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Review

Psychogenic nonepileptic seizures ☆

Richard J. Brown [a], Tanvir U. Syed [b], Selim Benbadis [c], W. Curt LaFrance Jr. [d,e], Markus Reuber [f,*]

[a] Division of Clinical Psychology, University of Manchester, Manchester, UK
[b] Department of Neurology, University Hospitals, Case Medical Center Faculty, Case Western Reserve University School of Medicine, Cleveland, OH, USA
[c] Department of Neurology, University of South Florida and Tampa General Hospital, Tampa, FL, USA
[d] Division of Neuropsychiatry and Behavioral Neurology, Rhode Island Hospital, Providence, RI, USA
[e] Departments of Psychiatry and Neurology, Brown Medical School, Providence, RI, USA
[f] Academic Neurology Unit, University of Sheffield, Sheffield, UK

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ABSTRACT

This review by three established clinicians/researchers and two 'rising stars' in the field of psychogenic nonepileptic seizures (PNES) describes recent progress in this area and highlights priorities for future research. Empirically testable models of PNES are emerging but many questions about the aetiology of PNES remain unanswered at present. Video-EEG has made it possible for doctors to make secured diagnoses of PNES in more cases. However, unacceptable diagnostic delays and misdiagnoses are still common. Non-specific EEG changes are often misinterpreted as evidence of epilepsy. A better understanding of the symptomatology of PNES may allow earlier and more accurate diagnoses using self-report questionnaires. The communication of the diagnosis and the engagement of patient in psychological treatment can be difficult. A recent pilot RCT has demonstrated the effectiveness of a psychological treatment in reducing seizures in the short term, but longer-term effectiveness is yet to be demonstrated.

1. Introduction

Psychogenic nonepileptic seizures (PNES) are episodes of altered movement, sensation, or experience resembling epileptic seizures, but not associated with ictal epileptiform discharges in the brain but which, instead, have a psychological origin. In the current diagnostic manuals most PNES are categorized as a manifestation of dissociative or somatoform (conversion) disorder [1,2]. This means that they are interpreted as an involuntary response to emotional, physical, or social distress. It is appropriate to discuss PNES in this special issue because they are one of the commonest differential diagnoses of epilepsy and are typically diagnosed by physicians specializing in the treatment of seizures. They are by far the most common nonepileptic condition diagnosed in epilepsy (video/EEG) monitoring units. The fact that research interest in PNES has grown exponentially since the introduction of video/EEG monitoring is encouraging for the future. However, the impressive number of publications on this topic in the last two decades also demonstrates there still are many questions to answer. In Sections 2–4, three experienced clinicians who have followed the developments of PNES research closely over this period discuss some questions that future research needs to address most urgently. Selim Benbadis focuses on topics related to the diagnostic process, Curt LaFrance writes about issues related to treatment, and Markus Reuber discusses the nature and experience of PNES. In Sections 5 and 6, two "rising stars" describe how they got involved in research in this area and what their plans are for the future: Tanvir U. Syed focuses on his work aiming to reduce diagnostic delay, and Richard J. Brown, on his development of a psychological model for PNES.

2. Diagnostic process

2.1. Selim Benbadis

Recent studies have shown that an accurate diagnosis of PNES is delayed by a mean of more than 7 years and that most patients are initially thought to have epilepsy [3]. As long as patients are misdiagnosed as having epilepsy, they are at iatrogenic risk. The misdiagnosis of PNES is costly to patients, the health care system, and society. Repeated workups and treatments for what is mistakenly thought to be epilepsy are estimated to incur $100 to $900 million per year in medical services [4]. Patients with PNES are prescribed antiepileptic drugs (AEDs) that do not treat, and may exacerbate, PNES [5], have multiple laboratory tests performed, and may not receive the necessary mental health care that could benefit them. Delayed diagnosis could lead to adverse effects from unneeded AEDs, iatrogenic

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* Corresponding author at: Department of Neurology, Royal Hallamshire Hospital, Glossop Road, Sheffield, S10 2JF, UK. Fax: +44 114 2713158.
E-mail address: markus.reuber@sth.nhs.uk (M. Reuber).

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complications from invasive procedures in continuous PNES ("nonepileptic psychogenic status") [6], medical costs resulting from unnecessary hospitalization treatment and workup, delayed referral to appropriate psychiatric treatment, and employment difficulties and disability [7].

Some of the most important directions and unresolved future directions in the diagnostic aspects of PNES can be divided into four components: (1) clinical suspicion, (2) errors in EEG use and interpretation, (3) video/EEG monitoring, and (4) especially difficult situations.

2.1.1. Diagnostic challenges at the stage of clinical suspicion

Psychogenic nonepileptic seizures are initially suspected in the clinic, on the basis of the history and examination. The most important differential diagnoses are epileptic seizures and syncope. Many "red flags" appear useful in clinical practice because they increase the likelihood of seizures being psychogenic, rather than epileptic. However, their specificity and sensitivity, against the eventual diagnosis by EEG/video monitoring, need to be tested in larger series. What is more, future studies should consider the diagnostic value of clusters of features from the history rather than a small number of single items. Such studies would be most useful if they described not only the sensitivity and specificity of particular items in the differential diagnosis of epilepsy and PNES, but also the distinction of syncope from the other two most common causes of blackouts.

Relevant items in the history include: *specific triggers* for seizures, such as "stress" and "getting upset," pain, certain movements, sounds, and lights; and the *circumstances* in which attacks occur, including occurrence in the physician's office or the waiting room or during the examination [8]. Which *features of the past medical history* can be useful? The coexisting poorly defined (probably psychogenic) conditions such as "fibromyalgia" and unexplained "chronic pain" are associated with psychogenic symptoms, with a high predictive value of 70–80% [8]. Most likely other "fashionable" unsubstantiated diagnoses such as "chronic fatigue" and seronegative chronic Lyme disease have the same value, but this has not been tested. A florid review of systems suggests somatization [9]. Some are overdiagnosed conditions, but others raise the question of association. Does the coexistence of "chronic pain," "fibromyalgia," or "intractable headaches" with PNES in a given patient indicate that these are psychogenic as well?

In contrast to the above, there are symptoms that argue in favor of epileptic seizures, but again the exact diagnostic value (sensitivity, specificity, predictive values), need to be better studied. Significant injury, including tongue biting, has been relatively well studied, but incontinence, despite being often cited, has not [10].

Recent work has shown that *how* patients speak about their seizures when they talk to their neurologists (rather than what symptoms they describe) may be useful in the diagnostic process [11]. However, these findings depended on careful post hoc analysis of transcripts of clinical encounters, and future research will need to show to what extent these observations can be useful "online," as physicians speak to their patients.

2.1.2. The issue of EEG interpretation errors

Overinterpretation of the EEG is an important reason why seizures are misdiagnosed as epilepsy so commonly. This is not specific to PNES, and other conditions such as syncope and benign nonspecific symptoms are often misdiagnosed as epilepsy based on a misread EEG, but because PNES are the most common condition misdiagnosed as epilepsy, this important issue should be the subject of more research. This problem is very serious and well known to referral epilepsy centers [12,13], but it has not been studied, partly because it is politically unpleasant. The reality is that most practicing neurologists who routinely read EEGs are not appropriately trained to do so [14]. Unfortunately, in discussions about who should be reading EEGs, professional associations are sometimes more concerned about protecting the livelihood of their members than the quality of care.

Because most EEGs ordered in routine U.S. practice are not for epilepsy (typically for encephalopathy), errors in interpretation have little impact on diagnosis, management, and outcome. For the diagnosis of seizures and epilepsy, however, the consequences of misreading are significant. If we are to assume that all neurologists who want to read EEGs are qualified to do so, EEG training should be more regulated. Epilepsy, seizures, and EEGs represent one of the most voluminous parts of general neurology and child neurology practice.

Some of the specific questions to be answered include the following. What EEG patterns are overread? Why are they overread? How can EEG training reduce the errors in interpretation? Should EEG training be mandatory during neurology residency (currently it is not)?

In countries where EEGs are interpreted by experts but are requested by clinicians lacking expertise in the use and limitations of this investigation (such as the United Kingdom), the risk of misdiagnosis is most commonly related to the overinterpretation of nonspecific findings [15]. In such health systems, the question that needs to be explored is whether access to requesting EEGs should be restricted to those clinicians who are sufficiently trained to understand what an EEG can and cannot show.

2.1.3. Diagnostic challenges at the stage of confirmation by video/EEG monitoring

The value of various semiological features has been extensively studied. Behaviors or signs strongly suggestive of PNES include the following: very gradual onset or termination; pseudosleep; and discontinuous (stop-and-go), irregular, or asynchronous (out-of-phase) activity including side-to-side head movement, pelvic thrusting, opisthotonic posturing, stuttering, and weeping [16–22]. Ictal eye closure is associated with PNES [23], and although this has been questioned [24], eye closure, especially when prolonged and associated with complete unresponsiveness, is quite specific for PNES. Behaviors that are modified by an examiner, such as avoidance of noxious stimuli, and nonanatomical progression of symptoms (various limbs moving at various times) can also help. Another useful sign is preserved awareness and ability to interact with the examiner during bilateral motor activity, which is relatively specific to PNES. Postictal responses such as whispering voice and partial motor responses have a strong association with PNES [25]. It is critical to recognize that no single characteristic is pathognomonic of PNES.

In the absence of a gold standard (a definitive method, such as pathology) against which to verify the diagnosis by video/EEG monitoring (VEEG), the second best method is to study interrater reliability (IRR). In the first study of the IRR of the diagnosis by VEEG, sampling a group of 22 epileptologists found substantial IRR for epilepsy and a moderate interrater agreement for PNES [26], indicating that there is a certain component of subjective "artful" judgment. When used properly, VEEG allows the diagnosis of paroxysmal seizure-like events and, in particular, the diagnosis of PNES, with a high degree of confidence. A closer look at the data revealed that for 12 of the patients, there was agreement among $\geq$19 reviewers, and for 17 of the patients, there was agreement among $\geq$17 reviewers, which suggested that the diagnosis is not difficult in most patients, but that there are a few difficult cases that account for an only moderate overall agreement. There are many different methodological ways to study IRR of VEEG (number of reviewers, types of reviewers, type of setting or study population, type and amount of data, amount and type of data given to make a diagnosis, availability of clinical history, etc.), and has been replicated, showing higher IRR. Using computer-aided methods of video and EEG or ECG analysis also may improve diagnostic accuracy.

2.1.4. Specific difficult situations

Future research should also focus on the subset of PNES that gives rise to special diagnostic difficulties. These include brief sporadic myoclonus-like episodes, episodes consistent with "simple partial"