AN APPROACH FOR FUNCTIONAL (PSYCHOGENIC NONEPILEPTIC) SEIZURES

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Introduction

In this session, we review the literature on one of the most challenging and sometimes frustrating patient populations for the neurologist, those with psychogenic nonepileptic (functional) seizures (PNES). It is here, where seizures present, that a combined neurologic-psychiatric perspective is essential for diagnosis and management [1]. To make the presentation both academically informative and clinically applicable, the difference between Conversion Disorder and Malingering is discussed. The descriptive overview is followed by presenting diagnostic and treatment research in somatoform disorders that is found in the literature and that we are conducting at Brown School / Rhode Island Hospital and the VA.

The key points that will be discussed in the presentation are as follows:
1) There are a plethora of observational, phenomenological and diagnostic information on PNES.
2) There is no serologic or imaging lab test that will definitively diagnose conversion disorders. PNES, however, are diagnosed with video EEG, the gold standard for PNES diagnosis.
3) We have a small but growing body of controlled data on PNES.
4) Anxiety and depression occur commonly in patients with PNES.
5) Reviewing the extant literature on conversion disorders and PNES treatment suggests that improved outcomes may be obtained with intensive, multi-modal treatment of patients with PNES.

Conversion Disorder *(from DSM-5)* [2]
    Diagnostic features
Conversion symptoms are changes or deficits in voluntary motor or sensory functioning that are not are explained by structural anatomical pathways or physiological mechanisms and are not intentionally produced. Motor symptoms or deficits include impaired balance, coordination, gait, paralysis or paresis, aphonia, dysphagia, urinary symptoms or seizures. Sensory symptoms include anesthesia or dysesthesia, diplopia, amaurosis, deafness and hallucinations. Physical signs that show clear evidence of incompatibility with neurological disease and internal inconsistency on exam (e.g. Hoover's sign, tremor entrainment test, paroxysmal tubular vision) are part of the new diagnostic criteria to "rule-in" the diagnosis. Psychological factors are judged to be associated with the symptoms or deficits but are not required for diagnosis.
    Culture/Gender
Conversion Disorders are reported as 2 to 3 times more common among women and occur across cultures, races, age-groups, educational training and socio-economic status. Conversion symptoms may vary across cultures based on cultural-specific norms of ways to express distress.
    Prevalence
According to the DSM-5, Conversion Disorder persistent symptoms incidence has ranged from 2-5/100,000 per year. Conversion disorder is found in 5% of referrals to neurology clinics. Misdiagnosis has decreased considerably with improved diagnosis. Comorbid depression, anxiety, PTSD and personality disorders are present in the majority of patients with PNES, along with cognitive, sleep, pain and other somatic complaints.
    Course
The onset of Conversion Disorder is generally from late childhood to early adulthood, between the age of 10 and 36 years. Onset in the elderly has been seen, but may signal an occult medical condition. Symptom recurrence is common. Prognosis may be better in children than in adults. The symptoms can be associated with disability.
    Differential diagnosis
An extensive evaluation of potential general medical conditions and careful review of the individual's present and past medical history, laboratory results, and neurological and general physical examinations are imperative. Prominent confounders are multiple sclerosis, myasthenia gravis and dystonias.

Conversion disorder is common in neurologic and medical practice. In contrast, malingering occurs less often, but can leave a more lasting impression on the clinician due to the experiential impact on the provider.

Malingering [2]
Diagnostic features

Malingering IS NOT a psychiatric condition, but refers to the intentional production of false grossly exaggerated physical and psychological symptoms, motivated by external incentives, such as avoiding obligations at work, school, or the military, to obtain drugs, financial compensation, win a law suit or avoid jail time.

Associated features

Malingerers may also have Antisocial Personality Disorder, display uncooperative behavior during a diagnostic evaluation and when prescribed medication, and receive a medical referral from an attorney.

Culture/Gender

Malingering may exist in any culture and gender.

Prevalence – None Specified

Course

Malingering may last until the personal motive is achieved.

Differential diagnosis

Malingering differs from Factitious Disorder in that an external motive is present for the malingerer. In factitious disorder, the individual feigns symptoms to assume a sick role, without external motivation. Malingering differs from Conversion Disorder and other Somatoform Disorders in that the symptoms produced by Malingering are intentional.

Advances in PNES diagnostic research

Diagnostic Measures

Video EEG (VEEG) is the gold standard for diagnosis of PNES [3] and has excellent interrater reliability [4], Adjunctive tests using serum prolactin assay can augment differentiation from epilepsy [5].

Neurohumoral studies in PNES

The findings on serum cortisol levels with NES are contradictory [6, 7]. Tunca investigated cortisol level during PNES and its relationship to depression, anxiety, the impairment of consciousness, blood pressure, and pulse rate [8]. Eighteen patients with seizures were studied. The authors concluded that the HPA axis is moderately impaired in conversion disorder. Furthermore they noted the difficulty and impracticality to suggest serum cortisol level as a good predictor in differential diagnosis of epileptic and conversion disorder seizures.

Certain serologic measures *have* been helpful in differentiating epileptic seizures (ES) from PNES. Prolactin (PRL) is secreted from the anterior pituitary and is inhibited by tuberinfundibular dopaminergic neurons in the arcuate nucleus of the hypothalamus [9]. Dopamine (DA) agonists induce a marked reduction in epileptic activity, and many dopamine antagonists (anti-psychotics) decrease the seizure threshold and increase prolactinemia[10]. Trimble found that elevated serum PRL in patients with generalized seizures helped distinguish ES from NES [11]. Studies have since been conducted measuring PRL in PNES, and with a lack of elevation of PRL, the average sensitivity to NES was 89% [12]. Further, ES vs. PNES PRL studies have since shown that serum levels are elevated on average in 88% of GTC epileptic seizures, in 64% of temporal complex partial epileptic seizures (CPS), and in 12% of simple partial epileptic seizures. False positives for epilepsy include treatment with DA antagonists and some TCAs, breast stimulation, and syncope, and false negatives occur with use of a DA agonist, or with status epilepticus, because PRL has a short half-life and may attenuate in post-ictal release [13]. PRL also does not rise after frontal seizures. The AAN Therapeutics and Technology Assessment Subcommittee published on the use of serum PRL in differentiating ES from PNES. The authors concluded that a twice normal relative or absolute serum PRL rise, drawn 10 to 20 minutes after the onset of the ictus, compared against a baseline non-ictal PRL, is a useful adjunct in the differentiation of GTC or CPS from PNES [5].

Neuroimaging studies in PNES

Structural neuroimaging abnormalities neither confirm nor exclude ES or PNES. PNES may occur in the presence of focal lesions, as confirmed by PNES case reports with CNS lesions [14]. A study of 20 patients with PNES comparing 40 healthy controls on MRI revealed that voxel based morphometry (VBM) and cortical thickness analyses in the patients with NES showed abnormal cortical atrophy of the motor and premotor regions in the right hemisphere and the cerebellum bilaterally. Also noted was a significant association between increasing depression scores and atrophy involving the premotor regions [15]. Functional neuroimaging studies in PNES are

limited. A negative ictal single-photon emission computed tomography (SPECT) scan does not imply a diagnosis of PNES nor does an abnormal scan mean epilepsy is present. A small series of ictal and interictal SPECT scans of patients with PNES revealed a few scans with lateralized perfusion abnormalities, but the findings did not change when the ictal and interictal images were compared [16]. Patients with epilepsy, in contrast, have dynamic changes when comparing ictal and interictal changes on functional neuroimaging. A study of 11 patients with PNES and 12 healthy controls comparing resting state fMRI revealed stronger connectivity values between areas involved in emotion (insula), executive control (inferior frontal gyrus and parietal cortex) and movement (precentral sulcus) [17]. Further studies of functional neuroimaging examining striatothalamocortical circuits controlling sensorimotor function and attention may yield insights into the neural and effective connectivity in PNES and other somatoform disorders [18].

Advances in Evidence Based PNES treatment
Pharmacologic and psychotherapeutic interventions have been studied and reviewed in patients with PNES [19]. Two pilot controlled RCTs using psychotherapy for PNES reveal preliminary data demonstrating success in reducing PNES frequency and comorbidities [20-23], with one of the trials using a treatment workbook for patients with patients with seizures (epileptic or nonepileptic) [24]. A pharmacologic double blind pilot RCT for PNES showed a 45% seizure reduction in the SSRI treated group and an 8% seizure increase in the placebo group [25].

Other important effects of treatment of somatoform disorders include the decrease in healthcare utilization. A study comparing CBT to wait list performed cost calculations for the 2 year period before and after treatment based on billing records and found a 25% reduction for outpatient and 36% reduction for inpatient care [26].

Treatment Approach for PNES Summary
Based on the clinical and research reports to date, the following assessment and treatment approach by a multi-specialty neuropsychiatric team is recommended [27]:

1) Proper diagnosis- vEEG for each patient with suspected PNES, refractory or pharmacoresistant seizures.

2) Presentation – explain the PNES diagnosis in a clear, positive, non-pejorative manner. The patient may make the diagnosis presentation to the family members if cognitively and emotionally capable. This process helps reveal the level of understanding and initial acceptance of the diagnosis by the patient. Clarifications can be made by the physician who is present. Communicate the diagnosis unambiguously to the referring physician and explain the need to eliminate unnecessary medications.

3) Psychiatric Treatment – conduct a thorough psychiatric assessment to identify *predisposing* factors (including comorbid psychiatric disorders), seizure *precipitants* and *perpetuating* factors. As diagnosis informs treatment, a dual armed approach ensues with pharmacotherapy and/or psychotherapy, as indicated by the individual needs of the patient with PNES.

Psychopharmacology begins with tapering and discontinuing ineffective AEDs for patients with lone PNES, unless a specific AED has a documented beneficial psychopharmacologic effect in the patient. In patients with mixed ES/NES, reduce high-dose or multiple AED therapy if possible. Use psychopharmacologic agents to treat mood, anxiety, or psychotic disorders.

Psychogenic NES are the result of a complex interaction between psychiatric disorders, psychosocial stressors, dysfunctional coping styles, and CNS vulnerability [28, 29]. Identifying the underlying stressors and providing supportive psychotherapy can help some patients but is often insufficient or ineffective. Studies identify three main comorbid diagnoses in patients with PNES: Major Depressive Disorder, Post Traumatic Stress Disorder, and Cluster B and C personality traits [30]. Three additional critical areas of dysfunction in the PNES population are: emotion regulation, family dynamics, and unemployment/disability [31], [32]. Poorer outcomes to treatment may be associated with the high number of comorbid psychiatric disorders and psychosocial stressors [33]. Therefore, therapy for NES may require combined psychological education, psychotherapy, and pharmacotherapy, while simultaneously eliminating ineffective AEDs. Prior-published treatment reports reveal that coordination between neurologists and psychiatrists / psychologists with accurate diagnosis and prompt initiation of psychotherapy and communication between care providers, patient and family yields higher treatment success. With a diagnosis of PNES, given the importance of the transition from a "neurologic" diagnosis to a psychiatric diagnosis, neurologists should stay involved with management of the patient with PNES [34].

Conclusion

Patients with PNES remain a conundrum in the neurologic and the psychiatric clinic. A number of interventions may be effective, but in the absence of adequately powered phase III trials, we do not know what the best treatment for the range of somatic symptom disorders are [35]. A roadmap for research was published as a result of an international workshop on PNES treatments [36] and the NINDS and AES prioritized PNES as a focus of research [37]. The advances made in PNES from utilizing a multidisciplinary approach [1], and results from more controlled trials will continue to inform treatments for PNES [38].

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