

## Original Research Reports

# A Retrospective Study of Polyallergy as a Marker of Nonepileptic Seizures in the Epilepsy Monitoring Unit

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**Background:** Distinguishing epileptic seizures from nonepileptic seizures (NES) can be difficult, given their similar motoric manifestations and a common comorbidity. Although video electroencephalography in an epilepsy monitoring unit ideally remains the gold standard for the identification of NES, a number of “soft signs” have been proposed to indicate a greater likelihood that convulsive episodes are NES rather than epileptic in nature. Trainees at our institution have cited the presence of multiple listed allergies as indicative of a higher likelihood of NES.

**Objective:** The goal of this study was to provide a statistical analysis of polyallergy and its association with patients with NES admitted for video electroencephalograph monitoring. **Methods:** Records of all epilepsy monitoring unit patients at St. Joseph’s Hospital and Medical Center

between 2006 and 2012 were reviewed for age, sex, electroencephalograph diagnosis, antiepileptic drugs previously tried, and allergy number. **Results:** A total of 1834 patient records were used for analysis. The group classified as nonepileptic had the highest average number of allergies at 1.56, whereas the group classified as epileptic had the lowest average number of allergies at 0.70. A logistic regression model revealed that for every increase in the number of allergies greater than zero, the odds of being nonepileptic increases by 1.38 times. **Conclusions:** This study supports polyallergy as a predictive sign for NES. Based on a logistic regression model, we claim that each additional allergy is associated with an increase in the likelihood of a nonepileptic diagnosis by 38%.

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## INTRODUCTION

Distinguishing epileptic seizures from nonepileptic seizures (NES) can be difficult, given their similar motoric manifestations and a reported comorbidity of approximately 20%.<sup>1</sup> Although video electroencephalography (EEG) remains the gold standard for the identification of NES, a number of “soft signs” have been proposed to indicate a greater likelihood that convulsive episodes are NES rather than epileptic in nature. These include the teddy bear sign,<sup>2</sup> pelvic thrusting,<sup>3</sup> a history of physical abuse,<sup>4</sup> pain medication use,<sup>5</sup> ictal stuttering,<sup>6</sup> voluntary nystagmus,<sup>7</sup> and eye closure.<sup>8</sup> For years, trainees at the Barrow Neurological Institute at St. Joseph’s Hospital and

Medical Center have also anecdotally included the “Caplan sign” among the ranks of these indicators of psychopathology. This eponymous designation (after the Chair of the Department of Psychiatry who frequently posited the association during hospital

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rounds) describes a finding of 4 or more allergies listed in the medical record as a potential medical record–based predictor of NES. The goal of this study was to examine the reliability of polyallergy in predicting NES in a cohort of patients admitted for video EEG monitoring. It is important to note that the term “polyallergy” is used to describe multiple reported or listed allergies in the medical record rather than explicitly diagnosed IgE-mediated allergic reactions. As such, this designation is likely to include multiple types of actual or perceived adverse reactions to a variety of substances.

### METHODS

An institutional review board proposal to review the Barrow Neurological Institute Epilepsy Monitoring Unit’s (EMU) patient records between 2006 and 2012 was approved by the institutional review board at St. Joseph’s Hospital and Medical Center, and data were collected according to the proposal’s protocol. This retrospective study collected, examined, and analyzed 1834 patient records, which were stored in a Word document format. A PERL script was devised and parsed through Word document files for age, sex, EEG diagnosis, antiepileptic drugs previously tried, and allergy number to produce an Excel spreadsheet for statistical analysis. For simplicity, we did not make a distinction between drug allergies and nondrug allergies. Univariate analysis of variance was used to compare continuous outcome variables. Analysis of variance was used to examine mean differences in outcome variables, number of allergies, age, and sex by EEG outcome group. The chi-square test was used to cross-tabulate categorical predictors by EEG outcome group. A logistic regression model was used to predict dichotomous outcome variable: epileptic or nonepileptic outcome. PERL version 5.12.3 was used. Excel 2008, MedCalc version 11.4, and SPSS version 20 were used (Table 1).

### RESULTS

A total of 1834 patient records of 690 (37.6%) men and 1144 (62.3%) women from the ages of 3 to 84 years were used for analysis. The following 4 groups were identified: (1) epileptic (episodes always with epileptiform discharges) with 787 (42.9%) cases, (2) nonepileptic (episodes never with epileptiform discharges)

**TABLE 1. Frequency By Sex of the Barrow Neurological Institute EMU Population From 2006–2012**

|        | Frequency | Percentage | Cumulative percentage |
|--------|-----------|------------|-----------------------|
| Female | 1144      | 62.4       | 62.4                  |
| Male   | 690       | 37.6       | 100.0                 |
| Total  | 1834      | 100.0      |                       |

with 647 (35.2%) cases, (3) nondiagnostic (no episode recorded on video EEG) with 331 (18%) cases, and (4) epileptic/nonepileptic (episodes both with and without epileptiform discharges) with 69 (4%) cases, as shown in Table 2. Our percentage of NES based on EMU diagnosis closely compares to the 32.3% rate reported by Martin et al. based on 1590 patient records.<sup>9</sup> The epileptic group represented 48.9% of the patients in the study by Martin et al., indicating that the frequency breakdown of different EMU group types is similar between New York and Phoenix. The counts, percentages, and adjusted standardized residuals for EEG by sex are shown in Table 3. The chi-square test suggesting the distribution of sex is not the same across EEG outcome group,  $\chi^2 = 36.89$ ,  $p < 0.001$ . We examined adjusted standardized residuals greater than  $\pm 1.96$  to identify which groups yielded an unexpected sex distribution. These results suggested that the epileptic group consisted of fewer women than expected and the nonepileptic group consisted of more women than expected. However, it should be noted that the epileptic, nonepileptic, and nondiagnostic groups each had more women than men, which may be expected, given that women comprised 62.3% of the total cases. The average number of allergies significantly varied by EEG group and is shown in Table 2. The nonepileptic group had the highest number of allergies on average at 1.56, whereas the epileptic group had the lowest number of allergies reported on average at 0.70. The average ages of patients across these 4 groups were also significantly different and have also been shown in Table 2. Effect sizes for both number of allergies and patient age are small, 0.03 and 0.04, respectively. *Post hoc* comparisons were used with the conservative Bonferroni correction applied, and they demonstrated that those in the epileptic group were significantly younger and had significantly fewer allergies than those in the nonepileptic and nondiagnostic groups did,  $p < 0.001$  for all significant comparisons. The distribution for average number of allergies by EEG group is also shown visually using a box plot in the Figure. For our final model, a

**TABLE 2. Means and Standard Deviations for Age and Number of Allergies By Group**

| Group                             | Age           |             | Number of allergies |           |
|-----------------------------------|---------------|-------------|---------------------|-----------|
|                                   | Mean (SD)     | 95% CI      | Mean (SD)           | 95% CI    |
| Epileptic                         | 32.51 (16.51) | 31.36–33.67 | 0.70 (1.33)         | 0.60–0.79 |
| Nonepileptic                      | 37.53 (16.86) | 36.23–38.83 | 1.56 (2.18)         | 1.39–1.73 |
| Nondiagnostic                     | 39.30 (16.60) | 37.51–41.09 | 1.21 (2.11)         | 0.99–1.44 |
| Epileptic and nonepileptic        | 35.30 (18.02) | 30.98–39.63 | 1.16 (1.61)         | 0.77–1.55 |
| Total                             | 35.61 (16.93) | 34.84–36.39 | 1.11 (1.86)         | 1.03–1.20 |
| <i>p</i> Value                    |               | <0.001      |                     | <0.001    |
| Effect size (partial eta-squared) |               | 0.04        |                     | 0.03      |

SD = standard deviation.

logistic regression predicting nonepileptic EEG was performed using age, sex, number of allergies, and number of antiepileptic drugs as predictors. All predictors were significant at the  $p < 0.001$  level, and the final model accuracy was 68.5%. For every 1-year increase in age, the odds of being nonepileptic increase by 1.01 times. Women were 1.62 times more likely to be classified in the nonepileptic group type than men were. For every additional antiepileptic drug tried, the odds of being nonepileptic decrease by 0.71 times. In contrast, for every increase in the number of allergies, the odds of being nonepileptic increase by 1.38 times (Tables 4 and 5).

## DISCUSSION

The rationale for investigating polyallergy, defined as the tendency to have multiple reported allergies, as a sign for nonepileptic events is 2-fold; in our anecdotal experience, reports of association are frequent, and nonepileptic events are theoretically thought to have their basis in an underlying psychiatric disorder—specifically, conversion disorder. Polyallergy may serve as a marker of psychopathology by a number of theoretical mechanisms. From a traditional psychodynamic perspective, conversion disorder is thought to be a manifestation of an unresolved conflict. Indeed, the

Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition-Text Revision lists the second diagnostic criterion of conversion disorder as “psychological factors are judged to be associated with the symptom or deficit because the initiation or exacerbation of the symptom or deficit is preceded by conflicts or other stressors” (although this criterion was dropped for Diagnostic and Statistical Manual of Mental Disorders-5). In this conceptual framework, the conversion reaction (in this case NES) is hypothesized as an unconscious defense against unresolved conflict. Medications intended to prevent or ameliorate these symptoms may be unconsciously perceived as a threat to this system of psychologic defense and thus produce a thwarting psychosomatic symptom of their own (e.g., rash, pruritus, tachypnea, and tachycardia), which is then reported as an allergy. This psychodynamic hypothesis could be further extended to other measures associated with medical treatment (e.g., adhesive tape used to secure an intravenous line) or potentially to foods associated with health (e.g., fruit). Here, the presence of an actual allergic reaction is less important than the patient’s report of a perceived adverse reaction.

Physical symptoms of conversion disorder mimic somatic illness (e.g., seizure-like episodes), but as they are not caused by somatic disturbances (e.g., no epileptiform activity), they are unlikely to respond to medications

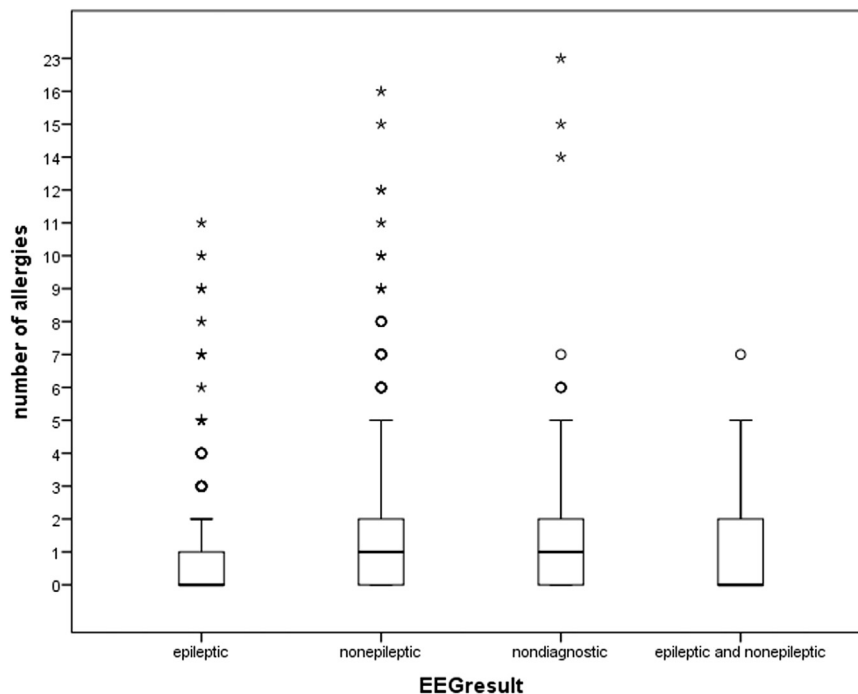
**TABLE 3. Cross-Tabulation for Sex by Group**

|        | Epileptic        | Nonepileptic     | Nondiagnostic    | Epileptic and Nonepileptic | Total       |
|--------|------------------|------------------|------------------|----------------------------|-------------|
| Female | 444 (39%) [−4.6] | 463 (41%) [6.0]  | 197 (17%) [−1.2] | 40 (4%) [−0.8]             | 1144 (100%) |
| Male   | 343 (50%) [4.6]  | 184 (27%) [−6.0] | 134 (19%) [1.2]  | 29 (4%) [0.8]              | 690 (100%)  |
| Total  | 787 (43%)        | 647 (35%)        | 331 (18%)        | 69 (4%)                    | 1834 (100%) |

Note: Bracketed numbers indicate adjusted standardized residuals.

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**FIGURE.** Box Plot of the Number of Allergies By Group. The Horizontal Line in the Middle of Each Box is the Median Value for Each Group. Circles and Asterisks are Outliers With Values That are 1.5 or 3 Times the Length of Each Box, Respectively. The Distribution of the Number of Allergies Looks Similar Across Groups. The Median Number of Allergies is Higher for the Nonepileptic and Nondiagnostic Group.



intended to treat the mimicked malady. This treatment resistance typically results in trials of multiple medications at escalating doses. In this context, it is more likely that the patient would experience adverse effects from these medication trials that may be labeled as “allergies.” Indeed, this mislabeling of medication adverse effects as allergies may itself represent a heightened somatic preoccupation with the body and perceived symptoms that are indicative of a somatoform disorder, thus increasing the likelihood of a conversion disorder.

Literature reports the teddy bear sign,<sup>2</sup> pelvic thrusting,<sup>3</sup> pain medication use,<sup>5</sup> ictal stuttering,<sup>6</sup> and eye closure during the event as markers for NES.<sup>8</sup> This study supports polyallergy as another sign for NES. This is the first study, to our knowledge, that quantifies the increase in likelihood of additional allergies or polyallergy as associated with the final EMU diagnosis of NES. Based on a logistic regression model, we argue that each additional allergy increases the likelihood of a diagnosis of NES by 38%. In contrast, each additional antiepileptic drug that was tried but deemed to be ineffective decreases the likelihood of being nonepileptic by 29%.

## CONCLUSION

Polyallergy is, to our knowledge, the first predictive sign of NES or any psychosomatic illness that can be assessed from review of the medical record alone, as previously reported signs are predicated on data obtained when the patient is admitted to a hospital or when a seizure-like episode is clinically observed. The limitations of this study include its retrospective design and the potential for confounding factors (such as autoimmune disease) to influence the number of reported allergies in the medical record. However, if

**TABLE 4.** Logistic Regression Model Predicting NES Diagnosis Based on Sex, Age, Number of AEDs, and Number of Allergies

|                     | OR   | 95% CI    | <i>p</i> | Accuracy |
|---------------------|------|-----------|----------|----------|
| Female              | 1.62 | 1.28–2.06 | <0.001   | 68.5%    |
| Age                 | 1.01 | 1.01–1.02 | <0.001   |          |
| Number of AEDs      | 0.71 | 0.67–0.76 | <0.001   |          |
| Number of allergies | 1.38 | 1.27–1.50 | <0.001   |          |

AEDs = antiepileptic drugs; OR = odds ratio.

**TABLE 5. Summary of Published Observations, Semiologies, and Laboratory Findings Associated With Increased Risk for NES**

|                            | Preictal                                                                                                                                                                                                                                                                                                                                                                   | Ictal                                                                                                                                                                                                                                                    | Postictal                                                                                                                                                                         |
|----------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Per history or observation | Polyallergy<br>Sexual abuse <sup>14</sup><br>Physical abuse <sup>15</sup><br>Trauma <sup>14</sup><br>Depression <sup>16</sup><br>Female <sup>17</sup><br>Differing metaphoric conceptualization <sup>18</sup><br>Increased body mass index <sup>19</sup><br>Depression <sup>1</sup><br>Long-term pain medication use <sup>5</sup><br>Florid review of systems <sup>3</sup> |                                                                                                                                                                                                                                                          |                                                                                                                                                                                   |
| Semiology                  |                                                                                                                                                                                                                                                                                                                                                                            | Teddy bear sign <sup>2,20</sup><br>Pelvic thrusting <sup>3</sup><br>Eye closure <sup>8</sup><br>Prolonged length of ictus <sup>21</sup><br>Change of semiology <sup>10</sup><br>Discontinuous activity <sup>22</sup><br>Voluntary nystagmus <sup>7</sup> | Stuttering <sup>6</sup><br>Whispering or partial motor responses <sup>23</sup>                                                                                                    |
| Laboratory findings        |                                                                                                                                                                                                                                                                                                                                                                            | Less activation of the autonomic nervous system <sup>25</sup>                                                                                                                                                                                            | Normal prolactin level <sup>26</sup><br>Normal serum creatine kinase level <sup>27</sup><br>Normal WBC level <sup>28</sup><br>Lack of reset in EEG “brain dynamics” <sup>24</sup> |

EEG = electroencephalogram; WBC = white blood cell.

these findings can be replicated and polyallergy can be demonstrated to be predictive of other psychosomatic illnesses (including other presentations of conversion disorder, somatic symptom disorder, and illness anxiety disorder), this may represent a novel method of prescreening large populations for these disorders. Given the remarkably high cost of health care utilization attributed to these patients and recent trends in health care funding and reimbursement in the United States (i.e., the Affordable Care Act that incentivizes physicians and hospitals to prevent unnecessary medical spending), the ability to predict these disorders based on the review of the medical records and to refer them to the correct venue of care (i.e., psychiatric evaluation) and away from costly and potentially harmful procedures and medications may prove to be quite valuable. The heightened costs of NES-related misdiagnosis stem from intubation and intensive care unit admission for misdiagnosed status epilepticus and are estimated at more than \$100,000 per patient.<sup>10</sup> In some cases, failure to promptly diagnose NES results in death due to unnecessary intubations.<sup>11</sup> Aside from outliers reported by Reuber et al.,

epidemiologically, NES is a significant neurologic condition, as the prevalence is between 2 and 33 per 100,000, which put in perspective, is on the same order of magnitude as multiple sclerosis, the most common cause of disability in young people.<sup>12</sup> Encouragingly, a study by a Scottish group reports that early awareness and diagnosis of NES results in marked reduction in health care demand on a causal basis.<sup>13</sup> Given NES's prevalence, financial costs, and adverse outcomes, further research is needed on polyallergy to assess whether it is as predictive of other manifestations of psychosomatic illness as it is of NES. Although polyallergy may have utility across a subpopulation, it is important to avoid its unwarranted use in stereotyping individual EMU patients.

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*reports that he is a member of the speaker's bureau for, is a consultant to, and a shareholder in Avanir Pharmaceuticals. Dr. Park, Mr. Bokma, and*

*Dr. Chapple disclosed no proprietary or commercial interest in any product mentioned or concept discussed in this article.*

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