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Authors

Robbins, Nathaniel M
Larimer, Phillip
Bourgeois, James A
et al.

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Number of patient-reported allergies helps distinguish epilepsy from psychogenic non-epileptic spells (pseudoseizures)

Nathaniel M Robbins[1,*], **Phillip Larimer**[2], **James A Bourgeois**[3], and **Daniel H Lowenstein**[2]

[1]Department of Neurology, Dartmouth-Hitchcock Medical Center, Lebanon, NH, USA

[2]Department of Neurology, University of California, San Francisco, CA, USA

[3]Department of Psychiatry, University of California, San Francisco, CA, USA

Summary

Psychogenic non-epileptic seizures (PNES) are relatively common, accounting for 5–40% of visits to tertiary epilepsy centers. Inpatient video electroencephalogram (vEEG) monitoring is the gold standard for diagnosis, but additional positive predictive tools are necessary given vEEG's relatively scarce availability. In this study we investigate if the number of patient-reported allergies distinguishes between PNES and epilepsy. Excessive allergy-reporting, like PNES, may reflect somatization. Using the electronic medical record, ICD-9 codes, and text-identification algorithms to search EEG reports, we identified 905 cases of confirmed PNES and 5187 controls with epilepsy but no PNES. Patients with PNES averaged more self-reported allergies than patients with epilepsy alone (1.93 vs. 1.00, $p<0.001$). Compared to those with no allergies, each additional allergy linearly increased the percentage of patients with PNES by 2.98% ($R^2=0.71$) such that with ≥ 12 allergies, 12/28 patients (42.8%) had PNES compared to 349/3368 (11.6%) of the population with no allergies (odds ratio = 6.49). This relationship remained unchanged with logistic regression analysis. We conclude that long allergy lists may help identify patients with PNES. We hypothesize that a tendency to inaccurately self-report allergies reflects a maladaptive externalization of psychologic distress, and that a similar mechanism may be responsible for PNES in some patients with somatic symptom disorder.

Keywords

PNES; allergies; epilepsy; somatization; pseudoseizure

[*]Corresponding Author: Dartmouth-Hitchcock Medical Center, Department of Neurology, One Medical Center Drive, Lebanon, NH, USA 03766, T: 603-650-5458, F: 603-650-5233, doctorrobbins@gmail.com.

Disclosures

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Introduction

Somatoform spectrum disease (SSD) is a general term encompassing a variety of conditions in which a patient experiences physical symptoms that are inconsistent with or cannot be fully explained by any underlying general medical or neurologic condition. SSDs are variably categorized and subtyped as functional neurological disorders, conversion disorder, hysteria, psychogenic disorder, dissociative disorder, psychosomatic disorder, Briquet's syndrome, nonorganic disease, medically unexplained symptoms, pseudoneurologic disease, hypochondriasis, and most recently - somatic symptom disorder.[1] This heterogeneity results from temporal fashions, poor understanding of the physiologic basis of these conditions, and definitional inconsistencies.

SSDs account for up to 30% of all patients referred for neurologic consultation, [2] though good epidemiologic studies are rare due to definitional ambiguities. SSDs affect the entire nervous system and all subspecialties. SSDs are generally considered diagnoses of exclusion but can be difficult to confirm; few diagnostic tests have a high positive predictive value, and a great deal of expertise in neurologic disease, anatomy, and physiology is required to ensure that the symptoms are not better explained by another disease.

Psychogenic non-epileptic seizures (PNES) are a form of SSD frequently seen in neurologic practice, accounting for 5 to 10% of outpatients in epilepsy clinics and 20 to 40% of inpatients in epilepsy monitoring units.[3] PNES benefits from a gold standard for diagnosis in the form of video electroencephalogram (vEEG) monitoring, in which the absence of epileptic activity during a witnessed typical event is often diagnostic for PNES. However, vEEG monitoring capabilities are limited to specialized centers.[4] As a result, the diagnosis of PNES is often delayed by a decade or more.[3] During this delay, patients undergo costly evaluations and are at risk for iatrogenic injury from medication toxicity, intubation for pseudostatus epilepticus, and rarely even device implantation or epilepsy surgery. Clearly, better tools for early and accurate diagnosis are necessary. To this end, a number of ictal (e.g. pelvic thrusting, forced eye closure, ictal stuttering, duration of event, kinetics of limb movements, heart-rate variability, generalized movements with preserved consciousness, lack of tongue biting and incontinence) and biopsychosocial (e.g. history of sexual abuse, comorbid chronic pain disorders, comorbid psychiatric disease, the "teddy bear sign") variables have been identified that help distinguish between PNES and epileptic seizures. However, all are limited in terms of sensitivity and specificity.[3, 5–7]

Polyallergy, also called "multiple chemical sensitivity syndrome" or "idiopathic environmental intolerance" is the excessive self-reporting of unproven allergies. Polyallergy has previously been associated with somatoform spectrum disorders[8] and may itself be better classified as a SSD, since studies have shown that true allergies are uncommon.[9] More recently, polyallergy has been identified as a risk factor for PNES diagnosis in an epilepsy monitoring unit, adding to the list of "soft signs" for differentiating PNES from epilepsy.[7, 10]

In this retrospective study, we aimed to confirm the association between number of patient self-reported allergies and a diagnosis of PNES. We also sought to extend these findings to

the outpatient setting; explore confounding factors such as comorbid psychiatric diagnoses and exposure to multiple medications; and explore whether specific self-reported allergies help predict a diagnosis of PNES.

Methods

Patient selection

This retrospective study was approved by the University of California San Francisco (UCSF) Committee on Human Research (IRB#14-15416). We searched the electronic medical record (UCSF's Epic-based APeX - Advanced Patient-Centered Excellence) for all patients seen at UCSF who met the following two criteria: 1) At least one encounter with a neurologist from June 1 2012 to March 31 2015 2) At least one International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis of epilepsy, convulsions, seizures, or a SSD (see Appendix A for a list of ICD-9-CM diagnoses used).

From this cohort we abstracted information on age, gender, medications, comorbid diagnoses, electroencephalogram (EEG) reports, and patient-reported allergies. We identified epilepsy controls if they had an ICD-9-CM diagnosis of epilepsy, no SSD ICD-9-CM diagnosis, and no PNES identified by EEG. Since PNES was poorly and inconsistently coded in the medical record, we identified PNES cases by searching EEG reports for text phrases diagnostic for PNES (see Appendix B for phrases used to search EEG text). Comorbid epilepsy was permitted in the PNES group. To ensure that our methods for searching ICD-9-CM codes and EEG text accurately classified patients into epilepsy and PNES groups, a neurologist (P.L.) reviewed 40 charts manually in a blinded fashion (20 selected randomly from each group), and the results were compared to ensure concordance with the automated categorization.

Statistical analysis

To compare the characteristics of the epilepsy group and PNES group in univariate analysis, we used Pearson's *Chi*-squared test for categorical variables and the student's *t*-test for continuous variables. To further explore the relationship between the number of self-reported allergies and a diagnosis of PNES, we constructed logistic regression models using a stepwise conditional approach that included all variables in which univariate analysis comparing the relationship with the outcome PNES yielded a p-value ≤ 0.05, as well as the category "has a comorbid depressive or anxiety disorder coded by ICD-9-CM," which was nearly significant and highly relevant clinically. In addition, we included all two-variable interaction terms in the model. Model fit was assessed with the Hosmer-Lemeshow test. Manual and automatic categorization of diagnoses (PNES verses epilepsy) was compared using Cohen's kappa (κ). All analyses were conducted using IBM SPSS v22.0.

Results

We identified 34,774 encounters with 7,107 patients from June 1, 2012 to March 31, 2015. Of these patients, 905 (12.7%) had an EEG interpreted as diagnostic for PNES, and 5,187 patients had an ICD-9-CM diagnosis consistent with seizure or epilepsy and no PNES by EEG, yielding a total sample of 6,092 patients. The remaining 1,025 patients with

ambiguous diagnoses (e.g. “loss of consciousness”) initially classified into the epilepsy group were excluded. In the blinded chart review to ensure methodologic reliability, level of agreement between the manual and automated determination was moderate to strong[11] (5/40, patients, or 12.5%, were miscategorized using the automated method; κ=0.75).

Illustrating the tendency towards underdiagnosis and miscoding of psychiatric disease, only 88 patients (9.7%) with EEG-proven PNES had an ICD-9-CM diagnosis that reflects the psychiatric nature of PNES (see Appendix A). Most of these patients were coded as “other convulsions (780.39).” Of the 905 patients with EEG-confirmed PNES, 747 had an ICD-9-CM coded diagnosis of comorbid epilepsy.

Of 6,092 patients in the final sample, the mean age was 33.4 years (range = 0 to 100; interquartile range 18 to 54). 51.3% of the sample was female. These 6,092 patients underwent a total of 16,057 EEGs: 6,689 outpatient studies and 9,368 inpatient studies.

The PNES and epilepsy groups differed significantly in a number of characteristics. The PNES group had a greater percentage with female gender (61.7% v 49.3%); greater mean number of prescribed antiepileptic agents (AEDs; 0.92 v 0.72); and greater percentage prescribed an antidepressant agent (12.3% v 5.6%). The two groups did not differ significantly in the proportion of patients with an ICD-9-CM diagnosis code for a depressive or anxiety disorder - conditions that have previously been thought to associate with PNES.[12] However, the study was not designed to look at specific psychiatric diagnoses. A comparison of characteristics between the PNES group and the epilepsy group can be seen in Table 1.

In addition, the PNES group differed significantly from the epilepsy group in total number of reported allergies (mean 1.93 v 1.00), number of allergies to AEDs (0.31 v 0.16), percentage with antidepressant allergy (3.8% v 1.1%), percentage with benzodiazepine allergy (3.8% v 1.6%), and percentage with at least one AED allergy (19.8% v 10.8%) – see Table 1. The PNES group constituted 12.7% of the sample as a whole, but 23.6% (361/1,527) of those with ≥ 2 allergies and 30.9% (112/362) of those with ≥ 5 allergies. Number of allergies was significantly and linearly associated with an increased risk of a PNES diagnosis (absolute increased risk for each additional allergy = 2.98%, R^2=0.71) such that with ≥ 12 allergies, 12/28 patients (42.8%) had PNES compared to 349/3,368 (11.6%) of the population with 0 allergies (odds ratio (OR) = 6.49). Figure 1 represents the relationship between number of self-reported allergies and the unadjusted odds of being diagnosed with PNES.

To investigate this relationship further, we constructed multivariate logistic regression models including the factors significantly ($p \leq 0.05$) associated with PNES in the univariate analysis described above, and we also included the presence of a coded diagnosis for a depressive or anxiety disorder, which was nearly significant. In addition, we tested all two-way interaction term combinations. Number of allergies remained significantly associated with a PNES diagnosis in logistic regression analysis (OR= 1.17 for each increase of one allergy; 95% confidence interval (CI)= 1.12–1.22), as did use of an antidepressant (1.98; 1.55–2.52), number of prescribed antiepileptic agents (1.07; 1.02–1.12), female gender

(1.47; 1.27–1.70), allergy to an AED (1.67; 1.27–2.19), and the interaction of number of allergies and presence of antiepileptic drug allergy (0.93; 0.88–1.00). Presence of anxiety or depression, allergy to an antidepressant agent, allergy to a benzodiazepine, number of AED allergies, and all other two-way interaction terms dropped out of the model. See Table 2 for results of logistic regression showing associations with a PNES diagnosis.

Discussion

Definitively diagnosing PNES has been demonstrated to substantially reduce health-care utilization and financial costs.[13, 14] In addition, correctly categorizing PNES as an SSD rather than a neurologic disease permits referral for appropriate PNES treatment with cognitive behavioral therapy and psychiatric medication for comorbid psychiatric disease if appropriate.[15] Accordingly, identifying positive predictive tests to aid in diagnosis is essential.

In this study, we demonstrate that the length of a patient-reported allergy list can help differentiate PNES from epilepsy. This confirms the recent findings of Reeves[10] and Park[7], and expands the generalizability to a mixed population of inpatients and outpatients. In addition, we identified a number of other factors that independently help to distinguish PNES from epilepsy.

While insufficiently sensitive or specific to be used in isolation, the relationship between polyallergy and PNES diagnosis is robust across populations and dose-dependent such that each additional allergy is associated with an additive risk. In other words, simply based on patient self-reported allergies, one can predict the odds of PNES independent of other biopsychosocial and clinical factors. Though vEEG monitoring remains the gold standard, this capability remains expensive and is not yet available in many areas.[4] Accordingly, identifying risk factors for PNES is important to help healthcare providers in all settings, helping them to make accurate diagnoses and choose appropriate treatments.

We chose to conduct this study using a population of epilepsy patients since a gold standard for diagnosing SSD exists in the form of vEEG monitoring. However, the relationship between polyallergy and SSDs may be present in other neurologic settings. Future studies should test this hypothesis in patients with subjective sensory complaints presenting to multiple sclerosis clinics, electrodiagnostic centers, and pain clinics, as well as in patients with functional movements disorders. In addition, prospective studies are needed to validate these results.

This was a retrospective study not designed to determine the mechanism underlying this relationship. However, cautious inferences can be drawn from comparison with the literature on multiple chemical sensitivity syndrome and SSD. It has been demonstrated that patients reporting numerous drug intolerances score higher on somatization screening questionnaires compared with the normal population, [9] and that patients with multiple chemical sensitivity have a higher prevalence of medically unexplained symptoms.[8] Similarly, patients with PNES have higher rates of somatization than patients with epilepsy, and somatization is associated with poorer quality of life overall in this population.[16] We

suspect that polyallergy occurs when a patient experiences feelings of psychologic distress, which may include physiologic symptoms, and externalizes these sensations by attributing them to an external medication rather than recognizing the psychologic cause. We hypothesize that certain patients with PNES suffer from a similar failure to recognize psychologic distress, and in those patients, polyallergy is a marker for an underlying somatic symptom disorder.

Finally, it should be noted that the majority of patients with PNES in our sample had few allergies (60.1% had ≤1 allergy and 87.6% had ≤ 4). Clearly SSD in the form of polyallergy is a confounding condition only in a minority of PNES patients. This finding may reflect the heterogeneity of PNES as a diagnostic category; PNES is more of a symptom than a specific diagnosis. Much like many conditions can lead to a syndrome of epilepsy, PNES likely results from a number of psychiatric conditions including dissociative disorders, trauma and stressor related disorders, personality disorders, and panic disorders, in addition to somatic symptom disorder.[17] Since each psychiatric condition has different risk factors and treatments, lumping PNES is likely counterproductive to both clinical efforts and research studies. For example, the 22 patients in our sample with an ICD-9-CM diagnosis of post-traumatic stress disorder averaged significantly more allergies than the 905 patients with PNES as a whole (3.9 ± 0.6 vs. 1.9 ± 0.1; p =0.001), likely reflecting the known propensity for somatization in that disorder.[18, 19] Future research should explore the heterogeneity of psychiatric diagnoses in PNES and look for risk factors and treatments based on subtypes. Given the high prevalence and substantial morbidity and cost associated with PNES, efforts to improve diagnosis and treatment for this condition are essential.

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Appendix A – International Classification of Disease, 9th Revision, Clinical Modification diagnoses used to identify non-epileptic spells and epilepsy

Non-epileptic	Epileptic
300.10	345.00
300.11	345.01
300.12	345.10
300.13	345.11
300.14	345.2
300.15	345.3
300.16	345.40
300.19	345.41
300.6	345.50
300.7	345.51
300.81	345.60
300.82	345.61

Non-epileptic	Epileptic
300.89	345.70
300.9	345.71
	345.80
	345.81
	345.90
	345.91
	348.81
	780.31
	780.32
	780.37
	780.39

Appendix B - Phrases used in EEG text identification algorithm

“none of the events have a scalp EEG correlate”
“none of the events have an electrographic correlate”
“no electrographic correlate”
“no scalp correlate”
“psychogenic”
“nonepileptic”
“non-epileptic”
“not epileptic”
“not associated with”

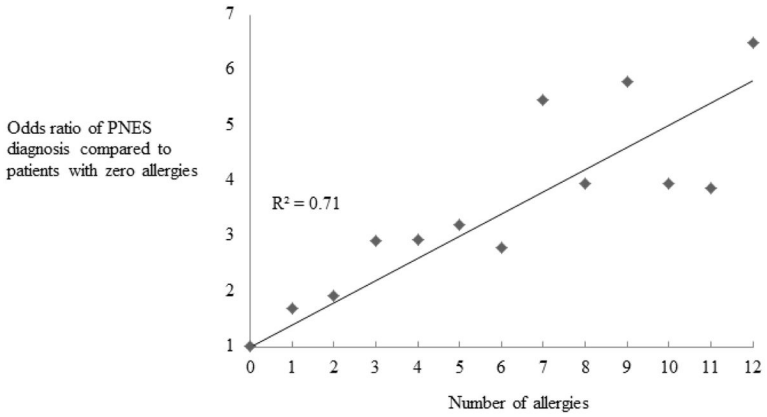

Figure 1.

Unadjusted odds ratio for psychogenic non-epileptic seizure (PNES) diagnosis based on number of allergies compared to patients with zero allergies

Table 1

Characteristics of the sample and comparison of non-epileptic and epileptic groups

Independent variable	Entire sample n (%)/mean (SD[a]) *n* = 6092	Non-epileptic group n (%)/mean (SD) *n* = 905	Epilepsy group n (%)/mean (SD) *n* = 5187	*p*-value[1]
Female gender	3113 (51.3)	558 (61.7)	2555 (49.3)	< 0.001
ICD-9 depression or anxiety[b]	5107 (83.8)	739 (81.7)	4368 (71.7)	0.05
Allergy to antidepressant	92 (1.5)	34 (3.8)	58 (1.1)	< 0.001
Allergy to benzodiazepine	117 (1.9)	34 (3.8)	83 (1.6)	< 0.001
Allergy to antiepileptic (AED)	738 (12.1)	179 (19.8)	559 (10.8)	< 0.001
On antidepressant	401 (6.6)	111 (12.3)	290 (5.6)	< 0.001
Age	33.44 (23.42)	32.72 (20.46)	33.57 (24.49)	0.26
Number of allergies	1.14 (2.34)	1.93 (2.71)	1.00 (2.16)	< 0.001
Number of AEDs	0.75 (1.56)	0.92 (1.50)	0.72 (1.44)	< 0.001
Number of AED allergies	0.18 (0.78)	0.31 (0.60)	0.16 (0.72)	< 0.001

[1] *Chi*-squared for categorical variables; two-tailed *t*-test of the means (equal variance not assumed) for continuous variables

[a] SD = standard deviation

[b] International Classification of Disease, 9th revision, Clinical Modification diagnosis of a depressive or anxiety disorder

Table 2

Results of logistic regression showing associations with non-epileptic seizure diagnosis

Independent variable	Exp(B); odds ratio	95% C.I. for Exp(B)	*p*-value
Number of allergies	1.17	1.12 – 1.22	< 0.001
Number of antiepileptic agents (AED)	1.07	1.02 – 1.12	0.006
On antidepressant agent	1.98	1.55 – 2.52	< 0.001
Allergy to AED	1.67	1.27 – 2.19	< 0.001
Female gender	1.47	1.27 – 1.70	< 0.001
Allergy to AED*number of allergies	0.93	0.88 – 1.00	0.035