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Fatigue as a precursor to polymyalgia rheumatica: an explorative retrospective cohort study

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Objectives: Polymyalgia rheumatica (PMR) is the commonest inflammatory disorder of older adults. Although not part of the recently published classification criteria, patients with PMR frequently complain of fatigue. We compared consultation for fatigue and sleep problems between individuals with and without PMR.
Method: Consulters receiving a Read-coded diagnosis of PMR at nine general practices between 2000 and 2009 were matched by age, gender, general practice, and year of consultation to four patients without PMR. Fatigue and sleep problems were defined using Read codes. Cox regression was used to determine the association between PMR diagnosis and consultation for a fatigue/sleep problem.
Results: In total, 549 PMR patients were identified. Their mean (SD) age was 73.9 (8.6) years and 71% of the participants were female. Prior to the index date, 33 PMR patients and 80 matched non-PMR patients consulted with fatigue (0.43 vs. 0.25 consultations per 10 000 person-years, $p = 0.006$). PMR was associated with significantly more multiple fatigue consultations in the 12 months before PMR diagnosis [hazard ratio (HR) 1.95, 95% confidence interval (CI) 1.23–3.08]; no significant difference was seen in rates of consultations for sleep problems between patients with and without PMR.
Conclusions: PMR patients were significantly more likely to have had multiple fatigue consultations before being diagnosed with PMR. Given the overproduction of inflammatory cytokines seen in PMR, this fatigue may represent a prodromal phase prior to consulting with more classical musculoskeletal symptoms. This suggests that clinicians should consider PMR as a potential diagnosis in older patients consulting with fatigue.

Polymyalgia rheumatica (PMR) is the commonest inflammatory disorder of older (>50 years) adults and is characterized by pain and stiffness in the shoulder and hip girdles and elevated inflammatory markers (1). Studies suggest that the majority of patients with PMR are diagnosed and managed exclusively in primary care (2, 3).

Making the diagnosis of PMR, especially if the presentation is atypical, can be challenging, particularly within primary care, where non-specific symptoms such as pain and stiffness are common. Systemic features such as malaise, fatigue, and sleep disturbance are common symptoms reported by patients with PMR (1), although they do not form part of the recently published classification criteria, perhaps reflecting their derivation from mainly secondary care populations (4, 5), and there is a lack of published information regarding the nature of any relationship.

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Studies suggest that PMR is associated with overproduction of key cytokines, including interleukin (IL)-6 (6), which may be associated with fatigue. In patients with rheumatoid arthritis, treatment with the IL-6 inhibitor tociluzimab was shown to improve fatigue and sleep quality, independent of effects on disease activity (7).

Given that fatigue is a common problem but may also be a symptom of PMR, the aim of this study was to investigate whether there was an association between PMR diagnosis and consultations for fatigue and sleep disturbance using a matched cohort study within a primary care database.

Method

Sampling frame

Data were extracted from the Consultations in Primary Care Archive (CiPCA), a primary care consultation database from nine contributing general practices in Staffordshire, UK (8). Practices contributing to CiPCA undergo regular training and audit to ensure morbidity coding is of a high quality (9), with practitioners

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encouraged and trained to enter at least one morbidity Read code for each clinical contact. CiPCA has been shown to give comparable consultation prevalence rates to national databases (8).

Patients

All patients aged ≥ 50 years receiving a first Read-coded diagnosis of PMR between 1 January 2000 and 31 December 2009 were identified and frequency matched for age, gender, general practice, and consultation within the year of PMR diagnosis in a 4:1 ratio to patients without a PMR diagnosis. Within the selected sample, diagnostic Read codes for consultations for fatigue and sleep problems during the study period were identified. A list of Read codes used throughout this manuscript is available from the authors on request. Approval for consultation download and research using the CiPCA database was gained from the North Staffordshire Research Ethics Committee (REC Reference: 03/04).

Analysis

The association between fatigue and sleep consultation was analysed in two separate time periods: before and after the index consultation date (date of PMR diagnosis, or matched date for non-PMR participants). Analyses were conducted in two stages: first, single-event Cox regression models were used to investigate the association of time from index date to consultation for a sleep problem or fatigue. Second, multiple-event Cox regression, to account for the potential correlation between repeat consultations, was used to assess the association between PMR diagnosis and all consultations for sleep problems and fatigue in the time period, allowing for the time from index date. Robust estimates of variance (10) were used in all models to allow for matching. Analyses of fatigue and sleep were conducted separately.

As there is a potential association between fatigue and sleep, adjustment was made for the alternative in all analyses (i.e. fatigue analysis adjusted for sleep consultation and vice versa) in the same time period (i.e. pre-diagnosis or post-diagnosis). In addition to this adjustment, all post-diagnosis analyses were also adjusted for consultation for the same condition in the pre-diagnosis time period. Results are presented as hazard ratios (HRs) with 95% confidence intervals (CIs). The models were examined using Schoenfeld residuals to ensure that they met the proportional hazards assumption.

Sensitivity analysis

To improve the accuracy of the PMR diagnosis, a more stringent definition of PMR was applied using the method that Smeeth et al used in their PMR study in the General Practice Research Database (11). In addition to a PMR Read code, those with PMR were required to have at least two prescriptions for oral corticosteroids in the 6 months following their PMR diagnosis. Furthermore, as PMR may mimic other disorders such as rheumatoid arthritis or malignancy, a sensitivity analysis excluding all patients who received a Read code for an alternative diagnosis within 6 months was undertaken. The analyses were then repeated to investigate any differences between the original definition and the more stringent definition of PMR. We also undertook a sensitivity analysis to investigate whether those PMR patients subsequently diagnosed with giant cell arteritis (GCA) were more likely to consult with fatigue or sleep problems.

Finally, an interaction term was fitted to the models to investigate when patients were consulting with fatigue/sleep problems in relation to their PMR diagnosis (using the more stringent definition). Time bands considered were 0–12 months (split into 3-month quartiles), 1–2 years, and 2–10 years either before or after their diagnosis.

All analyses were conducted in Stata version 13.0 (Statacorp LP, College Station, TX, USA).

Results

A total of 549 patients aged ≥ 50 years received a Read-coded PMR diagnosis and were successfully matched by age, gender, and general practice with 2196 patients without PMR. The mean (SD) age of the PMR patients was 73.84 (8.64) years and 388 (70.7%) were female. PMR patients were under observation for a median of 3.9 years [interquartile range (IQR) 1.1–6.7] before and 3.8 years (IQR 1.6–6.8) after the index date.

Fatigue

During the study period, 209 (7.6%) participants consulted with fatigue. Patients consulting with fatigue were more likely to be female (79% vs. 70%, $p = 0.006$). There was no association between fatigue consultation and age.

PMR patients had a higher rate of consultations for fatigue than those not diagnosed with PMR (PMR rate 0.43/10 000 vs. 0.25/10 000 person-years in non-PMR patients, $p = 0.01$). The risk of a single previous fatigue consultation was 74% higher in PMR patients than in non-PMR patients (HR 1.74, 95% CI 1.16–2.62) (Table 1). PMR patients were also at higher risk of multiple fatigue consultations before the index date (HR 1.95, 95% CI 1.23–3.08). Of the 33 PMR patients with fatigue consultations pre-diagnosis, 17 (51.5%) had multiple fatigue consultations, compared with 33 (41.3%) of the 80 non-PMR patients ($p = 0.54$). Twenty-seven patients were diagnosed as having GCA within 3 years of their PMR diagnosis and, of these, four (11%) consulted for fatigue. Rates of fatigue consultation pre-PMR diagnosis were higher in those later diagnosed with GCA (single fatigue consultation HR 3.8, 95% CI 1.09–13.3; multiple HR 3.8, 95% CI 1.19–12.07), although the CIs were wide.

Table 1. Rates of fatigue and sleep consultations in PMR and non-PMR patients.

	PMR patients (n = 549)	Non-PMR patients (n = 2196)	Main analysis*, HR (95% CI)	
			Single event	Multiple events
Fatigue, frequency (rate†)				
Pre-diagnosis	33 (0.425)	80 (0.245)	1.74 (1.16–2.62)	1.95 (1.23–3.08)
Post-diagnosis	31 (0.372)	81 (0.251)	1.41 (0.93–2.13)	1.58 (0.95–2.63)
Sleep problems, frequency (rate†)				
Pre-diagnosis	15 (0.188)	53 (0.161)	1.15 (0.65–2.06)	1.82 (0.85–3.93)
Post-diagnosis	16 (0.189)	68 (0.210)	0.88 (0.51–1.53)	0.58 (0.32–1.06)

PMR, Polymyalgia rheumatica; HR, hazard ratio; CI, confidence interval.
* Adjusted for opposite condition in same time period and for consultation for same condition in 'pre-diagnosis' period (post-diagnosis analyses only).
† Per 10 000 person-years.

Table 2. Rates of fatigue and sleep consultations in PMR patients and non-PMR patients in the sensitivity analysis.

	PMR patients (n = 422)	Non-PMR patients (n = 2196)	Sensitivity analysis*	
			Single HR (95% CI)	Multiple HR (95% CI)
Fatigue, frequency (rate†)				
Pre-diagnosis	26 (0.414)	80 (0.245)	1.71 (1.10–2.67)	1.99 (1.20–3.30)
Post-diagnosis	28 (0.445)	81 (0.251)	1.67 (1.09–2.56)	1.60 (0.96–2.68)
Sleep problems, frequency (rate†)				
Pre-diagnosis	12 (0.187)	53 (0.161)	1.16 (0.61–2.19)	1.80 (0.74–4.35)
Post-diagnosis	10 (0.155)	68 (0.210)	0.73 (0.38–1.43)	0.46 (0.22–0.94)

PMR, Polymyalgia rheumatica; HR, hazard ratio; CI, confidence interval.
* Adjusted for opposite condition in same time period and for consultation for same condition in 'pre-diagnosis' period (post-diagnosis analyses only).
† Per 10 000 person-years.

There was a weak association between fatigue and PMR after a diagnosis of PMR had been made (PMR rate 0.37/10 000 vs. non-PMR rate 0.25/10 000 person-years, p = 0.04; HR 1.41, 95% CI 0.93–2.13 for a single event and HR 1.58, 95% CI 0.95–2.63 for multiple events). The results were similar for those later diagnosed with GCA (data not shown).

The sensitivity analysis excluding those patients with alternative diagnoses (n = 10) did not change the study findings except that the association with post-PMR single fatigue diagnosis became stronger and was statistically significant (HR 1.67, 95% CI 1.09–2.56) (Table 2).

Investigation into the timing of fatigue consultations revealed that patients were most likely to have received single or multiple diagnoses of fatigue in the year before their PMR diagnosis, specifically in the previous 6–9 and 9–12 months (single event: HR 19.7, 95% CI 2.2–177.6, multiple events: HR 39.1, 95% CI 4.5–340.0 for 6–9 months; and single event: HR 6.8, 95% CI 1.5, 30.5, multiple events: HR 10.0, 95% CI 2.3–44.4 for 9–12 months) (Table 3). This association was less strong in time periods more than 12 months before the index date and after the index date. None of the models violated the proportional hazards assumption.

Sleep problems

During the study period, 146 (5.3%) of the participants consulted with sleep problems and, of these, 144 (99%) were for insomnia. Those consulting with sleep problems were more likely to be female (75% vs. 71%, p = 0.277) and slightly older (mean age 75.0 vs. 73.8 years, p = 0.097).

No difference in the rates of consultations for sleep problems either pre- or post-index date was observed, with similar pre-diagnosis consultation rates between PMR patients (0.19/10 000 person-years) and non-PMR patients (0.16/10 000 person-years, p = 0.63). Similar rates of consultations were also seen after diagnosis (PMR patients 0.19/10 000 vs. non-PMR patients 0.21/10 000 person-years; p = 0.83). A weak association was observed between multiple consultations for sleep problems and PMR before (HR 1.82, 95% CI 0.85–3.93) but not after the index date (HR 0.58, 95% CI 0.32–1.06).

The sensitivity analysis excluding those patients with alternative diagnoses (n = 10) made little difference to the study findings, with the exception that the association between PMR and multiple sleep conditions in the post-diagnosis period was strengthened and took on statistical significance, with those with PMR being less likely to consult regarding sleep (HR 0.46, 95% CI 0.22–0.94). None of the models violated the proportional hazards assumption.

Table 3. Hazard ratios (with 95% confidence intervals) stratified by time between index date and fatigue/sleep consultations (stringent PMR definition).

	0–3 months	3–6 months	6–9 months	9–12 months	1–2 years	2–10 years
Fatigue						
Pre-diagnosis						
Single	1.36 (0.38–4.79)	1.46 (0.31–6.88)	19.71 (2.19–177.6)	6.79 (1.51. 30.46)	1.71 (0.47–6.25)	1.12 (0.56–2.12)
Multiple	1.09 (0.30–3.92)	1.30 (0.27–6.14)	39.05 (4.49–340.0)	9.99 (2.25–44.43)	1.66 (0.41–6.72)	1.23 (0.56–2.70)
Post-diagnosis						
Single	1.01 (0.22–4.61)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	4.92 (1.00–24.15)	2.52 (1.08–5.88)	1.70 (0.95–3.04)
Multiple	1.01 (0.20–5.12)	1.29 (0.14–11.46)	0.00 (0.00–0.00)	11.37 (2.18–59.28)	2.07 (0.80–5.32)	1.53 (0.79–2.97)
Sleep						
Pre-diagnosis						
Single	0.78 (0.10–6.32)	0.83 (0.10–6.72)	1.93 (0.38–9.91)	4.98 (0.31–79.07)	1.16 (0.25–5.40)	1.06 (0.41–2.78)
Multiple	0.78 (0.10–6.34)	0.83 (0.10–6.71)	1.38 (0.27–6.97)	2.49 (0.23–27.36)	1.41 (0.40–5.02)	2.35 (0.88–6.32)
Post-diagnosis						
Single	0.00 (0.00–0.00)	1.04 (0.12–8.93)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.76 (0.17–3.36)	0.96 (0.43–2.17)
Multiple	0.00 (0.00–0.00)	0.74 (0.08–6.77)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.45 (0.10–2.02)	0.55 (0.24–1.31)

PMR, Polymyalgia rheumatica.

Discussion

This study suggests that patients diagnosed with PMR are more likely to have consulted their general practitioner (GP) for fatigue before a diagnosis of PMR is made, with a proportion of these patients consulting multiple times for fatigue. However, there was little association between PMR and consultation for sleep problems, either before or after the diagnosis of PMR was made.

PMR is an inflammatory disorder and these findings may in part be explained by the overproduction of inflammatory cytokines, particularly IL-6, seen in patients with PMR. It is possible that the steroid treatment used in diagnosed patients suppressed IL-6 production, thereby improving fatigue symptoms, and meaning that the rates of consultations for fatigue after diagnosis were similar between those with and without PMR. No association was found between a diagnosis of PMR and consultations for sleep problems either before or after diagnosis. This may be because no association exists or because any complaints of poor sleep coexisted with fatigue and were not recorded separately as sleep problems in the medical record.

There are currently no formal diagnostic criteria for PMR and recently published classification criteria for PMR do not include fatigue as a core criterion (3–5) despite it being a common feature reported by many patients (1). A key finding from this study is the high frequency of consultation for fatigue symptoms prior to a diagnosis of PMR being made. This suggests a potential 'pre-PMR' period during which time patients are experiencing symptoms but have yet to develop the classical bilateral shoulder and hip pain and stiffness symptoms. Although these findings need to be confirmed in other populations, this has potentially important implications for primary care clinicians who need to be aware of including PMR as a part of their differential diagnosis in older patients with a history of fatigue and ensure that patients are asked about other musculoskeletal symptoms. It is important to note that although a significant difference was found between PMR and non-PMR patients for fatigue pre-PMR diagnosis, there is still a large number of PMR patients who did not consult for fatigue. As the codes reflect the main reason for consultation, it may be that fatigue was discussed within the consultation but the consultation not coded as such if it was not the main reason for consultation. The effect of this, however, would have been to reduce the associations observed.

There are several strengths and weaknesses that need to be considered when interpreting the results of this study. First, data were derived from a large, validated primary care database, and participants were identified using diagnostic Read codes. In addition, although the diagnosis of PMR was made within primary care, previous work within this database showed that 44% of patients had been referred to secondary care rheumatology services, giving us increased confidence in the validity of the PMR diagnosis (3). We have further strengthened the confidence we have in the diagnosis of PMR by repeating all analyses only in those treated with oral corticosteroids and with no alternative diagnoses within 6 months of PMR diagnosis, and finding broadly similar results. However, this is a regional database, raising issues about wider generalizability, although previous work suggests that the CiPCA database is comparable to other national databases (6). In addition, GPs contributing data have undergone a structured training programme, which ensures that morbidity coding is of a high standard (7).

Diagnosing PMR remains a challenge in all clinical settings and, as yet, the epidemiology and clinical course of this disabling condition is not well characterized, especially in a primary care setting. This study goes some way to suggesting additional characteristics of PMR in its early stages; however, future research should build on this to allow a fuller understanding of the nature of PMR and ultimately aid clinicians in improving patient outcomes.

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