Epilepsy & Behavior 69 (2017) 69–74

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Diagnostic implications of review-of-systems questionnaires to differentiate epileptic seizures from psychogenic seizures

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ARTICLE INFO

Article history:
Received 16 August 2016
Revised 31 October 2016
Accepted 3 November 2016
Available online 23 February 2017

Keywords:
Review-of-systems
Computer-diagnostics
Screening
Pseudoseizures
Epilepsy
Video-electroencephalography

ABSTRACT

Objective: Early and accurate diagnosis of patients with psychogenic nonepileptic seizures (PNES) leads to appropriate treatment and improves long-term seizure prognosis. However, this is complicated by the need to record seizures to make a definitive diagnosis. Suspicion for PNES can be raised through knowledge that patients with PNES have increased somatic sensitivity and report more positive complaints on review-of-systems questionnaires (RoSQs) than patients with epileptic seizures. If the responses on the RoSQ can differentiate PNES from other seizure types, then these forms could be an early screening tool.

Methods: Our dataset included all patients admitted from January 2006 to June 2016 for video-electroencephalography at UCLA. RoSQs prior to May 2015 were acquired through retrospective chart review ($n = 405$), whereas RoSQs from subsequent patients were acquired prospectively ($n = 190$). Controlling for sex and number of comorbidities, we used binomial regression to compare the total number of symptoms and the frequency of specific symptoms between 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 RoSQs to differentiate PNES only from ES only, we used multivariate logistic regression, controlling for sex and the number of medical comorbidities.

Results: On average, patients with PNES or mixed PNES and ES reported more than twice as many symptoms than patients with isolated ES or PSLE ($p < 0.001$). The prospective accuracy to differentiate PNES from ES was not significantly higher than naïve assumption that all patients had ES (76% vs 70%, $p > 0.1$).

Discussion: This analysis of RoSQs confirms that patients with PNES with and without comorbid ES report more symptoms on a population level than patients with epilepsy or PSLE. While these differences help describe the population of patients with PNES, the consistency of RoSQ responses was neither accurate nor specific enough to be used solely as an early screening tool for PNES. Our results suggest that the RoSQ may help differentiate PNES from ES only when, based on other information, the pre-test probability of PNES is at least 50%.

1. Introduction

Early and efficient differentiation of psychogenic nonepileptic seizures (PNES) from epileptic seizures (ES) is critical to the successful treatment of both conditions [1–3]. Accurately characterizing the subtype of seizures in each patient helps physicians choose a medication that is most likely to reduce or eliminate seizures, and avoid the unnecessary risks of medications that are not likely to be effective [2,4–6]. Despite this, 50–90% of patients diagnosed ultimately with PNES were treated initially with anti-seizure medications (ASMs) [3,7], potentially delaying time to definitive diagnosis [8] while exposing patients to iatrogenic adverse effects. The most effective treatment of PNES is cognitive-behavioral-informed therapy to address the underlying psychological stressors that contribute to their seizures [9,10]. Diagnosing PNES earlier results in reduced cost and better short and long-term seizure control [2,4,5,11,12]. Unfortunately, the average delay from first

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http://dx.doi.org/10.1016/j.yebeh.2016.11.002
1525-5050/

seizure to diagnosis of PNES is over 8 years [8]. Given this clinical scenario, high quality, low cost, and objective screening tools to identify patients at risk for PNES are needed.

A major challenge in identifying the etiology of seizures as early as possible is the development of evidence-based methods that differentiate seizure types based on standardized information acquired early in the patient assessment. Almost all clinics ask patients to fill out standardized review-of-systems questionnaires (RoSQ) before they speak to a physician; evidence that these are effective in diagnosis of seizures is promising but limited [13,14]. Patients with PNES experience increased somatic sensitivity, as evidenced by medically unexplained symptoms and reporting more disability for less severe symptoms [1,12,13,15,16]. Additionally, most frequently, PNES are a component of conversion disorder in which patients convert psychological stressors into somatic symptoms or findings, one of which can be seizures [3,12,17]. However, conversion disorder frequently presents with other positive findings including pain, fatigue, lethargy, myalgias, constipation or diarrhea [3]. These symptoms may not be severe enough to warrant medical attention or treatment, but they are reported on RoSQs.

There is retrospective evidence that RoSQs may help identify patients at risk for PNES [13,14]. In a small dataset with many different formats of RoSQs, Robles and colleagues demonstrated recently that patients who noted >17% of symptoms on RoSQs were more likely to have PNES than ES with an area under the received operating curve (AUC) of 84% [13]. Their sample size was limited, however, by inconsistent availability of RoSQs in the electronic health record. Recently, Asadi-Pooya and colleagues also demonstrated that an alternate type of RoSQ achieved an AUC of 67% with a cut-off of 3 of 10 positive organ systems [14]. We extended their work by studying a larger retrospective dataset at an independent institution, as well as a dataset in which RoSQs were collected prospectively from almost every patient admitted for video-electroencephalographic (vEEG) monitoring, the definitive diagnostic modality for most patients with PNES [1]. We also controlled for sex and the total number of medical comorbidities to better describe effect of RoSQ responses, independent of these confounders. Additionally, we addressed how patients with mixed PNES plus ES, physiologic non-epileptic seizure-like events (PSLE), and inconclusive vEEG monitoring respond to RoSQs. This provides a more complete understanding of the differential diagnosis for seizures and the potential role of RoSQs in differentiating these populations.

2. Methods

Our patient population included all patients admitted to the UCLA adult vEEG monitoring unit between January 2006 and June 2016. Diagnosis was expert clinical opinion based on clinical history, physical exam, vEEG, and structural & diffusion magnetic resonance imaging; fluorodeoxyglucose-positron emission tomography magnetoencephalography and single-photon emission computed tomography also were used in some patients. We placed patients in five mutually exclusive categories: psychogenic nonepileptic seizures (PNES), physiologic nonepileptic seizure-like episodes (PSLE), epileptic seizures (ES), mixed nonepileptic & epileptic seizures, and inconclusive monitoring. We recognize that these are heterogeneous populations with many important subtypes, but the description of subtypes within PNES and ES is outside the scope of this article. Throughout this manuscript, we will specify mixed seizures when referring to any patients with both PNES and ES. We chose to keep patients with mixed PNES plus ES separate from patients with PNES because, while both have PNES, there is insufficient evidence to suggest that the mechanism and risk factors for PNES are the same in these populations [18]. Inconclusive monitoring occurred when patients did not experience sufficient characteristic events during monitoring to yield a definitive diagnosis.

Our population included two groups: retrospective patients (January 2006–April 2015) and prospective patients (May 2015–June 2016). We do not refer to these groups as “training” and “validation” because they differ from traditional training and validation sets in machine learning. The function of the retrospective group was to generate objective criteria for using RoSQs to differentiate between PNES and ES, whereas the function of the prospective group was to validate how well these criteria function in a real-world, unselected dataset.

Records from patients prior to May 2015 were acquired though retrospective chart review. In the retrospective patient group, patients or their caregivers filled out RoSQs in the outpatient neurology waiting room prior to their appointment or at home as part of the admission packet sent to them prior to vEEG admission. If the patient had not filled out their RoSQ prior to vEEG, they were given another form during admission and the form was collected by nursing staff. RoSQs from patients admitted after April 2015 were collected in person within 48 h of vEEG admission by an interviewer. If the patient had not filled out the form, the patient was provided another form and the interviewer returned later to collect the form. The goal of including an interviewer in the prospective group was to reduce the potential for selection bias from missing data. To assess the potential for selection bias, we report the leave-one-patient-out area under the receiver-operating curve (AUC) of our predictive algorithm on the retrospective group.

For patients with multiple available RoSQs, the earliest standard form was used. RoSQs collected after conclusive vEEG monitoring were excluded. If retrospective patients were re-admitted during the prospective period (e.g. due to an inconclusive first admission), they were excluded from the prospective analysis and, if necessary, their diagnosis was updated in the retrospective dataset. Because the first available RoSQ was used, there was no difference between the RoSQ data for patients that required more than one admission to yield a definitive diagnosis. Readmission reduced the frequency of inconclusive monitoring in the retrospective group. Age was recorded as the age at the time of RoSQ completion.

All patients or their caregivers filled out a standardized 78-item review of system questionnaire (see Supplemental Fig. 1). Two minor variations of the standard form were accepted, one of which omitted 3 items (75 total items), and the other omitted the same 3 items while splitting one item into two separate items (76 total items). All forms listed the same 14 organ systems. These standardized forms were used across all UCLA neurology providers. Caregivers' responses were used when the patient was unable to fill out the form due to physical or intellectual disability.

We analyzed the RoSQ responses using both population-level descriptive statistics and individual-level predictive statistics. For the population level analysis, the retrospective and prospective datasets were combined (for analysis of each dataset separately, see Supplemental Information). For all analyses, we controlled for patient sex and the number of medical comorbidities. For the descriptive analysis, controlling for confounders differentiated the effect of etiology on RoSQ responses conditionally independent from the effect of sex and medical comorbidities. For the predictive analysis, controlling for confounders demonstrated the additive value of RoSQ past that of knowing the patient's sex and medical comorbidities. A linear correction for age did not have a significant impact on the results (analysis not shown).

Descriptive multivariate binomial regression was used to determine if the total percent of positive responses or the likelihood of a positive response to each specific question differed between the 5 diagnostic categories on a population level. Inclusion of patients with inconclusive monitoring improved our ability to estimate and control for the effect of patient sex and number of comorbidities but otherwise had no effect on the results of the other 4 diagnostic categories. False discovery rate multiple testing correction was applied to analysis of each specific complaint. We also display the frequency of each diagnostic subclass, based on the number of RoSQ symptoms.

Predictive multivariate logistic regression was used to determine if the percent of positive RoSQ symptoms could differentiate between individual patients with PNES and ES. Patients with mixed ES plus PNES, PSLE, and inconclusive monitoring were excluded from predictive