1) The clinical aspects of PNES can at times resemble that of epileptic seizures but are distinguished by their lack of epileptiform activity on EEG. (1)

Misdiagnosis and delayed diagnosis of PNES present the most serious problem of this disorder and results in unaddressed psychiatric comorbidities and prolonged AED use, unnecessary hospital visits. (1) Correct and timely diagnostic testing of the patient with PNES is key for successful diagnosis and improved patient outcome. (1)

There are currently no universally accepted guidelines on the type or duration of treatment for the best PNES outcome. (2) (CBT-ip) with medication (sertraline) has been shown to be an effective treatment option in PNES with a favorable seizure reduction. (2)

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11. Biography

Christina Cosic was born in 1984, in Toronto, Canada. She is married with two children. Her oldest daughter suffers from severe refractory epilepsy. In 2016, Christina developed an epilepsy management application, along with her husband, brother, and sister-in-law, to help improve her daughter's epilepsy. The app is currently helping thousands of people with epilepsy around the world to identify their seizure triggers, manage the ketogenic diet, remember to take their medication, reduce their risk of SUDEP and share their seizure history with their medical team. Christina is passionate about neurology and hopes to specialize in Pediatric Neurology.