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Review

Biomarkers in the diagnosis and study of psychogenic nonepileptic seizures: A systematic review

T. Sundararajan [a], G.E. Tesar [a,b], X.F. Jimenez [a,*]

[a] Cleveland Clinic Department of Psychiatry and Psychology, United States
[b] Cleveland Clinic Epilepsy Center, United States

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ABSTRACT

Objective: Video electroencephalography (vEEG) is the gold-standard method for diagnosing psychogenic nonepileptic seizures (PNES), but such assessment is expensive, unavailable in many centers, requires prolonged hospitalization, and many times is unable to capture an actual seizure episode. This paper systematically reviews other non-vEEG candidate biomarkers that may facilitate both diagnosis and study of PNES as differentiated from epileptic seizures (ES).
Methods: PubMed database was searched to identify articles between 1980 and 2015 (inclusion: adult PNES population with or without controls, English language; exclusion: review articles, meta-analyses, single case reports).
Results: A total of 49 studies were examined, including neuroimaging, autonomic nervous system, prolactin, other (non-prolactin) hormonal, enzyme, and miscellaneous marker studies. Functional MRI studies have shown PNES is hyperlinked with dissociation and emotional dysregulation centers in the brain, although conflicting findings are seen across studies and none used psychiatric comparators. Heart rate variability suggests increased vagal tone in PNES when compared to ES. Prolactin is elevated in ES but not PNES, although shows low diagnostic sensitivity. Postictal cortisol and creatine kinase are nonspecific. Other miscellaneous biomarkers (neuron specific enolase, brain derived neurotropic factor, ghrelin, leptin, leukocytosis) showed no conclusive evidence of utility. Many studies are limited by lack of psychiatric comparators, size, and other methodological issues.
Conclusion: No single biomarker successfully differentiates PNES from ES; in fact, PNES is only diagnosed via the negation of ES. Clinical assessment and rigorous investigation of psychosocial variables specific to PNES remain critical, and subtyping of PNES is warranted. Future investigational and clinical imperatives are discussed.

1. Introduction

Psychogenic nonepileptic seizures (PNES) are a form of conversion disorder defined as paroxysmal episodes resembling epileptic seizures (ES) while lacking electroencephalographic (EEG) correlation [1,2]. Changes in diagnostic methods for PNES have evolved over the years, though video electroencephalography (vEEG) is currently considered the best diagnostic option in determining ES from PNES [2]. Nonetheless, this methodology is costly, available in selected clinical environments and of value only if a typical episode occurs during monitoring. Furthermore, while vEEG assessment firmly establishes the presence or absence of epileptic discharges, PNES can only be inferred and not established. Diverse theories have been proposed to describe core psychopathological deficits, traits, or mechanisms driving PNES [3–5], but no pathognomonic biological, psychological, or social marker has been identified.

Given the aforementioned limitations in the use of vEEG for diagnosing PNES, it is prudent to continue to understand the value of other diagnostic modalities. Much emphasis has recently been applied to presumed neurobiological underpinnings of PNES [6], with various lines of investigation seeking candidate biomarkers elucidating pathophysiology, in turn informing potential therapies [7]. Such a clear marker indicating the presence (or absence) of PNES is always in demand amongst clinicians. In order to assess the relative values of potential biomarkers, we conducted a systematic

* Corresponding author at: Neurological Institute, Cleveland Clinic Foundation, 9500 Euclid Ave., P57, Cleveland, OH 44195, United States. Tel.: +1 216 407 4994; fax: +1 216 445 7032.
E-mail address: jimenex2@ccf.org (X.F. Jimenez).

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review of the diagnostic and investigational utility of all candidate PNES biomarkers to date. We felt compelled to review this from both clinical and investigational angles as an update for the field in order to begin to prioritize diagnostic, treatment, and research imperatives relevant to PNES. Many studies are emerging focusing on the neuroimaging or other biological aspects of PNES; while we support this and feel there is a need for such investigations, we also aim to demonstrate a lack of attention to non-biological markers, such as psychosocial measures. PNES is a complex condition warranting a complex approach; we hope to illustrate with this systematic review that biological reductionism may not be useful in our investigational or (especially) clinical endeavors with PNES.

We hypothesized that this review would reveal a paucity of evidence supporting any one biomarker in the diagnosis or study of PNES and set out to test this with a systematic examination of existing literature.

2. Methods

We conducted an extensive literature search utilizing PubMed and the following terms: "psychogenic non epileptic seizures," "pseudoseizure," "non-epileptic attacks," "functional epilepsy," "hysterical seizure," "psychogenic seizure," "seizures," and "epilepsy." These terms were used in various combinations with a variety of terms used routinely in medicine as biomarkers of physiological functioning and/or disease: "hormone," "enzyme," "amino acid," "inflammatory marker," "cytokines," "cell," "neurotrophins," "neurotransmitter," "ammonia," "oxygen," "carbon dioxide," "metabolism," "heart rate," and "blood pressure." Finally, we also included terms capturing methodologies of assessment and/or sampling approaches: "galvanic skin response," "skin," "pupil," "autonomic nervous system," "serum," "cerebrospinal fluid," "computed tomography (CT)," "magnetic resonance imaging (MRI)", "functional MRI (fMRI)," and "neuroimaging." Studies published between 1980 and 2015 were screened initially, and additional articles were identified via references. Studies included had both ES and PNES patients with or without healthy controls (HC). Select case reports with pertinent findings were also included. Exclusion criteria included other forms of conversion disorder (including functional movement disorders), review articles, meta-analyses, and articles in languages other than English. We did not include electrographic studies including EEG/vEEG or single photon emission CT (SPECT) because these are neurophysiological tests currently considered to be the most robust or best available approaches to assessing ES versus PNES; vEEG specifically is considered the gold-standard of seizure diagnosis while SPECT is less commonly-utilized. Ultimately, a total of 49 articles were included for systematic review. A modified PRISMA flowchart for our systematic review methodology is given in Fig. 1. Post-review levels of evidence were applied to various

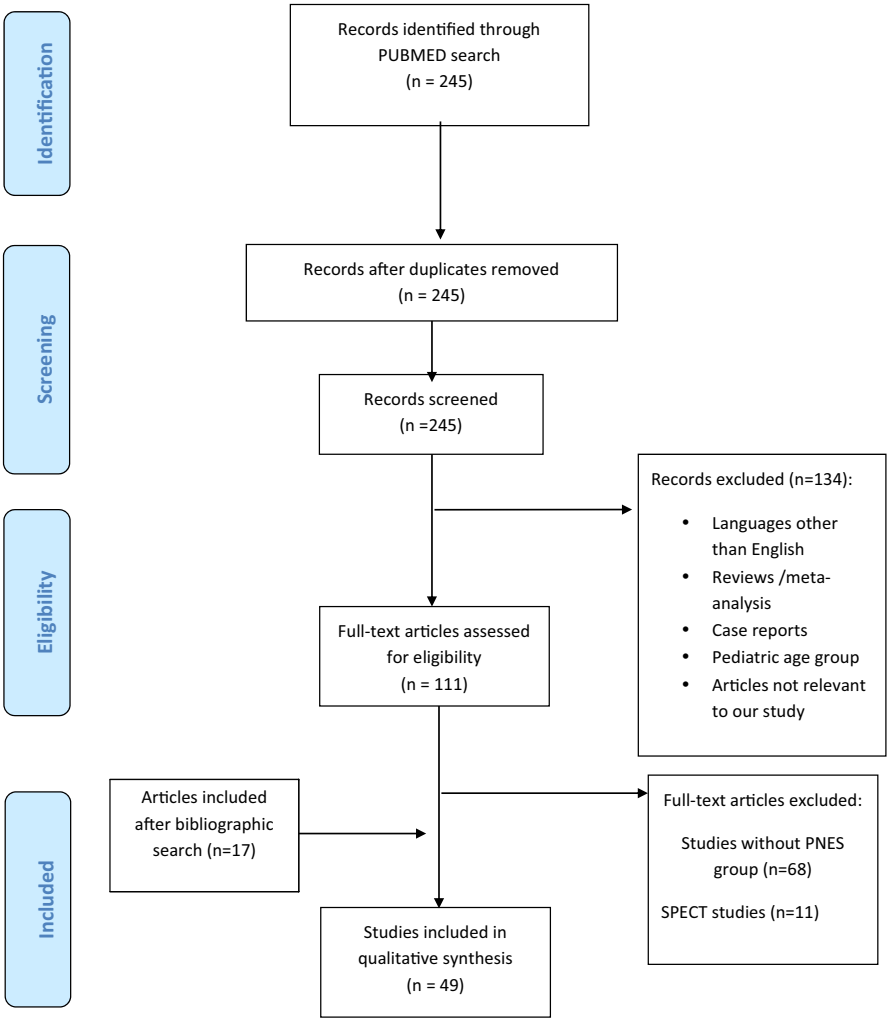

Fig. 1. Modified PRISMA flow diagram for the methodology.