Original article

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Fibromyalgia and seizures

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ABSTRACT - The purpose of this case-matched study was to determine how frequently fibromyalgia is associated with different paroxysmal neurological disorders and explore the utility of fibromyalgia as a predictor for the diagnosis of psychogenic non-epileptic seizures. The billing diagnosis codes of 1,730 new, non-selected patient encounters were reviewed over a three-year period for an epileptologist in a neurology clinic to identify all patients with historical diagnoses of fibromyalgia. The frequency with which epileptic seizures, psychogenic non-epileptic seizures, and physiological non-epileptic events were comorbid with fibromyalgia was assessed. Age and gender case-matched controls were used for a between-group comparison. Wilcoxon tests were used to analyse interval data, and Chi-square was used to analyse categorical data (p < 0.05). Fibromyalgia was retrospectively identified in 95/1,730 (5.5%) patients in this cohort. Females represented 95% of the fibromyalgia sample (age: 53 years; 95% CI: 57, 51). Forty-three percent of those with fibromyalgia had a non-paroxysmal, neurological primary clinical diagnosis, most commonly chronic pain. Paroxysmal events were present in 57% of fibromyalgia patients and 54% of case-matched controls. Among patients with fibromyalgia and paroxysmal disorders, 11% had epileptic seizures, 74% had psychogenic non-epileptic seizures, and 15% had physiological non-epileptic events, compared to case-matched controls with 37% epileptic seizures, 51% psychogenic non-epileptic events, and 12% physiological non-epileptic events (p = 0.009). Fibromyalgia was shown to be a predictor for the diagnosis of psychogenic non-epileptic seizures in patients with undifferentiated paroxysmal spells. However, our results suggest that the specificity and sensitivity of fibromyalgia as a marker for psychogenic non-epileptic seizures in a mixed general neurological population of patients is less than previously described.

Key words: seizure, fibromyalgia, neurology, spells, psychogenic, non-epileptic

Markers for the accurate diagnosis of paroxysmal "spells" are crucial. Incorrectly attributing a psychological diagnosis to patients with physiological events, or vice versa, can result in injury to the patient and inappropriate utilisation of healthcare resources (Vossler, 1995; Ficker *et al.*, 1998; Tatum and Spector, 2011). Fibromyalgia (FM) is characterised by chronic diffuse musculoskeletal pain that has been linked to a variety of psychiatric-based conditions (Clauw, 2014). FM has been associated with numerous neurological symptoms including fatigue, subjective memory problems, sleep disturbances, headache, and chronic pain as well as seizures (Centonze *et al.*, 2004; Schur *et al.*, 2007; Watson *et al.*, 2009; Ottman *et al.*, 2011; Queiroz, 2013). The mechanism for FM has

Correspondence: William O. Tatum Department of Neurology, Mayo Clinic, 4500 San Pablo Road, Jacksonville, Florida 32224, USA <tatum.william@mayo.edu> been postulated to involve deregulation of central sensory processing and sensitization (Schmahmann and Leifer, 1992; van der Kruijs *et al.*, 2012).

Psychogenic non-epileptic seizures (PNES) have previously been implicated as the prevailing type of paroxysmal events in patients with chronic pain and undifferentiated spells in tertiary care epilepsy surgery centres (Bowman and Markand, 1996; Benbadis, 2005a; Benbadis, 2009; Benbadis et al., 2009; Watson et al., 2009; Devinsky et al., 2011). PNES is theorized to reflect a dysfunctional response to a psychological trigger that initiates and perpetuates the symptoms associated with chronic pain (Bowman and Markand, 1996; Benbadis, 2005b), suggesting a potential link between the two conditions. The association of chronic pain and PNES has been evaluated using fMRI to show altered sensory processing and network activation of the parietal lobe and insular cortex (van der Kruijs et al., 2012). In a study of 28 FM patients who underwent video-EEG monitoring (VEM), FM was found to have a predictive value of 75% and specificity of 99% for the diagnosis of PNES (Benbadis, 2005a). However, because the diagnosis of FM was obtained through self-reporting, some of the diagnoses may have been inaccurate. In addition, these studies used small patient cohorts in tertiary care epilepsy surgery referral centres, limiting the generalizability of the findings. Therefore, we sought to replicate the findings from a prior study (Benbadis, 2005a) and investigate the relative frequency of FM comorbid with paroxysmal and non-paroxysmal neurological events using a case-matched control group at a developing epilepsy clinic mixed with general neurological patients.

Materials and methods

The primary goal of our study was to confirm the validity of the prior association of FM with PNES using a case-controlled study design in a large cohort of patients. A secondary aim was to assess the frequency of comorbidity between FM and different types of paroxysmal events. To address this goal, a comprehensive, consecutive analysis involving a retrospective chart review of all patients seen by a single epileptologist within a mixed epilepsy-general neurology clinic in Northeast Florida between 06/17/2009 and 06/15/2012 was conducted. The study was approved by the Mayo Clinic Institutional Review Board and performed in accordance with the ethical standards established by the institution. We defined a paroxysmal event as an abrupt, involuntary, episodic, behavioural episode with a clear onset and offset. Neurological symptoms presenting as a "seizure", "spell", "event", or "episode" were classified as epileptic seizures (ES), PNES, and physiological non-epileptic events

(PhysNEE). An example of primary non-neurological diagnosis included conditions such as diabetes mellitus (medical) or bipolar disorder (psychiatric). The primary clinical diagnosis was identified from the representative ICD-9 CM billing codes submitted by a single epileptologist (WOT) during the study period and verified by manual chart review. Inclusion criteria included adults >18 years of age, completed electronic health records, a primary diagnosis, and outpatient evaluation at Mayo Clinic Department of Neurology. The primary diagnosis reflected the main reason for consultation. Classification was based upon the clinical presentation, and supplemented with outpatient home videos and ancillary data for accuracy. Patients were excluded from the study if they were under the age of 18, if they were encountered outside of the clinic, if their medical records were incomplete, or if a clear diagnosis was not evident.

The medical records of all patients with a diagnosis of FM were reviewed and included in the analysis if the inclusion criteria were met. A case-control group was composed of a 1:1 cohort of patients seen in the clinic within 10 days of each case patient, with the same gender and age (within five years). Patients were randomly selected from a group of potential case-matches using random numbers generated by Microsoft Excel® (Microsoft Corporation, Redmond, WA). If a control was unavailable, a patient was selected based upon being closest in age and having been evaluated within 10 days of the FM case patient. Those in our study cohort who were not assigned as casematched controls were identified as an "unmatched" cohort. Age, gender, race, reason for referral, number of daily medications, highest level of education, marital status, employment status, number of co-morbidities in the past medical history, and the number and results of previous EEGs were recorded for analysis. VEM and rheumatology consultations were used as a confirmatory means of the clinical diagnoses and recorded when applicable.

Statistical analysis was performed using JMP version 9.0 software (SAS Institute Inc., Cary, NC). Wilcoxon tests were used to analyse the interval data. Chi-square tests were used to analyse categorical data (p = <0.05). Both between-group and within-group analyses were performed for the different cohorts of patients with and without FM and paroxysmal episodes.

Results

All encounters were verified by cross-checked billing codes to capture every patient with a completed record and primary diagnosis (n = 4,308). Additional patient records identified by billing codes that reflected return visits (n = 2,550) and procedural codes

(*n* = 28) were excluded from the analysis. A total of 1,730 consecutive, non-selected outpatient records were eligible for analysis. Ninety-five (5.5%) patients had a historical diagnosis of FM at the time of their first consultation (mean age: 53 years). Most were identified in the first year of the study. Definitive confirmation of the FM diagnosis by Mayo Rheumatology was made in 27.3% of patients with ES, 59.1% with PNES, and 60% with PhysNEE, but was highest for patients with non-paroxysmal disorders (70.8%). Of the FM patients, 9.3% had charts which included an unprompted disagreement with the diagnosis of FM during their initial consultation with the epileptologist.

Of the 95 patients with FM, 54/95 (57%) received a primary clinical diagnosis of ES, PNES, or PhysNEE. Syncope was the most common type of PhysNEE, with similar incidence of this diagnosis in patients with and without FM. The remaining 41/95 (43%) of those with FM had primary non-paroxysmal neurological diagnoses (primarily chronic pain). A similar number of the 1,005/1,635 (61%) patients without FM were diagnosed with a paroxysmal disorder (*figure 1*). Among patients with FM and paroxysmal disorders, 11% had ES, 74% had PNES, and 15% had PhysNEE, compared to case-matched controls with 37% ES, 51% PNES, and 12% PhysNEE (p = 0.009), and the large unmatched control cohort with 49% ES, 41% PNES, and 10% PhysNEE (p < 0.0001). There was not a

significant difference in the distribution of paroxysmal events in the case-matched versus unmatched control cohorts. Comparison between the FM patients and case-matched controls revealed that a historical diagnosis of FM had a 61% sensitivity, 64% specificity, 74% positive predictive value, and 49% negative predictive value for the diagnosis of PNES. In 20% of our patients with ES and 40% with PNES, VEM later validated the clinical diagnosis in every case.

No population differences were present between patients with FM and their corresponding casematched controls with respect to age (mean: 53 years), race, marital status, or reason for referral (figure 2). Patients with FM and case-matched controls were equally likely to have been primarily referred for seizures or spells compared to other neurological conditions (p = 0.8). The large unselected cohort of patients had a different gender distribution than the FM patient group, with 977/1,635 (59.8%) females in the unselected group compared to 90/95 (95%) in the FM cohort ($p = \langle 0.0001 \rangle$). This reflected the only difference present in those with and without FM in this cohort. Patients with FM reported more comorbidities, neurological diagnoses, daily medications, and psychiatric comorbidities (table 1). Patients with FM were underrepresented in education (p = 0.02) when compared to a case-matched control (figure 2). Employment was also more common among case-matched controls



Figure 1. Among the patients with FM, 6% (95% CI: 3%, 13%) had ES, 42% (95% CI: 33%, 52%) had PNES, 8% (95% CI: 4%, 16%) had PhysNEE, and 43% (95% CI: 34%, 53%) had non-paroxysmal neurological symptoms. In the case-matched control group, 20% (95% CI: 13%, 29%) had ES, 27% (95% CI: 19%, 37%) had PNES, 6% (95% CI: 3%, 13%) had PhysNEE, and 46% (95%: CI 37%, 56%) had non-paroxysmal neurological symptoms.

ES: epileptic seizures; FM: fibromyalgia; PhysNEE: physiological non-epileptic events; PNES: psychogenic non-epileptic seizures.



Figure 2. Demographics of a cohort of patients with FM (*n* = 95) and a case-matched cohort without FM (*n* = 95). FM: fibromyalgia.

(52%) than the patients with FM (33%; p = 0.009). The same number of EEGs were performed prior to clinical diagnosis in patients with FM compared to case-matched controls (p = 0.3).

Discussion

Similar to prior retrospective reports, our casecontrolled retrospective study found that undifferentiated paroxysmal events in patients with FM were significantly more likely to be PNES than ES or Phys-NEE. While our retrospective study result was identical to the prior retrospective reports relative to the comorbidity of FM with PNES (Benbadis, 2005a; Benbadis, 2005b), our case-matched study was designed to more thoroughly validate the relative differences in FM diagnoses between patients with PNES and those with other paroxysmal events. We found that the sensitivity and specificity of FM as a predictor for the diagnosis of PNES were much lower than previously reported. Moreover, our study provides further perspective, not obtained in previous research in this area, including

comorbid FM and PNES. Up to 60% of those with PNES had a Rheumatology-validated diagnosis of FM, and 40% had their clinical PNES diagnoses confirmed by VEM. There was not a difference between the number of patients who underwent VEM and those who did not in the FM versus case-matched control group (p = 0.57). Of our patients with FM, 40-45% had a non-paroxysmal, primary neurological diagnosis, providing a study group that was more diverse, and potentially more generalizable, than prior reports (Benbadis, 2005a; Benbadis, 2005b). Similar to other studies (Hirtz et al., 2007), we found various types of localized non-FM-related chronic pain to be the most common primary neurological complaint in patients with paroxysmal neurological events and concomitant FM. Headache, low back pain, and neck pain were common neurological FM comorbidities. The prevalence of FM in our patient population (5.5%) was in the high end of the range of 2.2-6.4% reported by other centres (Benbadis, 2005b; Queiroz, 2013). Our patients with PNES and FM had more medical/psychiatric diagnoses, used more medications, and

evaluation of the historical aspects of patients with

	Cohort	Mean	95% CI	<i>p</i> value
Reported current daily medications	FM	9.4	8, 11	< 0.0001
	Case-matched control	5.8	5, 7	
Number of diagnoses in past medical history	FM	10.6	9, 12	<0.0001
	Case-matched control	5.7	5, 6	
Number of non-paroxysmal neurological diagnoses in past medical history	FM	1.3	1, 2	<0.0001
	Case-matched control	0.5	0.3, 0.7	
Number of psychological diagnoses in past medical history	FM	0.7	0.5, 0.9	0.05
	Case-matched control	0.4	0.3, 0.6	

Table 1. Differences in medical history between patients with FM (n=95) and case-matched controls without FM (n=95).

CI: confidence interval; FM: fibromyalgia.

had lower rates of employment and education compared to the other groups. These findings are similar to other reports (Shaw, 2009; Clauw, 2014). Our cohort was composed almost entirely of middle-aged women, which may provide a confounding effect when extending our results to other populations. However, our PNES population was similar to other cohorts previously described (Benbadis, 2005a; Devinsky et al., 2011). An unexpected finding of our study was that 9.3% of patients reported unsolicited disagreement with their diagnosis of FM during their initial visit with the epileptologist. This may reflect the patient's perception that the ability of clinicians to differentiate the finite differences between physiological and psychological conditions is limited. Similar barriers to treatment may also exist in patients diagnosed with PNES, though this requires further explanation to address why nearly one third of patients with PNES fail to follow through for a recommended psychiatric evaluation after receiving their diagnosis (Acton and Tatum, 2013).

Our study has several limitations. Given this study's retrospective nature, selection bias may have been present. Continued, prospective and larger data collection may serve to further strengthen our findings. The cohort was obtained from clinic visits for a single epileptologist within a neurology department, potentially limiting the generalizability of our findings. Potential diagnostic accuracy and recording bias remained consistent throughout the study. However, given that previous retrospective studies in this area exclusively involved patients from tertiary care epilepsy centres, our study adds to the prior literature, providing a different study population, a case-matched control group, and focus outside the epilepsy monitoring unit to achieve a consistent comparative and clinically relevant result. However, our study's high

rates of women in the FM and case-matched control cohorts, and the effects of an insured population (no Medicaid or unfunded patients were included) further limit generalizability. There are a number of different types of treatments available for patients with FM, from antiseizure drugs to antidepressants, to cognitive behavioural therapies. While the focus of our study was on diagnosis and comorbid FM, the influence of specific FM treatments on the pattern of paroxysmal neurological events is an important area for future research to address utilizing a controlled longitudinal study design.

Our study may also have been limited by the lack of VEM confirmation of the clinical diagnosis in every case, and instead the clinical history and physical examination was used to differentiate patients with ES, PNES, or PhysNEE. However, it is important to consider that VEM is not feasible or necessary for many patients (Benbadis et al., 2004). Most epileptologists believe that the clinical impression rendered by experienced clinicians should remain the cornerstone of diagnosis for paroxysmal events even during VEM (Deacon et al., 2003; Benbadis et al., 2004; Engel, 2008; Sirven, 2010; Devinsky et al., 2011; Sahaya et al., 2011; Syed et al., 2011). In our real-life practice setting, 40% of patients clinically diagnosed with PNES had their diagnosis confirmed by VEM. For those within our cohort who did undergo VEM, the clinical diagnosis of ES or PNES was validated in 100% of cases to provide support for the clinical diagnosis. The high diagnostic accuracy may reflect the emergence of multiple different clinical features that are strong predictors for a correct diagnosis (Devinsky et al., 2011; Syed et al., 2011), in addition to more patients arriving with outpatient digitally-recorded videos used to supplement the diagnosis (Zeiler and Kaplan, 2009). We recognize that

the lack of VEM could have caused some patients to be overlooked, including those with a dual diagnosis, however, all semiologies (epileptic and non-epileptic) were considered in the final primary diagnosis. FM was confirmed by Rheumatology in up to 70% of patients in our study. Though, notably, confirmation of FM was lower in patients with ES than for those with PNES or PhysNEE, potentially reflecting a referral bias based upon prior association with psychogenic causes and the detail required for the clinical examination (Teive *et al.*, 2015).

Despite the limitations, our large case-controlled study of a mixed group of neurological patients provides level three evidence of the association between patients with FM and the different frequencies of comorbid paroxysmal events through the use of retrospective case-matched controls. These findings add new information regarding the previous association between FM and patients with paroxysmal events. Our findings help support the retrospective association between FM and PNES identified previously (Benbadis, 2005a). However, we suggest caution when considering the link between outpatients with FM and the diagnosis of PNES given the relatively lower sensitivity and specificity we found in our study compared to previous research demonstrating a higher sensitivity (Benbadis, 2005a).

Conclusions

Paroxysmal events were common and equally represented in patients with and without FM in this mixed epilepsy-neurological population. We found that in patients with undifferentiated paroxysmal events, a history of FM had a positive predictive value of 74% for the diagnosis of PNES, similar to previous retrospective studies. Using a case-controlled study design, we further verified that among FM patients, PNES occurred significantly more frequently than ES or PhysNEE. However, our results suggest that the association between PNES and FM was weaker in this mixed epilepsygeneral neurology cohort than previously recognized (Benbadis, 2005a), with a sensitivity of 61% and specificity of 64%. We recommend that comorbid FM be interpreted conservatively as a predictor in patients with paroxysmal events in a general neurological practice. Future prospective, multi-centred studies may further validate the utility and limitations of FM as a historical marker for PNES. \Box

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