Explaining fatigue in ANCA-associated vasculitis


Abstract

Objectives. To identify the determinants of fatigue among patients with ANCA-associated vasculitis (AAV).

Methods. A multicentre cross-sectional study was conducted. Subjects fulfilling the European Medicines Agency criteria for granulomatosis with polyangiitis (Wegener’s), microscopic polyangiitis and eosinophilic granulomatosis with polyangiitis (Churg-Strauss) were approached according to consecutive clinic attendance and invited to complete a questionnaire assessing fatigue and putative biopsychosocial determinants of this symptom. Concurrently, potential clinical determinants were recorded. Independent associations of fatigue were identified using forward stepwise logistic regression modelling and their overall impact expressed as population attributable risk (PAR).

Results. The majority (74.8%) of participants (n = 410) reported high levels of fatigue that were found to be significantly associated with numerous biopsychosocial and clinical factors. Sleep disturbance [odds ratio (OR) 5.3, 95% CI 2.7, 10.5] and pain (OR 3.8, 95% CI 2.0, 7.3) were the strongest independent associations of fatigue and, on a population level, each was more than twice as important as any other putative determinant (PAR 18.1% and 16.5%, respectively). Female gender (OR 2.1, 95% 1.1, 4.0), elevated CRP (OR 3.7, 95% CI 1.7, 8.1) and the dysfunctional coping strategies of behavioural disengagement (OR 2.4, 95% CI 1.04, 5.6) and denial (OR 2.4, 95% CI 0.9, 6.7) were also independently associated with fatigue.

Conclusion. The data suggest that AAV-related fatigue is multifactorial in origin. Sleep disturbance and pain were found to be most important, although inflammation, as measured by CRP, was also associated. This study has identified potentially modifiable determinants that will inform future interventions aimed at alleviating fatigue.

Key words: fatigue, ANCA-associated vasculitis, granulomatosis with polyangiitis, microscopic polyangiitis, eosinophilic granulomatosis with polyangiitis.

Introduction

The judicious use of immunosuppressants has transformed traditional outcomes for patients with ANCA-associated vasculitis (AAV). Mortality rates, previously exceeding 80% at 1 year [1], have been reduced to 20% at 5 years [2]. Person-centred outcomes have been applied to these now chronic diseases, of which self-reported fatigue appears most conspicuous. An international group of patients identified fatigue to be the greatest burden of their disease, outranking common clinical concerns such as dialysis and oxygen dependency [3]. More recently, we reported fatigue to be the principal cause of poor quality of life among this population [4]. Yet there are no interventions that have been shown to alleviate this key symptom in patients with AAV.
This, in part, relates to uncertainty about its underlying determinants. Thus far, studies have detected strong associations between fatigue and biopsychosocial factors such as depression, but not with clinical factors such as disease activity [5-8]. However, these small single-centre investigations were insufficiently powered either to fully assess the impact of clinical factors or to comprehensively identify independent associations through multivariable analyses.

This large multicentre study aimed to assess putative biopsychosocial and clinical determinants of fatigue among patients with AAV and to identify the most important independent associates that may be targeted in future fatigue-specific interventions.

Patients and methods

A multicentre hospital-based cross-sectional study was conducted where subjects were invited to complete a questionnaire and contemporaneous clinical data were recorded. The North of Scotland Research Ethics Committee (ref: 09/S0801/83) approved the study and written informed consent was obtained from patients according to the Declaration of Helsinki.

Subjects

Adult patients meeting the European Medicines Agency (EMEA) vasculitis classification algorithm for granulomatosis with polyangiitis (GPA, Wegener’s), microscopic polyangiitis (MPA) or eosinophilic granulomatosis with polyangiitis (EGPA, Churg–Strauss) were invited to participate according to consecutive outpatient clinic attendance at 11 rheumatology and renal departments in the UK.

Questionnaire

In addition to a measure of fatigue status, the questionnaire comprised self-report tools evaluating a number of potential biopsychosocial determinants of fatigue:

(i) Fatigue: the Chalder Fatigue Scale (CFS) [9] is one of the most commonly employed measures of fatigue [10, 11]. It has been validated in both general and diseased adult populations [10] and has been found to be both feasible and acceptable in AAV [5]. The 11 questions examine both physical and mental aspects of fatigue and the scores are totalled (range 0–11) with high scores indicating high levels of fatigue.

(ii) Depression and anxiety: the Hospital Anxiety and Depression Scale (HADS) is a succinct instrument developed to identify cases of depression and anxiety in those with physical illness [12]. Unlike other scales, the HADS purposely excludes any symptoms that may relate to physical disorders such as fatigue and insomnia, to prevent somatic diseases from affecting scores [13, 14]. In the context of AAV, it has been shown to be acceptable and discriminative with the general population [8]. It employs a Likert-style response to score 14 items (range 0–21 for each domain).

(iii) Sleep quality: the Estimation of Sleep Problems Questionnaire (ESQ) is a brief but reliable measure. It is known to perform well in both non-clinical and clinical populations [15, 16], concisely quantifying the most common symptoms of sleep dysfunction: difficulties in sleep onset and maintenance, early waking and non-restorative sleep. Participants were asked to indicate the number of days in the last month that they have experienced problems with each symptom: not at all, 1–3 days, 4–7 days, 8–14 days, 15–21 days or 22–31 days. The domain scores are totalled (range 0–20), with higher scores indicating greater sleep disturbance [15].

(iv) Coping: the Brief Cope (BC) assesses 14 generic coping styles of direct relevance to chronic diseases, which may be clustered into three subgroups: dysfunctional coping (denial, self-distraction, self-blame, substance use, venting, behavioural disengagement), emotion-focused coping (acceptance, use of emotional support, humour, positive reframing, religion) and problem-focused coping (instrumental support, planning, active coping). It has been cited in >1000 studies examining a variety of populations [17]. The 28 questions are scored on a 4-point ordinal scale with pairs relating to each of the 14 domains (range 2–8). Higher scores indicate greater use of the relevant coping style.

(v) Closed questions: gender, smoking, employment and pain status (any pain in the last month lasting for 1 day or longer).

For the purposes of analysis, the scores for all questionnaire tools, except HADS, were dichotomized (high/low) using previously established general population means [4] (see supplementary Table S1, available on Rheumatology Online). For HADS, the recognized cut-off of 8 for case-ness was selected [18]. Incomplete questionnaire measures were coded as missing data.

Clinical data

All participants were clinically assessed at time of recruitment and putative clinical determinants of fatigue were collated.

(i) Descriptors of clinical status: (a) Disease activity [Birmingham vasculitis activity score (BVAS) 3 [19]], where inactive disease was defined as BVAS = 0 and high activity as BVAS >3; (b) disease damage [vasculitis damage index (VDI) [20]], where damage was considered absent if VDI = 0 and severe if VDI >5; (c) co-morbidity [Charlson co-morbidity index (CCI) [21]] applied retrospectively to the period prior to diagnosis (so not to overlap with VDI) and scored as previous co-morbidity >0; (d) disease duration, from date of diagnosis, analysed by tertiles; (e) BMI, dichotomized at 25 kg/m² (WHO cut-point for overweight [22]).
(iii) Diagnosis: Classification according to (a) EMEA algorithm and (b) ANCA status.

(iii) Clinical phenotype: Previous organ involvement was recorded consistent with the nine BVAS categories.

(iv) Therapeutic exposures: (a) current prednisolone dose and (b) history of use of other immunosuppressants (cumulative dosage where data not heavily skewed).

(v) Blood laboratory measures: (a) estimated glomerular filtration rate (eGFR), (b) haemoglobin, (c) lymphocytes, (d) albumin and (e) CRP, categorized according to recognized norms.

Statistical analysis

A priori power calculations, based upon previous exploratory work [5], estimated a sample size of \( n = 350 \) in order to detect an important association [effect size, odds ratio (OR) 2.5] between disease activity and fatigue with 90% power and within 95% CIs. This assumes a 20% prevalence of active disease and 30% prevalence of fatigue in those with inactive disease. Such a sample size also adequately powers examinations of other putative clinical associations, including disease damage, CRP, anaemia, CYC exposure and renal function. All analyses were conducted using STATA 11.2 (Stata, College Station, TX, USA).

First, population characteristics were summarized employing mean and s.d. or median and interquartile range (IQR) according to their distributions. The unvariable (individual) relationships between fatigue and its putative determinants were assessed using \( \chi^2 \) tests and logistic regression. To permit identification of independent associations, those variables univariably identified as moderately to strongly associated (defined as \( P < 0.2 \) and whose population prevalence was \( > 10\% \) (so to only consider factors that have the greatest importance on a population level) were then submitted to a logistic regression model using a forward stepwise selection technique. All variables significant at \( P < 0.10 \) were retained and those with \( P > 0.15 \) were excluded.

The resultant independent associations were then entered into a standard logistic regression model in order to limit the impact of cumulative missing data and hence improve effect size precision, expressed as ORs. Finally, the overall impact of each independent association was prioritized by calculation of PAR [23].

Results

Patient characteristics

Of the 486 invited patients, 410 (84.4%) participated: 49.0% male; median age 63.5 (51.8–72.4) years. As demonstrated in Table 1, the majority fulfilled GPA classification criteria (64.6%), then MPA (23.2%) and EGPA (10.7%), with 85.9% ANCA positive. The cohort was generally stable (19.3% deemed active, mean BVAS 1.2) and established (median disease duration 61 months, IQR 26–120). Although post-diagnosis damage was common (median VDI 2, IQR 1–4), pre-diagnosis co-morbidity was not (median CCI 0, IQR 0–0). The majority (74.8%) of participants reported high levels of fatigue (CFS: median 7, range 0–77; additionally 28.4% reported anxiety, 24.6% depression, 57.3% high sleep disturbance and 61.9% pain in the last month.

Univariable analysis

In general, few clinical factors were individually associated with reported fatigue. No statistically significant relationships were detected with disease activity (OR 1.5, 0.8–2.8), although subjects demonstrating active levels of inflammation, as measured by raised CRP, were more than twice as likely to report high fatigue when compared with those without evidence of inflammation (OR 2.4, 1.3–4.3). The association between high fatigue and abnormal renal function also reached statistical significance (OR 4.3, 1.0–17.0); with larger effect sizes evident for those dependent upon dialysis (OR 2.6, 0.8–8.8). Otherwise, measures of disease status, therapeutic exposure, blood laboratory measures and diagnostic status did not significantly influence the reporting of fatigue (see supplementary Table S2, available at Rheumatology Online).

In contrast, associations with biopsychosocial factors were typically strong (see supplementary Table S1, available at Rheumatology Online). High sleep disturbance revealed the greatest magnitude of association (OR 6.9, 3.9–12.3), followed by the reporting of depression (OR 6.7, 2.8–15.9), pain (OR 5.5, 3.3–9.3), anxiety (OR 4.5, 2.1–9.3), unemployment (OR 4.5, 1.6–12.8) and female gender (OR 2.2, 1.3–3.5). With reference to coping

<table>
<thead>
<tr>
<th>Table 1 Population clinical characteristics (n = 410)</th>
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<tbody>
<tr>
<td>Variable</td>
</tr>
<tr>
<td>----------</td>
</tr>
<tr>
<td>Age, median (IQR), years</td>
</tr>
<tr>
<td>Males</td>
</tr>
<tr>
<td>Diagnosis</td>
</tr>
<tr>
<td>System involvement</td>
</tr>
<tr>
<td>BVAS &gt;0</td>
</tr>
<tr>
<td>VDI, median (IQR)</td>
</tr>
<tr>
<td>Disease duration, median (IQR), months</td>
</tr>
<tr>
<td>eGFR &gt;60 ml/min/1.73m²</td>
</tr>
<tr>
<td>Raised CRP</td>
</tr>
</tbody>
</table>

Values are n (%) unless otherwise stated. Total subjects vary due to some missing data. *According to local laboratory cut-offs.
behaviours, those subjects adopting the dysfunctional strategies of behavioural disengagement (OR 4.8, 2.4–9.4), self-distractlon (OR 2.6, 1.6–4.3) and denial (OR 2.5, 1.2–5.0) had a tendency to report high fatigue.

Multivariable analysis
Of the 20 moderately to strongly associated variables submitted to the logistic regression model, 6 were retained: sleep disturbance, CRP, pain, female gender and the coping styles of behavioural disengagement and denial (Table 2). High sleep disturbance, raised CRP and the presence of pain were most strongly associated, each independently quadrupling the odds of subjects reporting high fatigue. In population terms, sleep disturbance and pain each made more than twice the contribution to the reporting of fatigue than any other factor (Table 3).

Discussion
This large study has identified potentially modifiable associations of reported fatigue among patients with AAV. In particular, biopsychosocial factors such as sleep disturbance, pain and dysfunctional coping styles were found to be important; however, CRP levels were also independently associated, thus implicating an inflammatory component to this prevalent problem.

When faced with the complaint of AAV-related fatigue, physicians are initially inclined towards assessing potential clinical-related factors in an attempt to identify a reversible cause. It is often assumed that fatigue reflects disease activity; however, this study reinforces a previous cross-sectional study that also failed to detect a significant association between BVAS and fatigue [6]. Nonetheless, in the absence of robust biomarkers, BVAS is only a surrogate measure of disease activity that continues to be refined [19]. It, therefore, may not be sufficiently sensitive to detect all aspects of disease activity. This is especially possible during the prodromal phase of disease onset or flare, when patients may complain of fatigue [24] but none of the specific organ manifestations as defined by BVAS. In this context, the currently observed independent association between raised CRP and fatigue is noteworthy since CRP is considered a highly sensitive, albeit non-specific, measure of activity even during the earlier phases of disease [25, 26]. Therefore the CRP association may reflect at least in part, disease activity not captured by BVAS, and so in some circumstances fatigue could potentially be improved by the escalation of immunosuppression. Other routinely assessed clinical associations, such as anaemia and renal dysfunction, were of less importance, although the general stability of this study’s clinical cohort is recognized (e.g. only 5% of the sample recorded a haemoglobin <100 g/l) and therefore the capacity of our study to assess the impact of more severe clinical categories is limited.

Other clinical factors, including therapeutic exposures, do not appear relevant. Koutantji et al. [8] have reported higher levels of fatigue among patients on prednisolone doses >10 mg. Though there are plausible biological explanations, such as interference of the hypothalamic-pituitary adrenal axis, for why prednisolone may explain reported fatigue, this larger study has been unable to verify this previous observation. Ideally the sequelae of prednisolone therapy would be best assessed by recording cumulative doses; however, these are notoriously difficult to estimate retrospectively [27].

In line with existing studies [6, 8], large associations were observed between fatigue and the biopsychosocial factors of sleep disturbance and pain; indeed, on a population level, the combination of these symptoms was more than twice as important as all the other independent associations put together. Such patterns of association have also been commonly observed in RA [28] and other chronic illnesses [29] and so support the hypothesis that the generic impact of having a chronic disease may contribute more to the explanation of fatigue than disease-specific factors. While pharmacological treatments are available to treat pain and sleep disturbance, in practice these are often associated with side effects and sometimes dependence. As a result, hypnotics are no longer considered first-line treatment for sleep disturbance and non-pharmacological-based sleep hygiene interventions are preferred [30]. Although analgesics remain the mainstay of pain management, these may inadvertently worsen

**Table 2** Explanatory model of fatiguea among AAV patientsb

<table>
<thead>
<tr>
<th>Explanatory variable</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raised CRP</td>
<td>3.7</td>
<td>1.7–8.1</td>
</tr>
<tr>
<td>High sleep disturbance (ESPQ)c</td>
<td>5.3</td>
<td>2.7–10.5</td>
</tr>
<tr>
<td>Pain</td>
<td>3.8</td>
<td>2.0–7.3</td>
</tr>
<tr>
<td>High behavioural disengagement (BC)c</td>
<td>2.4</td>
<td>1.04–5.6</td>
</tr>
<tr>
<td>High denial (BC)c</td>
<td>2.4</td>
<td>0.9–6.7</td>
</tr>
<tr>
<td>Female</td>
<td>2.1</td>
<td>1.1–4.0</td>
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</table>

aCFS. b(n=303; total subjects vary due to missing data. cDichotomized at the general population mean.

**Table 3** Ranking of fatiguea associations according to PARb

<table>
<thead>
<tr>
<th>Explanatory variable</th>
<th>PAR, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>High sleep disturbance (ESPQ)c</td>
<td>18.1</td>
</tr>
<tr>
<td>Pain</td>
<td>16.5</td>
</tr>
<tr>
<td>Female</td>
<td>7.5</td>
</tr>
<tr>
<td>Raised CRP</td>
<td>6.5</td>
</tr>
<tr>
<td>High behavioural disengagement (BC)c</td>
<td>5.2</td>
</tr>
<tr>
<td>High denial (BC)c</td>
<td>2.4</td>
</tr>
</tbody>
</table>

aCFS. b(n=303; total subjects vary due to missing data. cDichotomized at the general population mean.
sleep disturbance by promoting daytime somnolence, which often leads to nighttime sleep disturbance and consequent exacerbation of daytime fatigue. Such vicious cycles certainly reflect experiences from the field of oncology, where the symptoms of pain, fatigue and sleep disturbance also commonly co-exist and have prompted investigation into non-pharmacological interventions with the capacity to address all symptoms concurrently [31]. Several non-pharmacological interventions have been employed to address fatigue in other chronic autoimmune conditions, with exercise and behavioural interventions shown to be beneficial [32]. AAV-specific non-pharmacological programmes for fatigue require development and testing. In addition to addressing sleep hygiene and pain management, such interventions should incorporate coping skills training to address the dysfunctional coping strategies of behavioural disengagement and denial, which have also been identified as important associations of fatigue in this study.

Some methodological factors must be considered in the interpretation of this study. First, as with all cross-sectional studies, causality is difficult to determine for some of the described associations. This is especially so for the identified biopsychosocial factors: while it seems reasonable to propose that pain leads to sleep disturbance, which in turn leads to fatigue. Contrarily, fatigue is known to lower pain thresholds [33] and sleep disturbance has previously predicted the onset of chronic pain [34]. Thus the true direction of association may be better understood by longitudinal or interventional study designs. The causality of the identified biological factors is less controversial and, overall, these results offer a hypothetical model for the determinants of AAV fatigue. Second, despite comprehensive data collection, other putative determinants, such as thyroid disease, have not been considered. Third, it is recognized that this study’s sample has been recruited from secondary and tertiary care facilities where clinicians are experienced in the management of AAV. While this is a frequent criticism of studies examining more common disorders where care may be delivered elsewhere, AAV clinical guidelines recommend that all patients receive input from expert centres due to their complexity and low prevalence [35, 36]. Consequently, it seems reasonable to assume that limiting recruitment to specialized centres has not greatly impacted the study’s external validity.

In summary, the data suggest that AAV-related fatigue is multifactorial in nature. The observed independent association with CRP alludes to an inflammatory component that may be alleviated by pharmaceutical intervention and encourages future exploration of fatigue-specific biomarkers. However, the majority of clinician-attending patients who report fatigue do not exhibit evidence of systemic inflammation or disease activity. These patients are more likely to benefit from non-pharmacological interventions addressing biopsychosocial symptoms such as pain, sleep disturbance and dysfunctional coping strategies. Further evaluation of such interventions is essential in order to address this vexing problem.

### Acknowledgements

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### Supplementary data

Supplementary data are available at *Rheumatology* Online.

### References

17 Carver CS. You want to measure coping but your protocol’s too long: consider the brief COPE. Int J Behav Med 1997;4:92–100.