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Diagnostic delay in psychogenic seizures and the association with anti-seizure medication trials

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ABSTRACT

Purpose: The average delay from first seizure to diagnosis of psychogenic non-epileptic seizures (PNES) is over 7 years. The reason for this delay is not well understood. We hypothesized that a perceived decrease in seizure frequency after starting an anti-seizure medication (ASM) may contribute to longer delays, but the frequency of such a response has not been well established.
Methods: Time from onset to diagnosis, medication history and associated seizure frequency was acquired from the medical records of 297 consecutive patients with PNES diagnosed using video-electroencephalographic monitoring. Exponential regression was used to model the effect of medication trials and response on diagnostic delay.
Results: Mean diagnostic delay was 8.4 years (min 1 day, max 52 years). The robust average diagnostic delay was 2.8 years (95% CI: 2.2–3.5 years) based on an exponential model as 10 to the mean of $\log_{10}$ delay. Each ASM trial increased the robust average delay exponentially by at least one third of a year (Wald $t = 3.6$, $p = 0.004$). Response to ASM trials did not significantly change diagnostic delay (Wald $t = -0.9$, $p = 0.38$).
Conclusion: Although a response to ASMs was observed commonly in these patients with PNES, the presence of a response was not associated with longer time until definitive diagnosis. Instead, the number of ASMs tried was associated with a longer delay until diagnosis, suggesting that ASM trials were continued despite lack of response. These data support the guideline that patients with seizures should be referred to epilepsy care centers after failure of two medication trials.

1. Introduction

Based on published reports, the average delay from first seizure to definitive diagnosis of psychogenic non-epileptic seizures (PNES) is over 7 years [1]. PNES often appear behaviorally similar to epileptic seizures, which commonly leads to a mistaken diagnosis of epileptic seizures (ES) because the prevalence of ES is much higher than that of PNES [2]. Key barriers to diagnosis include providers unfamiliar with PNES and limited access to care due to insurance or social support [3,4]. Understanding the reasons for this diagnostic delay are critical because, prior to accurate diagnosis, patients do not receive appropriate treatment while incurring direct and indirect annual costs similar to patients with medication resistant seizures, estimated at 20,995 euros [5,6]. Patients who are diagnosed earlier with PNES have an improved long-term seizure prognosis [7–9] and cost reduces substantially after diagnosis [10]. Treatment for ES can involve anti-seizure

Abbreviations: ASM, anti-seizure medication; ES, epileptic seizures; ILAE, International League Against Epilepsy; NA, not available; PNES, psychogenic non-epileptic seizures; UCLA, University of California Los Angeles; VEEG, video-electroencephalography.

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medications (ASMs), the ketogenic diet, neurostimulators and surgery, whereas standard treatment for PNES without co-morbid ES addresses underlying psychological distress with cognitive behavioral-inspired therapy and sometimes psychoactive medications, but not ASMs [11–13]. Approximately 10% of patients with PNES have comorbid ES, although this frequency varies substantially among reports [2,13,14].

A definitive diagnosis of PNES is based upon simultaneous video and electroencephalographic recordings (VEEG) [15]. Patients are referred to tertiary care centers for epilepsy where their evaluation can include VEEG when their seizures are resistant to ASM treatment, or when their history and seizure semiology is suggestive of non-epileptic seizures (NES) [16]. At our center, 50% of patients admitted for differential diagnosis of seizure-like episodes have PNES without co-morbid epilepsy, whereas 6% of patients admitted for epilepsy surgery evaluation have PNES alone [14]. Once referral has occurred, the time to diagnosis is short. Prior to referral, more than half of patients with PNES have been tried on at least one ASM [2,17]. The reported efficacy and duration of efficacy of ASM in patients with PNES has not been well established [18].

We hypothesize that positive responses to trials of ASMs contribute to the long delay in definitive diagnosis. In addressing this theory, we characterized the pre-referral treatment course of a large population of patients with PNES, which also contributes to the understanding of the natural history of PNES from onset to diagnosis. To our knowledge, this has not been discussed in the literature since 1990 [19].

2. Methods

We reviewed the medical records of all 1126 patients admitted to the UCLA adult epilepsy VEEG monitoring unit from January 2006 until April 2014, and identified 297 patients with PNES who were diagnosed as not also having epileptic seizures or physiologic non-epileptic seizure-like events. Patients with PNES who had one or more other seizures manifestations that were not recorded during VEEG were excluded because the unrecorded seizure(s) could be epileptic or physiologic. We performed retrospective chart review for all 297 identified patients with only PNES to determine age at diagnosis, age of seizure onset, and initial response in seizure frequency to each ASM. Delay to diagnosis was calculated as the difference between age at diagnosis and age of seizure onset. For delays less than 3 months, delay was recorded to the nearest day. For delays less than 1 year, the delay was recorded to the nearest month. An ASM treatment response was defined as 50% or more reduction in seizure frequency reported for the length of time needed to determine a frequency decrease, which was defined as a seizure-free period at least three times longer than their pre-treatment inter-seizure period. The three times longer interval was based on the International League Against Epilepsy (ILAE) definition of the period to observe to determine treatment response [16]. The 50% or more criterion was chosen because it is used as a clinically relevant outcome measure used in randomized clinical trials of ASMs for epilepsy; however, the measure did not replicate the clinical trials' use of blinded, prospective assessment over the same time period for all participants [20]. We use precise language to differentiate response to an ASM from success of an ASM trial: success and failure is based upon seizure freedom, not reduction in seizure frequency. To compare the response rate of medications for PNES, we used Fisher-exact statistics.

Delay to diagnosis was modeled using exponential regression. When describing delay alone, we report raw averaged and robust average. The robust average reduces the contribution of outliers with very long delays by averaging the log of delay. For regressions, the log of delay to diagnosis was modeled against linear effects of number of ASM trials and number of successful ASM trials controlling for sex. Exponential regression was used because delay to diagnosis was distributed exponentially over the population and is understood theoretically as a waiting time.

All patients consented for the use of their records in research, and the UCLA Institutional Review Board approved this study. This work is consistent with Declaration of Helsinki. De-identified raw data and code for this study is available at http://www.brainmapping.org/MarkCohen/research.html.

3. Results

Population demographics for the 297 patients with PNES are summarized in Table 1. Diagnostic delay was recorded in 268 patients (90%), with a raw mean of 8.4 years (95% CI 7.0–9.8 years). Of the 297 patients, 258 (87%) patients had 894 cumulative trials of ASMs prior to the diagnosis of PNES. The remaining 39 (13%) patients had not been treated with an ASM prior to assessment. The average delay to diagnosis for patients who took two or fewer ASMs was 5.9 years (95% CI 4.3–7.6 years). The robust average delay from first presentation at our center to diagnosis was 43 days (95% CI 33–55 days).

Of 354 medication trials with a detailed post-treatment seizure frequency, 10% (35/354) of ASM trials were associated with a period of seizure freedom whereas 30% (109/354) were associated with a reduction in seizure frequency by the criterion described above. No medication was significantly more or less likely to result in a response (Fisher exact tests, minimum pairwise $p > 0.09$). A clinically relevant response to at least one ASM was reported in 17% (44/258) of patients who tried at least one ASM. The response rate for more than one ASM is as follows: 7.7% (20/258) to at least two, 2.4% (7/258) to at least three, 1% (3/258) to at least four, 0.8% (2/258) to at least five, and 0.4% (1/258) to six. The frequency with which patients responded to each ASM is illustrated in Supplemental Fig. 1. Patients who reported a response to at least one ASM had significantly fewer ASM trials prior to referral than patients who did not respond to any ASM (2.9 vs 4.0 trials, respectively; t-test unequal variances, $p = 0.005$).

In total, 53 years of ASM trials were reported, with a median of 1 year per cumulative treatment. Of the 109 successful trials, 30 patients also reported the duration of response for 50 trials (46%). Fig. 1 illustrates the survival curve of medication response. The robust average duration of response was 2.0 years (median 14 months), if the patient responded initially (95% confidence interval:

Table 1
Ages and delays are in years unless otherwise specified. Robust average diagnostic delay was calculated as exp(mean[log(delay)]) Abbreviations: ASM, anti-seizure medication; CI, confidence interval; LB, lower bound; UB, upper bound.

	Percent female	Onset age	Assessment age	Diagnostic delay	ASM trials	ASM responses
Min		1 day	12	1 day	0	0
95 CI LB	68	29	37	2.2	2.78	0.17
Robust average	73	31	39	2.8	3.04	0.26
95 CI UB	78	33	41	3.4	3.30	0.35
Max		85	88	52	12	6