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An objective score to identify psychogenic seizures based on age of onset and history

Wesley T. Kerr [a,b,g,*], Emily A. Janio [b], Chelsea T. Braesch [b], Justine M. Le [b], Jessica M. Hori [b], Akash B. Patel [b], Norma L. Gallardo [b], Janar Bauirjan [b], Andrea M. Chau [b], Eric S. Hwang [b], Emily C. Davis [b], Albert Buchard [b], David Torres-Barba [b], Shannon D'Ambrosio [b], Mona Al Banna [b], Andrew Y. Cho [b], Jerome Engel Jr. [b,c,d], Mark S. Cohen [b,c,e,f], John M. Stern [c]

[a] Department of Biomathematics, David Geffen School of Medicine at UCLA, Los Angeles, CA, United States
[b] Department of Psychiatry and Biobehavioral Sciences, University of California Los Angeles, Los Angeles, CA, United States
[c] Departments of Neurology and Neurobiology, David Geffen School of Medicine at UCLA, Los Angeles, CA, United States
[d] Brain Research Institute, University of California Los Angeles, Los Angeles, CA, United States
[e] Departments of Radiology, Psychology, Biomedical Physics, and Bioengineering, University of California Los Angeles, Los Angeles, CA, United States
[f] California NanoSystems Institute, University of California Los Angeles, Los Angeles, CA, United States
[g] Department of Internal Medicine, Eisenhower Medical Center, Rancho Mirage, CA, United States

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ABSTRACT

Objective: Psychogenic nonepileptic seizure (PNES) is a common diagnosis after evaluation of medication resistant or atypical seizures with video-electroencephalographic monitoring (VEM), but usually follows a long delay after the development of seizures, during which patients are treated for epilepsy. Therefore, more readily available diagnostic tools are needed for earlier identification of patients at risk for PNES. A tool based on patient-reported psychosocial history would be especially beneficial because it could be implemented in the outpatient clinic.

Methods: Based on the data from 1375 patients with VEM-confirmed diagnoses, we used logistic regression to compare the frequency of specific patient-reported historical events, demographic information, age of onset, and delay from first seizure until VEM in five mutually exclusive groups of patients: epileptic seizures (ES), PNES, physiologic nonepileptic seizure-like events (PSLE), mixed PNES plus ES, and inconclusive monitoring. To determine the diagnostic utility of this information to differentiate PNES only from ES only, we used multivariate piecewise-linear logistic regression trained using retrospective data from chart review and validated based on data from 246 prospective standardized interviews.

Results: The prospective area under the curve of our weighted multivariate piecewise-linear by-sex score was 73%, with the threshold that maximized overall retrospective accuracy resulting in a prospective sensitivity of 74% (95% CI: 70–79%) and prospective specificity of 71% (95% CI: 64–82%). The linear model and piecewise linear without an interaction term for sex had very similar performance statistics. In the multivariate piecewise-linear sex-split predictive model, the significant factors positively associated with ES were history of febrile seizures, current employment or active student status, history of traumatic brain injury (TBI), and longer delay from first seizure until VEM. The significant factors associated with PNES were female sex, older age of onset, mild TBI, and significant stressful events with sexual abuse, in particular, increasing the likelihood of PNES. Delays longer than 20 years, age of onset after 31 years for men, and age of onset after 40 years for women had no additional effect on the likelihood of PNES.

Discussion: Our promising results suggest that an objective score has the potential to serve as an early outpatient screening tool to identify patients with greater likelihood of PNES when considered in combination with other factors. In addition, our analysis suggests that sexual abuse, more than other psychological stressors including physical abuse, is more associated with PNES. There was a trend of increasing frequency of PNES for women during childbearing years and plateauing outside those years that was not observed in men.

* Corresponding author at: UCLA Semel Institute, 760 Westwood Plaza, Room C9-420, Los Angeles, CA 90095, Unites States.
E-mail address: WesleyTK@UCLA.edu (W.T. Kerr).

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1. Introduction

To an untrained observer, psychogenic nonepileptic seizures (PNES) appear similar behaviorally to epileptic seizures (ES), but their cause and treatment are entirely dissimilar [1]. Patients with PNES, without comorbid ES, often are diagnosed mistakenly as having ES, but they do not benefit from treatment with antiseizure medications [2,3]. Therefore, accurate and early differentiation between PNES and ES facilitates the initiation of targeted treatment [4–8]. The average delay to diagnosis varies widely across centers from 2 years in the PNES-treatment trials to over 8 years at our center [3], during which time patients have diminished quality of life and high healthcare utilization [9,10].

There are multiple challenges to the early identification of PNES including unreliable patient or witness reported details regarding seizure behavior [11,12] and the limited sensitivity and specificity of interictal scalp electroencephalography [13]. In comparison to seizure behavior, patients' reports of other medical and social history typically are more accurate and detailed when the patient is interviewed sensitively.

The literature describing historical risk factors for PNES and ES is rich and has been comprehensively reviewed recently [1,14]. In brief, the most common features of patients with PNES are female sex, presenting to specialty epilepsy care in the fourth decade of life, history of sexual abuse, and a mild traumatic brain injury (TBI), and frequent, disabling seizures for many years. However, none of these features exclude the diagnosis of ES. In contrast, risk factors for ES include a history of severe TBI [15–20], meningitis or encephalitis [21], neurotoxin exposure [22,23], complex febrile seizures in childhood [24], premature birth [25,26], and a family history of epilepsy [27]. None of these risk factors exclude the diagnosis of PNES.

While historically associated factors have been demonstrated in small and moderate size populations, this investigation aims to evaluate prospectively an objective screening score based on the combination of these factors in a large, unselected population using patient-reported data that is available in an outpatient neurology or primary care clinic. By combining associated factors in a large population, the conditionally-independent diagnostic utility of each factor can be evaluated more accurately. Additionally, this investigation assesses the prevalence of these factors in the understudied populations of patients with mixed ES plus PNES and physiologic nonepileptic seizure-like episodes (PSLE) [28].

2. Methods

The patient population constitutes all patients admitted to the UCLA adult video-electroencephalographic monitoring (VEM) unit from January 2006 to November 2016. Clinical diagnosis was based on expert clinical opinion determined from the available clinical history, physical exam, VEM, MRI, FDG-PET, and sometimes MEG and SPECT. Both MEG and SPECT were obtained when the treating physicians decided it would be clinically useful. We placed patients in five mutually exclusive categories: PNES, PSLE, ES, mixed nonepileptic plus ES, and inconclusive monitoring. Although the populations are heterogeneous, with many important subtypes, the description of subtypes within PNES and ES is outside the scope of this article. We define PSLE as nonepileptic seizures caused by nonpsychological factors including syncope, complex migraines, dementia, and tremors [29]. Throughout this manuscript, mixed seizures indicate patients with both PNES and ES. Differentiating between mixed seizures and PNES is important because patients with mixed seizures would benefit from antiseizure medication treatment, and because there is insufficient evidence to suggest that the mechanisms and risk factors for PNES are the same in mixed seizures and isolated PNES [28].

Inconclusive monitoring occurred when patients did not have sufficiently informative episodes during monitoring to yield a definitive diagnosis for all types of seizures that a patient reported, if these patients reported more than one characteristic seizure type. While patients with inconclusive monitoring represent a mixture of the other groups, we separate this group to provide information about its relative composition. Inclusion of these patients also allows inclusion of all patients in our analysis, thereby reducing the potential for selection bias, and improves the control for confounding variables while otherwise not affecting the results or conclusions regarding the other diagnostic categories.

Although all patients were adults during VEM, they were not necessarily adults during the clinical interview. There is evidence that pediatric PNES and late-onset PNES may differ from adult-onset PNES, but the existing literature uses varying criteria to define pediatric and late-onset. Therefore, we opted to include all subjects in our analysis, with the recognition that if the factors associated with pediatric and late-onset PNES differed from adult-onset PNES, this would result in reduced predictive performance that could be explored in more depth in later studies.

2.1. Clinical databases descriptions

Our population includes two sets of patients based on whether their data were acquired retrospectively (January 2006–April 2015) or prospectively (May 2015–November 2016). Records from patients admitted prior to May 2015 were acquired though retrospective chart review. In the interest of developing an early screening tool, if multiple notes were available, we used a single neurology note from the earliest clinical encounter that provided a description of the patients' seizures and pertinent history. This included both outpatient and inpatient encounters. Detailed social history including psychological stressors and history of abuse was obtained only if deemed appropriate by the neurologist that authored the note. Patients admitted after this date underwent standardized interview with a trained nonneurologist researcher (E.A.J., S.D., W.T.K., or M.AB.) within 48 h of VEM admission. To simulate the data that would be available during an outpatient visit, no information from the health record was used to supplement the patient-provided history except height, weight, sex, and age data. Information from the neurologist's admission note was not included or referenced prior to interview. If retrospective patients were readmitted during the prospective period (i.e., due to inconclusive initial monitoring), they were excluded from the prospective analysis. Information from the standardized interview was not used, and their diagnosis was updated in the retrospective dataset. This reduced the frequency of inconclusive monitoring in the retrospective group and ensured that the historical information was blinded to VEM results. Age

Table 1
Patient reported historical factors considered to potentially contribute to our model. Indentation reflects additional details within a larger category. Abbreviations: body mass index (BMI), traumatic brain injury (TBI).

Factor description
Age of seizure onset
Delay to assessment
Febrile seizures
Family history seizures
Neuroinfection
Neurotoxin
Premature birth
Traumatic brain injury (TBI)
Concussion/mild TBI
TBI with prolonged deficits
Precipitating event
Psychological stressor
Sexual abuse
Physical abuse
Obesity (BMI ≥ 30)
Employed or student
Handedness