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Psychogenic Non-Epileptic Spells

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1. Introduction

The psychogenic non-epileptic spells are the most frequent referrals to the specialized epilepsy center because of the intractable nature of the spells. Psychogenic non-epileptic spells (PNES) are also referred to as “pseudoseizures”, psychogenic seizures, non-epileptic seizures or stress-related spells [1]. PNES is a form of conversion disorder but misdiagnosis and delay in diagnosis is common [2,3,4]. The reason for misdiagnosis is overinterpretation of the EEG and lack of data regarding the semiology of the spells. The gold standard is to capture these spells for definitive diagnosis under medical withdrawal in an epilepsy monitoring unit by video-EEG. The PNES are not epileptic seizures but they are extremely disabling and adversely affect quality of life [5,6].

2. Epidemiology of psychogenic non-epileptic seizures

The prevalence of PNES was reported by Benabadis and colleagues in a retrospective review. Benbadis et al conducted a retrospective review of available prevalence, incidence, and hospital-based data to estimate the prevalence of PNES. The prevalence was based on the following generally accepted data: prevalence of epilepsy is 0.5-1%, and proportion of intractable epilepsy is 20-55%, and 10-20% of patients referred to epilepsy centers are found to have PNES. From these data, using a prevalence of epilepsy of 0.5% to 1%, a low estimate was determined to be 1/50,000 and a high estimate was determined to be 1/3,000. The conclusion of this retrospective review was that there was a prevalence of 2 to 33 people per 100,000 [7]. The only population based study which estimated the incidence of PNES was conducted

by Sigurdardottir et al. Sigurdardottir and colleagues conducted a retrospective chart review of all long-term video EEG studies made in Iceland from January 1992 to December 1996 in order to determine the incidence of PNES. All patients were aged 15 or greater and had been diagnosed with PNES at National University Hospital (Landspítalinn), Iceland. The diagnosis of PNES was determined by clinical observation and EEG, and all of these patients underwent long-term video-EEG monitoring (LVEM). A total of 14 patients met the inclusion criteria and were aged 16-54 years (mean 27.6). There were 11 female patients (78.6%). There was an average annual population of 200,191 persons aged 15 years or greater for a total of 1,000,955 persons over the entire study period. The incidence of PNES was 1.4 in a 100,000 population. The 15-24 year old age group had the highest age-specific incidence. The incidence decreased in subsequent older age groups. Half of the patients (N=7) also had epilepsy, with the majority having generalized tonic-clonic seizures only (N=3), followed by Generalized tonic clonic seizures (GTC) and myoclonus (N=2), tonic seizures (N=1), and absences (N=1). 2 of 7 patients with PNES and without epilepsy were on antiepileptic drug (AED) treatment prior to PNES diagnosis. The researchers concluded that the incidence in people aged 15-24 years was ~5% of the incidence of epilepsy and 4% of reported epilepsy from Iceland for persons aged ≥ 15 years [8]. Szaflarski and colleagues conducted the retrospective study which determined the incidence of PNES in a medium-sized urban community. Adult patients who underwent prolonged video and EEG monitoring (PVEM) were identified between January 1, 1995 and December 30, 1998 at the University Hospital or Veteran Administration Medical Center in Cincinnati, OH. Patients were classified into four groups: definite PNES, possible PNES, possible epilepsy, and definite epilepsy. A board-certified electroencephalographer reviewed all tracings and videos. Population characteristics were examined with univariate analysis and comparison of similar features between patients with PNES and those with epilepsy were analyzed with bivariate analysis. During the study period, 600 patients were monitored with 3 patients at the Veteran Affairs Medical Center and 174 at the University of Ohio fulfilling the residence criteria. Definite PNES was diagnosed in 77 patients and definite epilepsy was diagnosed in 85 patients. Also, there was an increase in the incidence of PNES over the study from 1.88/100,000 in 1995 to 4.6/100,000 in 1998 (mean incidence 3.03/100,000). Patients aged 25-45 years had the highest incidence of PNES (4.38/100,000). Groups of patients with PNES had a shorter average duration of illness before diagnosis and were more likely to have a history of psychiatric disorders (48.6% versus 30.4%; $p=0.023$) than definite epilepsy patients. Epilepsy patients were more likely to be treated with more antiepileptic drugs before admission than PNES (4.85 versus 2.53; $p<0.001$). No significant differences were found in the PNES compared with epilepsy groups in gender (women 73% versus 60%), age (37.2 versus 37 years), or history of febrile seizures, head trauma, or family history of epilepsy. The authors conclude that improved access to PVEM and higher clinician awareness may be related to the increasing incidence of PNES over the study period [9].

2.1. Psychogenic non-epileptic seizures in different population subgroups

2.1.1. *Psychogenic non-epileptic seizures in women*

Psychogenic seizures are more common in women. Women account for approximately 70 to 80% incidence of PNES, but the incidence varies depending on the etiology [6,10, 11,12]. There are certain factors that contribute to the increase risk of PNES. The most important factor is the history of sexual abuse seen more commonly in women. This issue has also been addressed historically by Freud based on his observations. Freud's earlier observations describe Hysteria which is now the basis of the concept of psychogenic non-epileptic seizures. Hysteria is a Greek word which means "wandering uterus" and is related to history of sexual abuse in women and repressed sexual drives [13,14]. Alper and colleagues in a case series described the history of sexual abuse in approximately 25% of the patients with PNES [12].

2.1.2. *Pseudoseizures in the elderly*

There are several studies which show the prevalence of pseudoseizures in the elderly. McBride et al performed a retrospective chart review in elderly patients in order to determine the utility and results of video-EEG monitoring. All patients admitted to the epilepsy monitoring unit at Columbia-Presbyterian Medical Center from January 21, 1991 to April 12, 1999 aged 60 years and older were reviewed. Reasons for admission included diagnosis of paroxysmal events, further characterization of known seizure, pre-surgical evaluation, medication adjustment or toxicity, and evaluation to rule out non-convulsive status epilepticus or subclinical seizures. Ninety-four patients were identified with 99 admissions, with five patients having two separate admissions, comprising 8% of all admissions. There were 62 females and 37 males. On average, patients were 70 years old and ranged from 60-94. The mean length of the stay was 3.8 days and ranged from 1-14 days. The most common reason for admission was to diagnose the nature of paroxysmal events (56%). A total of 118 epileptic seizures were recorded in 46 patients. Ninety-eight non-epileptic events were recorded in 27 patients. Both epileptic seizures and non-epileptic events were found in four patients. Of those with non-epileptic events, 13 patients had psychogenic seizures. There were epileptiform discharges in 26% of patients with non-epileptic events and 76% of patients with epileptic events had interictal epileptiform discharges. The authors concluded that in the majority of patients, video-EEG monitoring in elderly patients led to a definitive diagnosis. Also, they concluded that non-epileptic events are common in the elderly, including PNES, and are often misdiagnosed and mistreated as epileptic seizures [15]. Abubakr et al performed a retrospective chart review study to report the results of video/EEG recordings in patients aged 60 and older at the new Jersey Neuroscience Institute. An electronic medical record search between December 1999 and December 2001 was reviewed for all elderly patients admitted to the epilepsy monitoring unit (EMU) found 58 patients who underwent video/EEG. The elderly population accounted for 17% of EMU admissions. The reasons for video/EEG monitoring for study patients were diagnosis of events (33 patients, 57%), characterization and localization of seizure (21 patients, 36%), adjustment of medication (2 patients, 3%), and non-convulsive status epilepticus (2 patients, 3%). Study subjects were ranged between 60-91 years old and 45% were females. Six

patients had psychogenic non-epileptic seizures (PNES), with five of them being women and 4 of them being greater than 70 years old. One patient presented with abdominal spasms and the others with motor symptoms. Two of six patients had a suspected diagnosis of PNES on admission. Physiologic non-epileptic seizure was the most common diagnosis and occurred in 26 patients (45%). The diagnosis of non-epileptic seizures in 27% of these patients resulted in AED discontinuation. The most common seizure type was complex partial seizures and occurred in 23 patients (40%). Six of these patients had both complex partial seizures and secondary generalization. The authors concluded that in the majority of cases, video/EEG monitoring in the elderly results in a definitive diagnosis and assists physicians with antiepileptic drug therapy management decisions [16]. Kawai et al conducted a retrospective review of video-EEG monitoring in geriatric veterans from 1999 to 2006. All patients admitted to the epilepsy monitoring unit at Michael E. DeBakey Veterans Affairs Medical Center of Houston, Texas were reviewed. Of the 440 admissions during this time, 71 of these patients were aged 60 and older, which included multiple admissions. Ninety-four percent of these were males, and the average age was 68 years. The mean duration of monitoring studies was 73.7 hours (range 2-96 hrs). Thirty-four of 71 patients (48%) had typical events, including 12 with epileptic events (35%). Nine patients (75%) had temporal lobe seizures, 2 patients (17%) had extratemporal seizures, and 1 patient (8.3%) had poorly localized seizures. The most common etiology was not identifiable (7 patients), and intracranial hemorrhage and history of tumor resection (2 patients). Non-epileptic events were seen in 22 of 71 patients (65%). Ten patients (45%) had PNES and 12 patients (55%) had physiologic non-epileptic seizures. Of the patients with non-epileptic seizures, 14 of 22 (65%) were on AEDs before video-EEG monitoring with 6 having PNES and 8 having physiologic non-epileptic seizures. The authors concluded that video-EEG monitoring in elderly patients was useful to guide physicians to the appropriate diagnosis and treatment of paroxysmal seizure-like symptoms [17].

2.1.3. Psychogenic Non-Epileptic Seizures (PNES) in children

Psychogenic non epileptic seizures (PNES) in children are transient, episodic alterations in behavior that mimic true epileptic seizures but without abnormal electrical discharges. PNES was found in 3.5 % [18] in one study and 7% [19] in another study in children that were evaluated in neurology clinics for persistent seizures. There is a paucity of literature regarding this entity in children and adolescents. In most cases, there is delay in the diagnosis of months [11,18,20]. During the delay, patients are labeled as being epileptic and are usually started on antiepileptic medication. Poor response to the medication and frequent visits to the emergency room are common. The cost of misdiagnosing PNES as epileptic seizures is very high from economic and psychosocial aspects. The distinction of PNES from epileptic seizures is difficult to be made solely on clinical grounds. The clinical manifestations of PNES vary according to age as reported by some investigators. Younger children tend to manifest more subtle motor activity which includes eye fluttering, head shaking, staring, unresponsiveness and limpness. In contrast, adolescents tend to manifest prominent motor activity which includes side to side head movements, thrashing or flailing movements of the extremities, generalized arrhythmical jerking and pelvic thrusting [11]. Triggering factors include school phobia, familial problems, social difficulties with peers or friends and sexual abuse [18,20]. Comorbid conditions include

anxiety disorders and mood disorders [19,21]. The differential diagnosis of PNES is broad and includes frontal lobe seizures, vasovagal syncope with anoxic seizures, breath-holding spells, self-stimulatory behavior, gastroesophageal reflux, stereotypes, complex motor tics, parasomnias, paroxysmal kinesigenic and non-kinesigenic dyskinesias.

PNES should be strongly suspected when there are atypical clinical features, poor response to medications in spite of adequate trials and when several routine electroencephalograms have been reported within normal limits [22]. Metrick et al conducted a retrospective chart review and analyzed the records of children referred for the treatment of intractable epilepsy. A total of 222 records were found for children aged <16 years admitted to the MINCEP Epilepsy Program for Children in St. Paul, Minnesota for evaluation and treatment of refractory seizures between August 1986 and August 1988. Children with normal and abnormal intelligence were included. All children had at least 24 hours of video-EEG monitoring. Of the 222 children admitted, 27 patients (12%) had non-epileptic events on video-EEG monitoring. Study subjects were aged 7 months to 16 years (median 8.4 years) with 18 females. The study called these 4 different group pure psychogenic events (5 patients), psychogenic events plus epileptic seizures (3 patients), pure non-epileptic physiologic events (5 patients), and non-epileptic physiologic events plus seizures (14 patients). Parents or caretakers identified a history of multiple seizure types in all groups except the children with pure psychogenic seizures. Twenty-two patients (64%) had a history of status epilepticus. Twenty-five of 27 patients had a history of interictal epileptiform abnormalities on previous routine EEGs. Eight patients (30%) had their AEDs completely discontinued after the non-epileptic events were identified. Nine other patients (33%) were able to reduce the number of AEDs in the treatment regimen. The researchers concluded that in all children with refractory seizures or multiple seizure types a diagnosis of non-epileptic events should be considered [23]. Prolonged video electroencephalogram is the gold standard for diagnosis and an effort should be made to capture the typical spells that may occur spontaneously or induced by provocative measures. Definite diagnosis is made when several episodes are captured which are not associated with abnormal EEG changes. Careful consideration must be given to the fact that lack of epileptic changes in the electroencephalogram does not conclusively indicate that the episode is PNES. Frontal lobe seizures and some complex motor seizures originating from deep seated focus may manifest motor activity and normal electroencephalograms resembling PNES. Prolonged video electroencephalograms capturing several typical events may be required to make the correct diagnosis. Measuring serum prolactin levels to distinguish PNES from epileptic seizures is not routinely used in children and may have several limitations. Once the diagnosis is established, information needs to be conveyed to the family and patient in a non-judgmental tactful manner and patient needs to be referred to a mental health specialist to determine appropriate therapy which include counseling and if required psychotropic medication to treat co-morbid conditions. Prognosis in children is much better than in adults and a significant percentage were PNES free several years after the diagnosis was made [22,24].

2.1.4. *Patients with dual diagnosis of both seizures and Psychogenic Non-Epileptic Seizures*

The most complicated patients are those who have both epilepsy and Psychogenic non-epileptic seizures. The gold standard remains prolonged video-EEG monitoring in an epilepsy monitoring unit to characterize all events for definite diagnosis. Ten to 40 % patients with PNES also have true epilepsy as reported in the literature [25-29]. Interictal EEG abnormalities have also been reported in patients with PNES but they should not be interpreted as evidence of epilepsy [30].

Benbadis and colleagues performed a retrospective chart review study to determine the proportion of patients with psychogenic non-epileptic seizures (PNES) who also have evidence of epilepsy. The authors reviewed all adult patients with PNES who underwent EEG-video monitoring from January 1 to December 31, 1999. Patients were excluded if their episodes mimicked simple partial seizures or if they had a loss of consciousness. One or both board-certified electroencephalographers determined if there was evidence for epilepsy defined by epileptiform discharges, including sharp waves or spikes, spike-wave complexes, polyspikes, or any ictal pattern. Over this one-year period, 211 patients were monitored and 32 patients (15%) were diagnosed with PNES. Study patients mean age was 33.8 (range 19-72) and 20 (62%) were females. Three patients (9.4%) of the 32 patients with PNES had interictal epileptiform discharges, 20 (62%) had completely normal EEG, 6 (19%) had normal variants (three wicket spikes, three small sharp spikes), and 3 (9.4%) had mild nonspecific abnormalities (mild slowing or asymmetry). The three patients were on lower doses or no antiepileptic drugs. The authors concluded that epilepsy coexists with PNES in a small portion of patients [31]. Martin et al conducted a retrospective study to examine the frequency of epilepsy in patients with a definitive diagnosis of PNES by video-EEG monitoring from July 1, 1998 to December 31, 2002. All patients consecutively admitted to the video-EEG monitoring unit at the University of Alabama at Birmingham Hospital were reviewed. Patients were referred for characterization of paroxysmal events for undiagnosed events with uncertainty of epileptic seizures versus psychogenic events, probable epileptic seizures with classification of seizure type, or probable epileptic seizures with localization of seizures for possible surgery. This was the first video-EEG monitoring for all patients with the average duration of 3 days (range 1-7 days). A total of 1,590 patients received a definitive diagnosis and were included in the study of 2,007 patients receiving video-EEG monitoring. PNES was diagnosed in 514 patients (32.3%) with 29 of these patients (5.3%) having both PNES and epilepsy. Other than PNES, non-epileptic diagnoses occurred in 65 patients (3.2%), including sleep disorders, migraine, panic attacks, dysautonomia, movement disorders, TIA, cough syncope, and vestibular symptoms. The authors concluded that in patients referred for video-EEG monitoring there is little overlap between epileptic seizures and PNES when strict diagnostic criteria are applied [32]. Kirmani et al conducted a retrospective chart review of all patients with epilepsy admitted to the Scott and White Hospital epilepsy monitoring unit in Temple, TX from 2008-2011. Fourteen patients who were admitted to the EMU due to increased frequency of seizures or for characterization of new kinds of spells were found to have epilepsy and concomitant PNES. The mean age of study patients was 43 years (range 21-67 years) with 10 females (71.5%) and four males (28.5%). The majority of patients had partial epilepsy (N=11, 78.6%) followed by generalized epilepsy

(N=3, 28.4%). Concurrent psychological disorders were seen in 12 of 14 patients, including depression (64%), anxiety (50%), and physical/sexual abuse (29%). On average, study patients were on 2.6 AEDs (range 1-5) and had failed 2.1 AEDs (range 0-9). Eleven patients (78.6%) improved with regular counseling. Three patients (21.4%) with mental retardation did not show improvement with regular counseling. The authors concluded that video-EEG monitoring is helpful to characterize increased frequency and new episode characterizations as well as the need for a multidisciplinary team approach between neurologists, epileptologists, psychiatrists, and psychologists to best manage these patients [33]. The reason for dual diagnosis is the development of psychiatric problems in patients with chronic long standing epilepsy or the presence of concomitant psychiatric disorders [34]. Most of the patients generally have fairly well controlled epilepsy when they develop PNES but still represent a difficult group of patients regarding management [35,36].

3. Clinical semiology of Psychogenic Non-Epileptic Seizures

Careful history plays a key role in the diagnosis of non-epileptic events. The history should include the seizure triggers and careful history of the semiology of the seizures from the witness. The history should also include the duration, alteration of consciousness, type of convulsive movements experienced during a seizure, presence or absence of tongue bite, urinary incontinence, autonomic symptoms, emotional symptoms like weeping or crying and eye opening and closure as these will all help in establishing the correct diagnosis.

The PNES usually occur in front of the witness or in a clinical setting [37]. The PNES occur during daytime but not during sleep. Presence of nocturnal events raise suspicion for epileptic rather than nonepileptic seizures [38]. The other finding is the frequency of seizures. Non-epileptic seizures are more common than epileptic seizures and frequency may range from daily spells to several times a week [39].

Ictal features of PNES include purposeful or semipurposeful movements, thrashing, writhing, side-to-side head jerking and pelvic thrusting which are different from synchronized tonic – clonic activity in true epileptic seizures [38-40]. Leis and colleagues conducted a retrospective chart review study to analyze ictal features in patients with psychogenic seizures undergoing video-EEG monitoring. At the Epilepsy Unit of University of Iowa, 254 patients were monitored, and 47 (18%) had psychogenic seizures and videotaped recordings to analyze their typical events. Twenty-seven patients were female (57%) and 20 were men (43%). There was a mixed seizure disorder in 11 of 47 patients (23%). The most common ictal presentation was unresponsiveness without predominant motor manifestations. The motor characteristics of out-of-phase limb movements, side-to-side head movements, and pelvic thrusting had been previously considered to distinguish psychogenic seizures, they were observed infrequently (19%, 15%, and 8% respectively). Antiepileptic drug therapy was administered to 35 patients (74%) for their spells. Of these 35 patients, 25 (69%) had pure psychogenic seizures. Six of these 25 patients (4 women, mean age 27 years) with pure psychogenic seizures were treated pharmacologically for status epilepticus entirely due to observation without even a cursory

neurologic exam or chart review. Aggressive treatment of status epilepticus in 1 patient escalated to the point of respiratory arrest in 1 woman who was 2 months pregnant. A psychogenic cause to these spells was not considered in the differential diagnosis until all the patients failed to respond to pharmacologic treatment. The authors concluded that in treatment of seizures, even in the acute care of presumed status epilepticus, the diagnosis must not be based solely on inspection and should be supported by the history and physical examination findings [41]. The other study which provided detailed semiology of PNES was conducted by Seneviratne and colleagues. Seneviratne et al conducted a retrospective study of the semiology of PNES captured by video-EEG monitoring and categorized the observed patterns. From January 2002 to June 2007 the medical records were reviewed of all adult patients who underwent monitoring (mean 3, range 1-8 days) at two tertiary care epilepsy centers. Patients with PNES and no background of epilepsy were selected for the study. Sixty-one patients were identified with 330 PNES events with a mean number of 5 events recorded per patient. There were 45 females and 16 males with a mean age of 38 years (range: 16-83 years). Three types of motor manifestations were detailed on visual analysis of PNES events. 1) Rhythmic Motor PNES: 47.6% of all PNES events, rhythmic tremor, trembling, or rigor like movements of the upper limbs more commonly than the lower limbs. 2) Hypermotor PNES: 3.3 % of all PNES events had hyperkinetic or hypermotor movements with violent thrashing, punching or kicking involving the extremities or trunk. 3) Complex Motor PNES: 10% of all PNES events had complex motor movements with complex and multifocal asymmetrical movements of both proximal and distal extremities with flexion, extension, and ab/adduction. 4) Dialeptic PNES: 11.2% of all PNES events had prolonged, motionless, unresponsive patients with no motor manifestations who appeared to be in a coma-like state unresponsive to external stimuli. 5) Nonepileptic auras: 23.6% of all PNES events had various subjective sensations without any external manifestations described by the patients as "I feel weird", "zoning out", and "I am going through a trance". 6) Mixed PNES: 5.2% of all PNES events had a combination of types 1-5. Eighty-two percent of cases had the same semiologic type in a given patient. The authors concluded that the PNES patients they studied had highly stereotypic events within and across individual patients [42].

The other features including clenched mouth during a tonic seizure and injuries on the tip of the tongue rather than the sides points towards the diagnosis of PNES [43]. Ictal eye closure is also considered a sign of a psychogenic event [43,44]. Chung et al conducted a retrospective study of video-EEG monitoring data to study whether persistent ictal eye opening and closure was reliable to differentiate between ES and PNES. From July 2003 to June 2004, 234 consecutive patients (age 6-65 years) underwent long-term video-scalp EEG monitoring at the Barrow Neurologic Institute. 221 patients had a total of 938 ictal events (median number of seizures per patient=4). Fifty-two of 221 patients (23.5%) had PNES and 156 (70.6%) had ES. Seventy-five percent of patients with PNES were female. During habitual seizures, 50 of 52 PNES patients consistently closed their eyes for the entire duration of the seizure and a few who closed their eyes forcefully with facial frowning. However, 152 of 156 patients with ES had their eyes deviated to one side or were open. Rhythmic eye blinking was seen during tonic-clonic activity, followed by postictal confusion with eye closure. There was a positive predictive value of 0.943 (sensitivity of 96.2% and specificity-

ty of 98.1%) of ictal eye closure indicating a high likelihood of PNES. Conversely, true epileptic seizures had an ictal eye opening and had a high positive predictive value of 0.987 (sensitivity 98.1% and specificity 96.2%). Thus the authors concluded that careful history taking of seizure semiology may help discern between ES and PNES and home video clips of a seizure may help to make the diagnosis without long-term monitoring [44]. Autonomic symptoms are absent in PNES but weeping, ictal stuttering, partial preservation of consciousness and later recall of the ictal event also suggest PNES [38,45,46]).

4. Diagnosis of Psychogenic Non-Epileptic Seizures

The evaluation and diagnosis of PNES requires careful history and diagnostic testing. Ali et al conducted a literature review of PNES to make suggestions for treatment and to aid clinicians in identifying PNES episodes. The mean time between developing clinical symptoms and establishing a correct diagnosis of PNES is 7.2 years. Physicians can facilitate early diagnosis by referring patients with atypical features for video-EEG monitoring. General features that can raise a physician's suspicions include high seizure frequency with multiple emergency room visits, association with multiple other psychiatric disorders, comorbid personality disorders, abuse history, lack of response with treatment, and lack of loss of control over bladder or bowel during episodes. PNES pre-ictal features include pseudo sleep, which shows a sensitivity of 56% and specificity of 100% for pseudoseizure. PNES events typically are witnessed and begin gradually at time of stress or visual/auditory stimuli. Ictal features of PNES include asynchronous contractions, non-stereotypic movements that change during the episode, and a lack of rapid contractions with slow relaxation pattern seen in true epileptic clonic seizures. Patients may exhibit side-to-side head movements, forceful eye closure, and ictal vocalizations. Post-ictal features are easy to recognize, and physicians should watch for a short duration (~1 minute) shallow, irregular, and quiet breathing pattern, as well as the absence of confusion, headache, and fatigue. Lab findings that are not present after PNES episodes but are present after epileptic seizures are elevated serum prolactin, creatine kinase, ammonia, and white blood cell count. Video-EEG is highly recommended for patients with atypical features and in one study found that 24 percent of subjects had been misdiagnosed with epilepsy that had an accurate diagnosis of PNES. When a patient is informed of their diagnosis, they should be referred to a psychiatrist for treatment and neurologists remove AEDs, but the complete care away from neurology until the spells have decreased. The authors believe this is due to the disruption of the rapport that neurologists have with the patient, negatively affects the outcome of PNES, and premature discharge to psychiatry may increase patient resistance to accept the diagnosis. Predictors of good outcome include shorter duration of spells, presentation in children and adolescents, mild psychiatric history, identifiable acute psychological trauma, and independent living. The authors conclude that skilled clinicians can make a diagnosis based on clinical findings and their guidance can be used to help clinicians make the diagnosis of PNES [47].

Prolonged video-EEG monitoring is now considered the gold standard. Additional studies include Single positron emission computed tomography (SPECT), saline provocation during video-EEG monitoring, serum prolactin levels, and neuropsychological testing.

4.1. Role of video-EEG monitoring in the diagnosis of PNES

Benbadis et al conducted a retrospective chart review study of patients who underwent video-EEG monitoring at an epilepsy center in order to investigate the disposition outcomes from January to December 2012. The charts of all adults and children sent for inpatient video-EEG monitoring (>24 hours) were reviewed at University of South Florida-Tampa General Hospital. During that period of time, there were 251 patients monitored for 1-7 days (mean=2.8 days). Non-epileptic events were found in 30% of patients (N=75). Six of the 75 patients had evidence of coexisting epilepsy. Of the 69 patients with non-epileptic events without coexisting epilepsy (pure non-epileptic events), psychogenic non-epileptic seizures (PNES) were found in 61. Patients diagnosed with PNES had their AEDs gradually discontinued and were referred for mental health treatment. Fifty-eight patients with epileptic events were candidates for resective surgery, 47 with epileptic events were non-surgical candidates, and in 57 patients no events were recorded. The authors concluded that there are many possible outcomes of video-EEG monitoring, and in their case the two largest groups were PNES (30%) and surgical candidates (23%) [48].

Zhang et al conducted a retrospective study to compare the clinical outcomes after video-EEG monitoring of patients diagnosed with PNES and epileptic seizures (ES). From November 2006 and January 2008, patients were followed after admission for elective video-EEG monitoring. Sixty-two of an eligible 103 patients agreed to follow up via telephone or mail questionnaires after discharge from monitoring. Follow up occurred for 6-16 months. ES without PNES was identified in 66% of patients (N=41), followed by PNES without ES in 18% of patients (N=11), 10% (N=6) had both ES and PNES, and 6% (N=4) with indeterminate diagnoses. Improvement of overall condition was reported in ~50% of patients in each group. Both groups showed a decrease in seizure frequency and had a significant decrease in AED use at follow up. The PNES group showed a greater more sustained decrease in AED use at follow up than the ES group. The ES group reported a statistically significant improvement in Seizure Worry ($P=0.003$), Medication Side Effects ($P<0.001$), and Social Function ($P<0.001$) [49]. Benbadis and colleagues conducted a retrospective review to analyze the yield of short-term outpatient EEG monitoring for suspected PNES. Seventy-four adult cases of short-term outpatient EEG video monitoring were found from October 2000 to January 2003 at University of South Florida-Tampa General Hospital. Each short-term monitoring session lasted between 1-2 hours. The suspected diagnosis of PNES was confirmed in 66% of cases (N=49). No event was induced in 23 patients and 2 patients had an induced event that was not habitual type. The authors concluded that for confirmation of a suspected diagnosis of PNES, short-term outpatient video EEG monitoring obviated the need for long-term inpatient video EEG monitoring [50].

4.2. Role of additional diagnostic techniques in the evaluation of Psychogenic Non-Epileptic Seizures

Cragar et al conducted a literature review to analyze the possible alternatives to video-EEG for diagnosis of PNES. The literature was searched from 1967 through November 2001 using keywords in the PsychINFO database and were divided into 7 categories of alternative PNES diagnostic techniques: demographic/medical history variables, seizure semiology, provocative testing, prolactin levels, single photon emission computed tomography (SPECT), psychological testing, and neuropsychological testing. Medical history variables included history of abuse, psychiatric treatment history, frequency of seizures (not shown in four studies to have a significant difference between epilepsy and PNES groups), epileptic spells are more likely to occur during sleep and are more stereotyped, older age of onset and duration of seizure disorder, variable semiology, and length of spells (six studies all concluded that PNES spells last longer than all types of epilepsy spells). A saline induction provocation test has a 74% sensitivity, but does not always induce spells. Prolactin levels estimate the average sensitivity to be 89% and are suggestive of epilepsy, but a negative outcome is not highly predictive of PNES. The use of SPECT data to differentiate PNES from epilepsy is not recommended as a first choice due to expense, radioactive materials, and difficulty of interpretation due to muscle and movement artifact. Review of SPECT studies suggests an average sensitivity of 72% across different types of scans and is 59% specific to epilepsy when there is a presence of SPECT abnormalities. The use of the MMPI to diagnose PNES patients is 70% of epilepsy and PNES patients may be correctly diagnosed by using the Wilkus et al (1984) classification rules. The MMPI-2 may add diagnostic utility above other variables such as the medical history, but this utility was not elaborated on. Neuropsychological testing does not adequately differentiate PNES from patients with epilepsy, or both, and all 3 groups test results' suggest cognitive impairment compared to the normal population. The authors concluded that it is unlikely that the gold standard, video-EEG monitoring, will be replaced by any of the alternative techniques they reviewed, yet may be more helpful as complementary diagnostic tools [51]. Devinsky et al conducted a retrospective chart review in order to compare the clinical features of patients with epileptic seizures (ES) and nonepileptic seizures (NES) to only ES or only NES. A total of 387 consecutive admissions for video-EEG monitoring yielded 248 patients with ES (64%), 40 patients (10%) with other physiologic disorders, 99 patients (25%) with NES, and 20 patients (20%) with ES+NES. These were matched to 20 ES and 20 NES patients. These patients were 70% female with a mean age of 32 (19-57 years old). All patients underwent a saline provocation test and all ES/NES patients developed NES after ES. In patients with ES/NES, their ES seizures were similar to ES only seizures and NES were similar to NES only spells. The electrodiagnostic and neuroimaging studies in ES/NES patients were similar to ES patients, but their psychiatric interview and inventories were similar to NES patients. In ES/NES patients, the ES and NES events were different from each other, but may be stereotypic and differentiated during video-EEG recording. Once the different events are characterized, the more prevalent or disturbing types can be identified and referred for the appropriate psychiatric or AED treatment [52].

Studies of patients undergoing video-electroencephalogram (vEEG) reveal that the majority of patients with NES meet criteria for a diagnosis of conversion disorder [53,54]. The most

recent version of the Diagnostic and Statistical Manual of Mental Disorders (DSM), the DSM – Fifth Edition (DSM-5), lists conversion disorder in the somatic symptom and related disorders category (American Psychiatric Association [APA], 2013) [55]. A diagnosis of conversion disorder requires a minimum of one symptom involving a change in voluntary motor or sensory function, along with evidence of “incompatibility” between known medical conditions and the symptom (e.g., vEEG capturing a paroxysmal episode). The symptom cannot be better accounted for by other medical or mental disorders, and psychosocial functioning is significantly impacted. Stress or trauma correlating with the time of symptom onset is supportive evidence for a diagnosis but, in contrast to the prior DSM, is not required [55]. Another change with the DSM-5 is that a clinician does not have to judge whether the presenting symptom is unintentionally manifested for diagnosis of conversion disorder. However, if there is clear evidence that the symptom is deliberately produced, a diagnosis of factitious disorder or malingering is more appropriate [55].

Although the majority of patients with NES are diagnosed with conversion disorder, NES may also be diagnosed as somatization disorder, dissociative disorder NOS, post-traumatic stress disorder, and undifferentiated somatoform disorder [54]. Comorbid psychiatric diagnoses are common for patients with NES and, in addition to frequently diagnosed conversion disorder, consist of other somatoform disorders, posttraumatic stress disorder (PTSD), dissociative disorder, psychotic disorders, anxiety, and depression, along with the majority of patients endorsing a history of abuse [54,56,57]. It is clear that patients with NES are a heterogeneous group and pharmacological and psychological treatment should be determined by the underlying cause and psychiatric disorder [56,58,59].

5. Treatment

The correct diagnosis plays an important role in the management of PNES -- the earlier the diagnosis, the better the outcome [60].

Reuber and House conducted a literature review of treatment options for psychogenic non-epileptic seizures. After the diagnosis of PNES is made and communicated to the patient, they should be referred to a mental health practitioner. There is no specific treatment for PNES, but most brief psychological therapies are based on cognitive-behavioral therapy (CBT) most commonly used in patients with normal intellectual functioning. CBT tends to be less effective in patients with a history of more severe and chronic somatization and benefit from longer term contact with a clinician focusing on stress management and living with symptoms. Family therapy is also recommended but no specific recommendations were made for families of a patient with PNES. Treatment of co-existing psychiatric or neurologic disorders is recommended. The authors conclude that PNES should be diagnosed early with prompt referral for psychiatric assessment [61]. Bora et al conducted a retrospective review of the sociodemographics, clinical characteristics, and psychiatric diagnoses of patients with PNES. Data from 2000-2008 from long-term video EEG monitoring (LVEM, lasting ~5 days) from a specialized epilepsy center in Turkey was analyzed. During this period of time, 440 patients with refractory epilepsy or indeterminate diagnoses underwent LVEM and 67 patients had a diagnosis of

PNES (mean age: 30; 75% female) with 233 episodes recorded. At the time of monitoring, 56.7% were taking antidepressant medication and 100% were taking AEDs, most patients were on multiple AEDs. Six patients (9%) had concurrent epilepsy, with complex partial epilepsy being the most common (N=4). Both the neurologist and psychiatrist diagnosed all of the PNES patients with conversion disorder. Twenty-one percent of patients (N=13) were diagnosed with only a conversion disorder, while most were diagnosed with another axis I or axis II diagnosis, most commonly major depression (31%, N=19), followed by generalized anxiety disorder (15%, N=9). The authors concluded that ongoing education and cooperation between neurologists and psychiatrists are critical to properly diagnose and manage patients with PNES [62]. Drake et al conducted a retrospective review of patients with severe PNES with frequent and prolonged spells that mimicked status epilepticus in order to identify clinical and psychometric features to assist diagnosis. Twenty patients were admitted to the Epilepsy Unit of The Ohio State University Hospitals from July 1982 to July 1989. The mean age was 27.9 years old and 19 of 20 were female (95%). The clinical seizures averaged more than 2 minutes in length and were atypical with common back arching and pelvic thrusting. For the spells that continued patients received IV diazepam, phenytoin, and phenobarbital. Sixteen of the 20 patients had been previously diagnosed as epileptic due to observed seizures or abnormal EEG findings both with and without additional seizures. Five patients' PNES spells stopped spontaneously, 4 ceased with the suggestion that improvement was forthcoming, and 11 required intubation due to respiratory arrest. Four patients were cognitively impaired, 10 patients had conversion or somatization disorders, and 10 received psychiatric diagnoses of personality disorders (5 borderline and 5 mixed borderline-histrionic types). At a later date, 14 patients (70%) were found to have experienced a recent acute situational stress prior to their spell. The patients with conversion disorder had their AEDs discontinued and gradually improved, while cognitively impaired individuals were helped by situational changes, behavior modifications, or neuroleptics. Patients with personality disorders continued having attacks and eventually ceased following up [63].

Pharmacological treatment of NES consists of the use of antidepressants, particularly SSRIs [64]. In a prospective study, venlafaxine reduced the frequency of NES as well as symptoms of depression and anxiety [65]. A pilot study comparing sertraline to placebo demonstrated a lower frequency of paroxysmal events associated with sertraline but no differences were observed for quality of life and psychosocial functioning between the groups [66].

A literature review of psychological treatments of NES found that various psychological interventions are beneficial with no particular treatment being superior [67]. In a review of eye movement desensitization and reprocessing (EMDR) therapy for medically unexplained symptoms, which included a small group of NES patients in the sample, findings indicated that EMDR may be an effective treatment, especially when there is an identifiable trauma [64]. A study examining brief augmented psychodynamic interpersonal therapy for the treatment of NES indicated a significant reduction in paroxysmal event frequency, with 25% of the participants being event free for an average of 3.5 years following therapy, as well as reduced reliance on healthcare services [68]. A randomized control trial (RCT) found that the addition of cognitive-behavioral therapy (CBT) for treatment of NES resulted in a significantly greater reduction in the frequency of paroxysmal events than standard medical care alone [69]. Similarly, another study utilizing CBT demonstrated that 11 of 17 patients who completed 12

CBT sessions were episode-free by the final session and experienced improved functioning and quality of life as well as decreased psychiatric symptoms [70]. In addition, group psychotherapy for treatment of NES has demonstrated effectiveness for reducing the frequency of paroxysmal events [71,72]. Research has provided some evidence that various psychological interventions are effective for the treatment of NES, however, most studies were not well conducted and there needs to be more research conducted that utilizes RCT [68,70].

6. Prognosis

Most studies that have assessed the prognosis in patients after PNES diagnosis suggest that only 25 to 38 percent of patients achieve complete seizure freedom [73-77]. Children have been reported to have better prognosis than adults [60].

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