Epilepsy & Behavior 45 (2015) 151–154

Contents lists available at ScienceDirect

Epilepsy & Behavior

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

Brief Communication

# Review-of-systems questionnaire as a predictive tool for psychogenic nonepileptic seizures

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ARTICLE INFO

*Article history:*
Received 18 December 2014
Revised 31 January 2015
Accepted 3 February 2015
Available online 23 March 2015

*Keywords:*
Epilepsy
Seizure
Psychogenic nonepileptic seizure
Review of systems

ABSTRACT

Patients with refractory epilepsy undergo video-electroencephalography for seizure characterization, among whom approximately 10–30% will be discharged with the diagnosis of psychogenic nonepileptic seizures (PNESs). Clinical PNES predictors have been described but in general are not sensitive or specific. We evaluated whether multiple complaints in a routine review-of-system (ROS) questionnaire could serve as a sensitive and specific marker of PNESs. We performed a retrospective analysis of a standardized ROS questionnaire completed by patients with definite PNESs and epileptic seizures (ESs) diagnosed in our adult epilepsy monitoring unit. A multivariate analysis of covariance (MANCOVA) was used to determine whether groups with PNES and ES differed with respect to the percentage of complaints in the ROS questionnaire. Tenfold cross-validation was used to evaluate the predictive error of a logistic regression classifier for PNES status based on the percentage of positive complaints in the ROS questionnaire. A total of 44 patients were included for analysis. Patients with PNESs had a significantly higher number of complaints in the ROS questionnaire compared to patients with epilepsy. A threshold of 17% positive complaints achieved a 78% specificity and 85% sensitivity for discriminating between PNESs and ESs. We conclude that the routine ROS questionnaire may be a sensitive and specific predictive tool for discriminating between PNESs and ESs.

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## 1. Introduction

Psychogenic nonepileptic seizures (PNESs) represent an important subset of apparently pharmacoresistant epilepsy. Psychogenic nonepileptic seizures are often misdiagnosed as epileptic seizures (ESs) in the community, leading to unnecessary, and potentially harmful, treatment in the form of inappropriate use of antiepileptic medications, invasive procedures during prolonged seizures, and the economic burden of frequent hospital admissions [1]. One-third of the patients with PNESs will have 'prolonged status', and up to three-quarters of these cases may be recurrent, leading to unnecessary treatment and, sometimes, death [2,3]. It has been calculated that, on average, PNES diagnosis is delayed by approximately seven years [4].

The distinction of PNESs from ESs is sometimes difficult even for the experienced clinician. Certain clinical and demographic characteristics have been described that increase the likelihood of PNESs including female gender, psychiatric history, history of abuse, prolonged spells, nonstereotyped movements, eye fluttering, preserved awareness, and episodes triggered by observers [5–7]. Ictal stuttering is a specific, but not a sensitive, marker of PNESs [8]. However, the diagnosis of PNESs is still often difficult to make, and it accounts for 10–30% of the admissions to the epilepsy monitoring unit (EMU) [2,5]. Conversely, up to 20% of the patients with a presumed diagnosis of PNESs referred for video-electroencephalography (VEEG) may have ESs or physiologic nonepileptic events [9].

Functional somatic comorbidities are more common in patients with a presumed diagnosis of PNESs than in those with a diagnosis of epilepsy [10]. We observed that patients clinically suspected to have PNESs tend to report more somatic complaints in our review-of-systems (ROS) questionnaire. Hence, we systematically analyzed whether documenting multiple complaints in the ROS questionnaire would aid in the diagnosis of PNESs. We retrospectively analyzed the ROS questionnaire of patients ultimately diagnosed with PNESs in the EMU and compared them to patients diagnosed with ESs to determine the discriminant value of the routinely administered questionnaire.

*Abbreviations:* PNESs, psychogenic nonepileptic seizures; ESs, epileptic seizures; EMU, epilepsy monitoring unit; VEEG, video-electroencephalography; ROS, review of systems; MANCOVA, multivariate analysis of covariance; ROC, receiver operating characteristic; AUC, area under the curve.

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http://dx.doi.org/10.1016/j.yebeh.2015.02.003
1525-5050/Published by Elsevier Inc.

## 2. Material and methods

### 2.1. Subjects

We performed a retrospective analysis of patients admitted to the Baylor Comprehensive Epilepsy Center EMU from January 2011 through May 2014. Patients with a definite diagnosis of PNESs or ESs were included. We excluded patients with mixed PNESs and ESs, physiologic nonepileptic events, and inconclusive diagnosis due to failure of capturing a 'typical event'. Additionally, patients with a history of intellectual disability were excluded. All included patients had a self-reported ROS questionnaire in their electronic charts. The majority of patients responded to the ROS questionnaire during their initial epilepsy clinic visit or during their initial neurosurgical evaluation. The study was approved by the Baylor College of Medicine Institutional Review Board.

### 2.2. ROS questionnaire

There were four different ROS questionnaire formats (presented as supplementary material). These questionnaires were given to the patients in the clinic per availability, accounting for this variability. One questionnaire format included a continuous list of symptoms, and the remainder included a list of symptoms subdivided by system. Overall, the total number of symptoms available for selection ranged from 41 to 79 items, with the exception of one questionnaire had 29 items. One questionnaire format appeared to have two versions containing 61 or 64 questions.

The ROS questionnaires of patients with PNESs and ESs were analyzed. Each item answered positively was given a score of one across the different questionnaires. To account for the differences in the number of items between the questionnaires, the positive responses were summarized as a percentage of the total number of items in the questionnaire. The different questionnaires used are given as supplementary material.

### 2.3. Data analysis

All statistical analyses were performed using R version 3.1.0.

Multivariate analysis of covariance (MANCOVA) was used to compare groups with PNESs and ESs with respect to the percentage of positive complaints. To control for the potential confounding effects of baseline characteristics, the following were included as covariates: gender, age at evaluation, age at epilepsy onset, psychiatric history, and a history of abuse. Quantile–quantile plots and histograms were used to evaluate the need for transformations. Observations located more than 1.5 times outside the interquartile range of the quartiles were considered outliers. A square-root transformation was performed on percentage data to eliminate right skewness.

Tenfold cross-validation was used to assess the ability of a discriminant function based on the percentage of positive complaints in the ROS questionnaire to predict PNES diagnosis. Because of nonnormality of percentage data, logistic regression was used for classification [11]. To measure general classification performance, a receiver operating characteristic (ROC) curve was constructed by calculating sensitivity and specificity over various cutoff levels. The area under the curve (AUC) was then calculated as a general measure of performance. Cutoff levels that maximized the Youden index were used to identify the percentage of positive complaints in the ROS questionnaire that best predicted PNES/epilepsy classification.

## 3. Results

Among the 342 patients admitted to the EMU during the time period of the study, 298 patients were excluded because of the incomplete chart information or exclusion criteria noted above. Of the 44 patients included, 21 had PNESs, and 23 had ESs. Baseline characteristics of these patient groups are shown in Table 1. Groups with PNESs and ESs were similar with respect to gender, age at evaluation, self-reported psychiatric history, and history of abuse. Compared to the group with ESs, the group with PNESs had a significantly later age of epilepsy onset.

Table 1 includes a comparison of the percentage of positive complaints in the ROS questionnaire for the groups with PNESs and ESs. From MANCOVA, patients with PNESs were found to have a larger percentage of positive complaints in the ROS questionnaire than patients with epilepsy ($F = 20.78$, $p < 0.0001$). Typically completed ROS forms are shown in Supplementary Fig. 1. Fig. 1A compares the sensitivity and specificity of the percentage of positive complaints in the ROS questionnaire in predicting PNES/epilepsy classification. This corresponded to an area under the curve (AUC) of 0.845, indicating excellent discrimination [12]. Fig. 1B shows the estimated sensitivity, specificity, and Youden index at various cutoff thresholds. The Youden index was maximized at a threshold of 36.0%, which corresponded to classifying subjects as having PNESs if there were greater than 17% positive complaints in the ROS questionnaire or to classifying subjects as having epilepsy, otherwise (Supplementary Table 1, Fig. 1C). Use of this threshold yielded a specificity of 78.3% and a sensitivity of 85.7%.

## 4. Discussion

Our study demonstrates that patients with PNESs have a higher number of complaints in the routine review-of-systems questionnaire compared to patients with epilepsy. With a cutoff of 17% of the ROS items reported as positive, there is 78.3% specificity and 85.7% sensitivity of the diagnosis being PNESs, with a higher specificity of diagnosis at higher cutoffs. The likely explanation for the greater number of symptoms reflected in the ROS questionnaire with regard to patients with PNESs is related to its classification as a somatoform or a conversion disorder [2,13]. Although the underlying psychopathology of PNESs remains to be fully characterized, this may lead to patients with PNESs having more 'somatic complaints' than patients with ESs. This is also supported by previous reports of patients with PNESs having higher scores in somatization questionnaires compared to patients with

**Table 1**
Demographic characteristics and comparison of the percentage of positive complaints in the ROS questionnaire for patients with ESs and PNESs. ESs, epileptic seizures; PNESs, psychogenic nonepileptic seizures; ROS, review of systems; SD, standard deviation.

| | ESs (n = 23) | PNESs (n = 21) | *p*-Value |
|---|---|---|---|
| Gender (male)[a] | 10 | 6 | 0.36 |
| Age at evaluation (years, mean ± SD)[b] | 43.2 ± 14.1 | 38.8 ± 11.8 | 0.32 |
| Age of epilepsy onset (years, mean ± SD)[b] | 20.7 ± 17.7 | 33.1 ± 13.4 | 0.005* |
| Psychiatric disorder[a] | 4 | 9 | 0.10 |
| History of abuse[a] | 1 | 2 | 0.60 |
| Percentage of positive complaints in the ROS questionnaire | | | |
| Mean (±SD) | 11.15 ± 14.22 | 36.96 ± 18.00 | |
| Range | 0.00–49.20 | 9.80–70.70 | |

[a] Fisher's exact test.
[b] Mann–Whitney U test.
* Significant difference at the 0.05 level.