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Psychosocial Factors and Antiepileptic Drug Use Related to Delayed Diagnosis of Refractory Psychogenic Nonepileptic Seizures

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Running head: Diagnostic Delay for Psychogenic Nonepileptic Seizures

Abstract

Objective: We analyzed clinical and psychosocial factors in patients with refractory psychogenic nonepileptic seizures, seeking characteristics that could hasten diagnosis.

Background: Psychogenic nonepileptic seizures remain a diagnostic challenge. Prognosis is best if patients are treated within 2 years of symptom onset. Psychosocial factors have been shown to provide important information for differential diagnosis.

Methods: Over a year and 1132 consecutive patients, our hospital's Epilepsy Unit suspected 93 patients of having psychogenic nonepileptic seizures and confirmed refractory psychogenic nonepileptic seizures in 67. We referred these patients to our psychiatric consultation unit for detailed diagnostic interviews, and 53 of them followed through. Two months after the psychiatric evaluation we gave them a psychiatric intervention, explaining the diagnosis and treating their comorbidities. We also tracked the patients' use of antiepileptic drugs for 3 months, from just before the psychiatric evaluation until a month after they started the intervention.

Results: Women, patients with an inadequate primary support group, and patients who had tried many antiepileptic drugs were most likely to have their diagnosis of psychogenic nonepileptic seizures delayed by >2 years after onset. A stepwise logistic regression showed that the 2 best predictors of late diagnosis were lack of availability of a primary support group and patients trying many antiepileptic drugs.

Conclusions: Clinicians evaluating patients with questionable seizures should raise their suspicion of psychogenic nonepileptic seizures especially in female patients with an insufficient primary support group and a history of taking multiple antiepileptic drugs.

Key Words: *psychogenic nonepileptic seizure, epilepsy, early diagnosis, antiepileptic drug, psychosocial factors*

Psychogenic nonepileptic seizures (PNES) are transient paroxysmal events that affect aspects of behavior, perception, sensation, or consciousness in ways that mimic epileptic seizures. The overlap in symptoms makes continuous video-electroencephalography (EEG) recording the gold standard test to distinguish PNES from true epileptic seizures. However, video-EEG is not always available. This poses a major challenge to diagnosing PNES (O'Sullivan et al, 2006; Parra et al, 1999).

PNES is a psychiatric diagnosis that is usually made after ruling out organic diseases. Although there has been some research into patterns of emotional dysregulation among patients with PNES (Uliaszek et al, 2012), the lack of a defined psychiatric characterization of the disorder contributes to an estimated diagnostic delay of about 8 years (Bodde et al, 2009a). Early diagnosis of PNES helps patients avoid unnecessary antiepileptic drug treatment and is a major determinant of better long-term prognosis (Buchanan and Snars, 1993; Lempert and Schmidt, 1990).

According to a critical review by Bodde et al (2009b), the psychiatrist evaluating patients with refractory PNES needs to recognize the disorder's psychosocial as well as clinical aspects. It is important to identify psychiatric disorders and psychological stressors that might be treated (Tojek et al, 2000). In particular, the psychiatrist should determine whether patients have an unstructured family, social, or job environment, because this can play a role in the pathogenesis of PNES and is a potential target for psychotherapeutic intervention (Bodde et al, 2012).

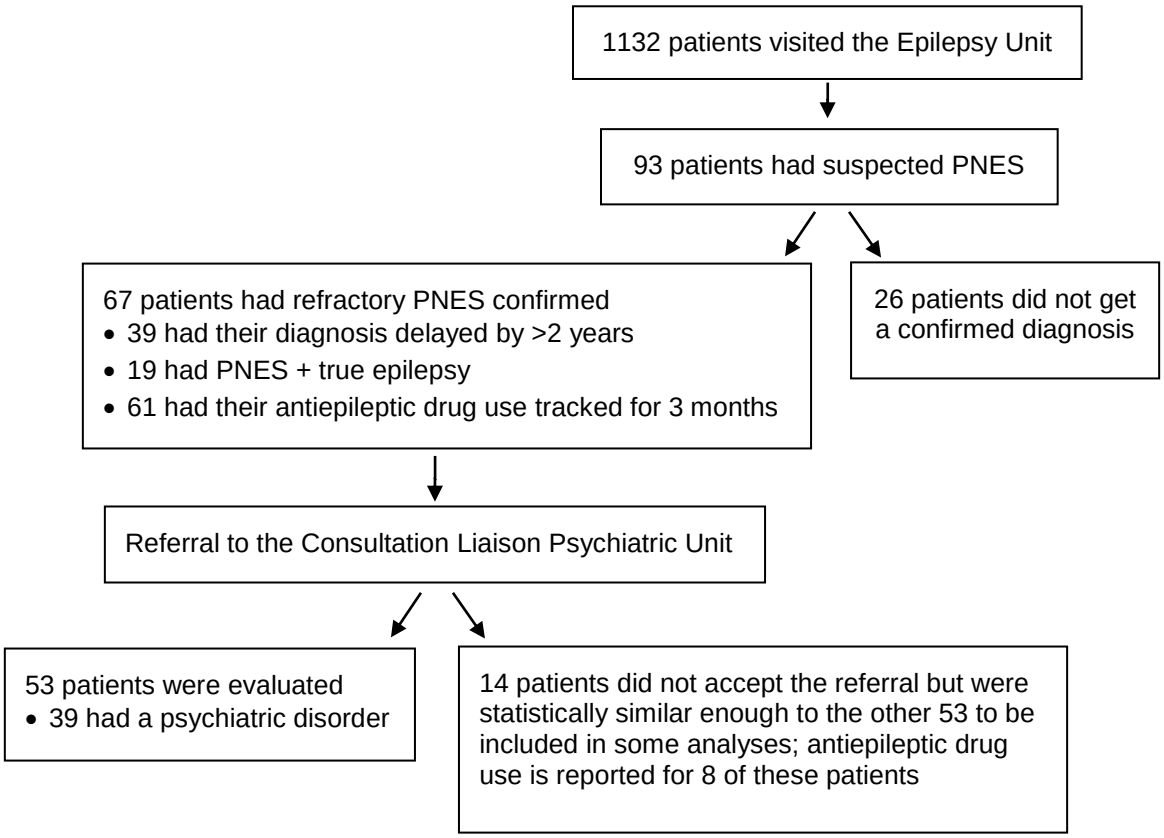
This study examined the role of clinical and psychosocial aspects of PNES in delaying the diagnosis for patients who were eventually found to have refractory PNES.

METHODS

This was a cross-sectional study of patients with refractory PNES, with additional follow-up of the patients' antiepileptic drug use. The patients had been referred to us at the Consultation Liaison Psychiatry Unit of the Hospital Universitari Vall d'Hebron, a tertiary referral center in Barcelona, Spain.

Of 1132 consecutive patients seen at the Epilepsy Unit over the course of the year 2012, PNES was suspected in 93 (Figure 1). Three of our experienced epileptologists (authors M.T., X.S.P, and E.S.) gave the patients a full diagnostic work-up that included clinical evaluation, neuroimaging, conventional EEG, video-EEG, and long-term follow-up visits. The 3 epileptologists concurred in diagnosing refractory PNES in 67 (73%) of the 93 patients. For the purposes of the study, we defined refractory PNES as PNES that had a major impact in a patient's quality of life. We studied only those patients whose PNES was refractory.

FIGURE 1. Sequence of patient evaluations for psychogenic nonepileptic seizures (PNES) and referrals for psychiatric evaluation and intervention.



The epileptologists determined that of the 26 remaining patients, some had nonrefractory PNES and others had conditions that made it impossible to diagnose PNES, eg, severe mental retardation, acute or severe medical conditions, or inability to complete the medical interview.

As recommended by the guidelines of the International League Against Epilepsy (Kerr et al, 2011), the 3 epileptologists explained the PNES diagnosis to each of the 67 patients in a clear, positive, nonpejorative manner, and then discussed the need for the patients to cut back on or stop the antiepileptic drugs that they had been taking. The epileptologists offered each patient an evaluation at our Consultation Liaison Psychiatry Unit; 53 (79%) of the patients followed through.

One consultant psychiatrist (author A.R.U) evaluated each of the 53 patients. Before starting the evaluation, she recorded the number of antiepileptic drugs that the patient was taking; she did not record drug doses. Then she gave the patient a standard diagnostic evaluation comprising a semi-structured interview established by hospital consultation-liaison protocol, and the Structured Clinical Interview (First et al, 2002) for the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, Axis I disorders, text revision (American Psychiatric Association, 2000). Depending on the patient's psychiatric history, these interviews took 1 to 3 sessions, all held during the same week and lasting for a total of 2 to 6 hours.

With these clinical interviews, the psychiatrist obtained background about psychosocial factors such as the patients' work, financial and social status, and availability of and problems with their primary support group, as defined by the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, text revision Axis IV criteria (American Psychiatric Association, 2000). Using the psychiatrist's notes, we

recorded separately the "availability of" and "problems with" each patient's primary support group.

After completing the psychiatric evaluations, the psychiatrist agreed with the 3 epileptologists that all 53 patients had refractory PNES.

We then gave each patient a personalized psychiatric intervention. For most of the patients, we started the intervention 2 months after the psychiatric evaluation. First, we explained to patients the cause of their symptoms. Then we treated any psychiatric comorbidities, with medication if necessary. We continued reducing the patients' antiepileptic drugs, following the epileptologists' recommendations noted in the medical record. As needed, we changed the patients to different antiepileptic drugs that were more suitable given their psychiatric disorder. Also as needed, we referred patients to our consultation liaison clinical psychologist (author S.G.F.). We continued the intervention for as long as each patient needed it. Some patients remained in long-term psychiatric treatment.

As mentioned, before beginning the psychiatric evaluation the psychiatrist had recorded the number of antiepileptic drugs that the patients were taking. As a follow-up, 1 month into the psychiatric intervention she again recorded the number of antiepileptic drugs that the patients were taking. Thus, we had drug records covering a 3-month span, starting 2 months before the intervention and continuing 1 month into it. We will here call these 3 months the drug "tracking period."

As noted, 14 (21%) of our original 67 patients with confirmed refractory PNES did not accept our offer to be evaluated at the Consultation Liaison Psychiatric Unit. However, 8 of these patients continued to attend their scheduled outpatient visits at the Epilepsy Unit. There they received an explanation of the cause of their symptoms and their antiepileptic drug use was tracked. We found no statistical differences between

these 14 patients and the other 53 patients in age, sex, or types of psychogenic seizures. We included the 8 patients in our demographic analyses reported in Table 1, our antiepileptic drug use calculations, and our predictive model of diagnostic delay.

The study project was approved by the local Research Ethics Committee (PR AG 232-2011). All participants gave written informed consent before taking part.

Statistical Analyses

We divided our 67 patients into 2 groups: those who had had their PNES symptoms for ≤ 2 years before we confirmed their diagnosis, and those who had had their symptoms for > 2 years. We chose a 2-year cut-off point because the existing literature had established that intervention within 2 years is most likely to improve prognosis (Bodde et al, 2012; Buchanan and Snars, 1993).

As an independent variable, we chose a mixed diagnosis of PNES plus true epilepsy. Patients who have both disorders should be considered as clinically different from those who have PNES alone, especially regarding antiepileptic drug treatment.

We used odds ratios (for dichotomous categorical variables), chi-squared tests (for categorical variables with ≥ 3 levels), and *t* tests (for continuous variables) for comparisons between groups and repeated measures of the number of drugs prescribed. We used nonparametric techniques (Mann-Whitney, Kruskal-Wallis, and Wilcoxon tests) for comparisons when the sample size was insufficient or variables were not normally distributed. Finally, we performed a stepwise logistic regression using variables that we had found to be statistically different ($P < 0.05$) between the patient groups with earlier and later diagnosis.

For all analyses, we used SPSS 18.0 for Windows (SPSS Inc, Chicago, Illinois). All statistical hypotheses were 2-tailed, and we used a 95% confidence interval for all calculations.

RESULTS

For our 67 patients with confirmed refractory PNES, the mean delay from onset of symptoms to confirmation of the diagnosis was 7 ± 8 years (range: 0 to 33 years). Only 28 (42%) of the patients received an early diagnosis, within 2 years of PNES onset. The other 39 (58%) were diagnosed after 2 years. For our subgroup of 53 patients who had agreed to psychiatric evaluation, the percentages were the same: 22 received a diagnosis within 2 years and 31 received a diagnosis after 2 years.

Sociodemographics

Table 1 lists the sociodemographic findings for our 67 patients. More women than men were diagnosed ≥ 2 years after onset (odds ratio = 0.346, 95% confidence interval = 0.121-0.991, $P > 0.05$). Patients with a primary support group were more likely to be diagnosed within 2 years (odds ratio = 8.280, 95% confidence interval = 0.972-70.529, Fisher's $P > 0.05$). More than 60% of the patients had disrupted family dynamics and environmental psychosocial stressors, but these factors did not contribute significantly to diagnostic delay.

TABLE 1. Sociodemographic Characteristics of 67 Patients* with Refractory Psychogenic Nonepileptic Seizures (PNES)

	Time of PNES Diagnosis					
	Early (≤2 years) (n = 28)		Late (>2 years) (n = 39)		Significance	
	M	SD	M	SD	*t*	*P*
Age	37.75	16.48	39.95	11.43	-0.609	0.546
	Patients Number	%	Patients Number	%	Odds Ratio	95% Confidence Interval
Setting						
Outpatient	25	41	36	59		
Inpatient	3	50	3	50	0.694	0.129-3.725
Ethnicity						
White	25	44.6	31	55.4		
Other	3	27.3	8	72.7	2.151	0.516-8.966
Sex						
Women	15	33.3	30	66.7		
Men	13	59.1	9	40.9	0.346	0.121-0.991
Education						
Primary or secondary	19	39.6	29	60.4		
Higher	5	62.5	3	37.5	2.544	0.543-11.912
Work status						
Employed, student, or homemaker	13	50	13	50		
Inactive	12	38.7	19	61.3	1.583	0.551-4.548
Marital status						
Married or with a partner	15	38.5	24	61.5		
Single or divorced	11	45.8	13	54.2	0.739	0.264-2.069
Children						
Yes	10	31.2	22	68.8		
No	18	51.4	17	48.6	0.429	0.158-1.166
Availability of a primary support group						
Yes	26	49.1	27	50.9		
No	1	10	9	90	8.667	1.025-73.296
Problems with primary support group						
Yes	21	39.6	32	60.4		
No	7	58.3	5	41.7	2.133	0.597-7.618
Other psychosocial or environmental problems						
Yes	16	42.1	22	57.9		
No	8	47.1	9	52.9	0.818	0. 259-2.583

*Psychosocial data are incomplete for some of the 14 patients who did not accept psychiatric referral. For these 14 patients: Education n = 3. Work status n = 4. Marital status n = 10. Children n = 14. Availability of a primary support group n = 10. Problems with primary support group n = 12. Other psychosocial or environmental problems n = 2.

M = mean. SD = standard deviation.

Types of PNES Events

In our 67 patients, we did not find significant differences between the types of psychogenic seizures experienced by the groups with early and late PNES diagnoses (Table 2). Most common in both groups were major motor seizures (affecting 62% of

the 67 patients), followed by minor motor (37%) and nonmotor (30%) seizures; 31% of the patients had 2 or more types.

TABLE 2. Seizure Types and Psychiatric Diagnoses in Patients with Refractory Psychogenic Nonepileptic Seizures (PNES)

	Time of PNES Diagnosis					
	Early (≤ 2 years)		Late (> 2 years)		Significance	
	Number of Patients	% of 28	Number of Patients	% of 39	Odds Ratio	95% Confidence Interval
Type(s) of psychogenic seizures (n = 67)					0.8	0.325-
Major motor					89	2.433
Minor motor					0.8	0.515-
Nonmotor	18	64.3	24	61.5	65	2.356
	11	39.3	14	35.9	2.0	0.649-
	6	21.4	14	35.9	53	6.261
Mixed diagnosis: PNES + epilepsy (n = 67)						
Yes	7	25	12	30.8	0.7	0.251-
No	21	75	27	69.2	50	2.237
		% of 22		**% of 31**		
Psychiatric diagnosis (n = 53)						
Yes	17	77.3	22	71	1.5	0.437-
No	5	22.7	9	29	43	5.448

Of our 67 patients, 19 (28%) had a mixed diagnosis of PNES and true epilepsy (Table 2). We found no significant differences in the prevalence of combined PNES and epilepsy between the groups with early and late PNES diagnoses. Neither did we find a significant difference between the pure PNES group and the mixed diagnosis group in any sociodemographic variable or in the types of seizures experienced.

Psychiatric History

Of the 53 patients who underwent psychiatric evaluations, 39 (74%) had a history of a psychiatric disorder (Table 2). We did not find significant differences between the early and late diagnosis groups for psychiatric conditions. The most frequent diagnoses were depression in 17 (32.1%) of the 53 evaluated patients, anxiety in 15 (28.3%), other conversion disorders in 14 (26.4%), adjustment disorder in 11 (20.8%), and personality disorder in 8 (15.1%). A definitive psychiatric diagnosis was difficult to obtain in some of the patients because of their long histories of diffuse symptoms and of seeking care from multiple specialists.

Three patients, 2 of whom had pure PNES and 1 who had a mixed diagnosis, were at high risk for suicidal thoughts. All 3 patients had been taking several antiepileptic drugs. However, we could not prove an association between the patients' suicidal thoughts and any specific antiepileptic drug and/or the reduction in the number of drugs that the patients took during the tracking period.

Antiepileptic Drug Treatment

For our 53 patients, we compared antiepileptic drug use between the groups with early and late PNES diagnosis. Not surprisingly, the patients with an early diagnosis had tried fewer antiepileptic drugs (mean of 1.59 ± 1.30) than those with a late diagnosis (mean of 2.55 ± 1.82); $t = -2.111$, $P < 0.05$.

We calculated the reduction in number of antiepileptic drugs that the patients took during the 3-month tracking period, from just before the psychiatric evaluation to 1 month into the intervention. The reduction was greater in the late diagnosis group (average reduction: -1.32 ± 1.60) than the early diagnosis group (-0.68 ± 0.99), but did not reach statistical significance ($t = -1.794$, $P = 0.079$). At the end of the month, the

groups had a nonsignificant difference in the mean number of antiepileptic drugs that they were taking: 0.91 ± 0.87 in the early diagnosis group versus 1.23 ± 1.38 in the late diagnosis group; t = -1.022, P = 0.312.

Of the 14 patients who had refused referral for psychiatric evaluation, we were able to track drug use in 8 because they continued to visit the Epilepsy Unit. When we added these 8 patients' drug numbers to our calculations and analyzed the resulting group of 61 patients, we found significant differences for drugs taken at the start of the tracking period (1.46 ± 1.27 for the early diagnosis group versus 2.72 ± 1.93 for the late diagnosis group; t = -2.896, $P < 0.005$) and for reduction of use during the 3 months (0.62 ± 0.98 for the early diagnosis group versus 1.46 ± 1.79 for the late diagnosis group; t = -2.167, $P < 0.05$). We found a nonsignificant difference for drugs taken at the end of the 3 months (0.88 ± 0.86 for the early diagnosis group versus 1.26 ± 1.34 for the late diagnosis group; t = -1.241, P = 0.220).

Among the 53 patients who had accepted psychiatric evaluation, those with a mixed diagnosis started the tracking period taking 3 ± 1.80 antiepileptic drugs versus 1.85 ± 1.59 in the group with PNES alone; t = 2.293, $P < 0.05$. Over the 3 months, both groups had essentially identical mean reductions: -1.07 ± 1.33 drugs in the patients with a mixed diagnosis versus -1.05 ± 1.45 in the patients with PNES alone; t = 0.046, P = 0.964. However, a month into the intervention, the groups were taking a significantly different number of drugs: a mean of 1.93 ± 1.21 in the mixed diagnosis group versus 0.79 ± 1.06 in the group with PNES alone; t = 3.319, $P < 0.005$. The results were virtually identical when we added the 8 patients whose drug use was tracked despite their refusing psychiatric evaluation.

In the 53 patients who had accepted psychiatric evaluation, we compared the most-used antiepileptic drugs in the 14 patients who had a mixed diagnosis against the

most-used drugs in the 39 patients who had pure PNES. At the start of the tracking period, of the 14 patients with mixed diagnoses, 8 (57.1%) were taking levetiracetam, 7 (50%) valproate, and 4 (28.6%) carbamazepine. At the end of the 3 months of tracking, 6 patients (42.9%) were taking levetiracetam, 4 (28.6%) valproate, and 4 (28.6%) clonazepam. In contrast, at the start of tracking, of the 39 patients with pure PNES, 17 (43.6%) were taking levetiracetam, 13 (33.3%) valproate, and 7 (17.9%) clonazepam. Three months later, 6 of the patients (15.4%) were taking levetiracetam, 6 (15.4%) clonazepam, and 4 (10.3%) valproate.

Predictors of Diagnostic Delay

Among the 61 patients whose antiepileptic drug use we could track, the variables that differed statistically between the groups with early and late diagnosis were female sex, primary support group availability, and past antiepileptic drugs. We used these variables to construct a stepwise logistic regression model. The regression results showed that the main predictors of diagnostic delay were lack of an available primary support group (odds ratio = 12.445, 95% confidence interval = 1.304-118.731) and a higher number of past antiepileptic drugs taken (odds ratio = 1.889, 95% confidence interval = 1.203-2.999). Despite these broad confidence intervals, the model had an acceptable goodness of fit, with 88.6% sensitivity and 52% specificity, 73.3% correct classification overall, and a Nagelkerke R-squared of 0.319 (31.9% of variance explained).

DISCUSSION

It is relatively common for patients to present to clinicians with complaints that turn out to be PNES. The patients in our study had seizures for an average of 7 years

before they received an accurate diagnosis. Many of our patients had disrupted family dynamics, despite a primary support group. The typical patient who was diagnosed > 2 years after the onset of symptoms was a woman who lacked a primary support group and who had tried several antiepileptic drugs.

Our results point out that psychosocial factors should be considered in confirming a PNES diagnosis. Our sample's main demographic and social characteristics were in line with the literature: middle age, mostly women, most patients with only a primary education, and most with chronic social stressors (Abubakr et al, 2003; Baillès et al, 2004; Bodde et al, 2009b; Galimberti et al, 2003; Reuber, 2008; Reuber and Elger, 2003). Family dysfunction during a patient's childhood has been reported as a causal factor in PNES, and many studies have shown it to be both a possible etiology and a therapeutic target (Krawetz et al, 2001; Moore et al, 1994; Salmon et al, 2003). As noted, many of the patients in our sample had disrupted family dynamics and environmental and psychosocial stressors, despite a primary support group. In 2011, LaFrance et al reported that family dynamics could help predict these patients' quality of life.

The prevalence of PNES in epilepsy units has been estimated at 15% to 30% of patients (Bodde et al, 2009a). Most published series describe similar rates among patients with drug-resistant epilepsy. However, the rate of confirmed PNES in our study was only 6% (67 of 1132 consecutive patients).

This low prevalence has several possible explanations. One is that our patients came from an epilepsy unit that treats patients with a wide variety of seizure disorders, not just antiepileptic drug-refractory disease. Furthermore, we included in our study only patients whose PNES was making a major impact on their quality of life. Our ability to confirm PNES was also limited by the difficulty of the diagnosis: We were

never able to confirm suspected PNES in 26 (28%) of the 93 patients in whom we suspected it, even with highly experienced diagnosticians, long-term follow-up, and availability of prolonged video-EEG monitoring (Bodde et al, 2009a, 2009b).

Despite physicians' best efforts to explain PNES in a non-threatening way, some patients reject the diagnosis. This issue has prompted psychiatrists and epileptologists to create guidelines for the best ways to communicate the diagnosis (Hall-Patch et al, 2010). In our study, we used these guidelines to explain the diagnosis to our 67 patients with confirmed PNES. Even then, when we referred them to the Consultation Liaison Psychiatry Unit, 14 (21%) did not keep their appointment, although 8 of them continued to visit the Epilepsy Unit. The potential stigma of a psychiatric diagnosis and the belief that their recovery depended more on somatic than psychological factors may have scared the patients away (Stone et al, 2004).

A high proportion of patients with PNES have comorbid psychiatric disorders (Reuber, 2008). In our sample, 74% of the patients who underwent psychiatric evaluation were found to have psychiatric disorders, mainly depression and anxiety. However, many of our patients had a long history of poorly defined psychological or psychiatric issues and treatments by other physicians, thus hindering standard psychiatric diagnosis (Bodde et al, 2012). Correctly identifying psychiatric comorbidities could play an important role in treating patients with PNES. As mentioned above, so could detection of disrupted psychosocial factors (Kanner et al, 2012).

Early diagnosis is essential to improve the prognosis of patients with PNES (Bodde et al, 2009b, 2012; Buchanan and Snars, 1993). In our study, the patients who received a late diagnosis were mostly women, lacked primary support, and had a history of inappropriate antiepileptic drug use. We cannot say with certainty why more women

received a late diagnosis. All these findings may indicate that diagnosing and treating patients with PNES requires a biopsychosocial model of illness, focusing on family dynamics (McHugh and Slavney, 1998).

The main reason that patients with PNES are given unnecessary antiepileptic drugs is that they are believed to have drug-resistant epilepsy (Müller et al, 2002). Among our patients with and without true epilepsy, the highest percentage took the potentially hazardous drug levetiracetam (Hurtado et al, 2006). Patients can be spared the side effects of antiepileptic drugs through the combined efforts of the epileptologist and psychiatrist (Müller et al, 2002). In our study, a month after they began the psychiatric intervention, patients were taking significantly fewer antiepileptic drugs than 3 months earlier. Still, most of the patients had to continue antiepileptic drugs for a time after the start of the intervention because tapering in patients with PNES usually requires slow titration.

We tried to stop—or at least reduce the number of—antiepileptic drugs that our patients were taking, to minimize the potential for further psychological and systemic effects. For patients with combined PNES and epilepsy, we tried to continue just 1 drug, to prevent the epileptic seizures. For patients with pure PNES, we tried to stop all drugs. When making these attempts, we explained to the patients that antiepileptic drugs cannot help treat PNES and can actually be dangerous.

However, many of our patients, especially those with longstanding disease, could not tolerate stopping their drugs. When the doses were lowered or tapered off, patients started complaining of feeling uncomfortable or having neuropsychiatric symptoms like irritability and emotional lability. Many patients started taking the drugs again on their own. If taking medication made patients feel better, we did not insist that

they abandon their drugs immediately, even such a risky drug as levetirazetam. Instead, we monitored their continuing drug use and encouraged them to stop eventually.

Our study had several limitations. Conducted in a tertiary care setting, the study included only a small number of patients with confirmed PNES that had a major impact on their quality of life. Further, there was no control group. Finally, because of a lack of time and resources, we could not give a structured interview for personality disorders. Although the lack of information on personality disorders limits the reliability of our findings on comorbid psychiatric disorders in the sample, this lack also reflects real daily practice, where we hope our results can be applied. Overall, however, these limitations may hamper the generalizability of our results to other clinical settings.

In conclusion, it can take many years for patients with PNES to receive an accurate diagnosis. Most patients with a long diagnostic delay are women, suffer from a lack of a primary support group, and have tried several antiepileptic drugs. Most predictive of late diagnosis are a lack of a primary support group and more antiepileptic drugs. However, with adequate intervention, some patients can reduce their use of antiepileptic drugs. Addressing disrupted family dynamics in these patients may be an important factor in treatment.

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