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Fatigue: a principal contributor to impaired quality of life in ANCA-associated vasculitis

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Abstract

Objectives.—To describe quality of life (QoL) in an ANCA-associated vasculitis (AAV) cohort and make comparisons with a general population sample. In addition, we aimed to take preliminary steps to identify potential disease and psycho-social factors which may determine QoL impairment.

Methods.—A population-based case–control study was designed. All AAV patients resident in Grampian, Scotland, were invited to participate as cases. Controls were identified from a random sample of persons registered with four local general practices. Participants completed a questionnaire comprising validated generic and symptom-specific tools in the assessment of QoL. In addition, all cases were clinically assessed and putative disease factors recorded. Cases and controls were compared and, in addition, disease and psycho-social associations were explored for identified QoL impairments.

Results.—In total, 74/90 (82%) cases and 781/2000 (39%) controls participated. Cases reported a significant impairment in physical health ($P < 0.0001$), but not mental health ($P = 0.85$), compared with controls, as measured by Short Form-8 (SF-8). Following adjustment for age and sex, persons with AAV were more than twice as likely to report mild/moderate fatigue [odds ratio (OR) 2.0; 95% CI 1.1, 3.8] or severe fatigue (OR 2.5; 95% CI 1.4, 4.5) compared with controls. Furthermore, among cases, fatigue was found to be strongly associated with impaired physical health ($P < 0.0001$), while disease factors such as disease activity and damage were not ($P = 0.60$ and 0.27, respectively).

Conclusions.—Patients with AAV report impaired physical but not mental health. Specifically, fatigue is a principal complaint and appears to be a major determinant of impaired QoL.

Keywords

ANCA-associated vasculitis; Wegener's granulomatosis; Microscopic polyangiitis; Churg–Strauss syndrome; Vasculitis; Quality of life; Fatigue

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Introduction

ANCA-associated vasculitis (AAV) is a group of multisystem auto-immune diseases comprising Wegener's granulomatosis (WG), microscopic polyangiitis (MPA) and Churg–Strauss syndrome (CSS). Previously regarded as invariably fatal [1], advances in therapy have led to their becoming chronic diseases with 5-year survival rates exceeding 80% [2].

Despite these improvements, morbidity remains significant [3]. This relates to both direct disease influences, such as accrued damage or ongoing activity, and indirect consequences, such as exposure to potent immunosuppressive regimes [4]. Intuitively, one would expect such disease variables to impact on a patient's quality of life (QoL). However, in studies with other chronic diseases a greater emphasis has been placed on the psycho-social burden of illness as a determinant of QoL impairment [5-8].

To date, there have been few studies describing QoL in AAV patient groups [9-12]. In general, the generic Short Form-36 (SF-36) [13] questionnaire has been employed. Although useful and widely used as a measure of general health status, this tool does not measure specific symptoms, can lack disease-specific relevance and may be less responsive to clinical changes. Uni-dimensional, symptom-specific QoL measures provide greater detail. Such knowledge is important in understanding the mechanisms of QoL impairment and tailoring subsequent management plans. Furthermore, no study design has adopted general population controls, essential for contextualizing observations.

This study's primary outcome was to describe aspects of QoL in our cohort of AAV patients and make comparisons with a general population sample. We principally utilized symptom-specific measures of QoL, but also a generic tool. It was hypothesized that AAV cases would report poorer QoL compared with controls across all measures. In addition, we looked to explore both disease and psycho-social factors, which may determine QoL impairment, providing potential targets for future management plans.

Methods

Design and subjects

We conducted a case–control study. Cases were patients with the diagnosis of AAV who met the ACR criteria for WG [14], CSS [15] or the Chapel Hill consensus conference definition for MPA [16], and who were resident in the Grampian region of Scotland (population ~535 000 [17]). The area is served by a multidisciplinary 'vasculitis clinic', where all patients with the diagnosis of AAV are managed. The clinical database provided details of all patients as of August 2007. Cross-referencing with local nephrology, rheumatology and pathology databases was undertaken to ensure complete regional case identification. Diagnosis was substantiated following review of medical records.

Controls were recruited through a parallel population survey of adults, aged between 25 and 70 years, living in the Aberdeen city area of the Grampian region. Subjects were selected using simple random sampling from the patient lists of four general practices whose respective catchment areas cover a mixture of socio-economic backgrounds and age groups. In the UK almost all persons are registered with a general practitioner, for when they receive initial medical care, and this therefore provides a suitable population frame.

Questionnaire assessment

All cases and controls were asked to complete a questionnaire at home. This comprised five tools designed to measure aspects of QoL previously identified as problems in other chronic auto-immune diseases [18, 19]:

i. The SF-8 Health Survey provides a measure of general health status [20]. This instrument is a scaled down version of the SF-36 Health Survey [13], a generic measure of QoL frequently used in the study of chronic diseases including AAV [10, 12]. Although less precise, the SF-8 correlates strongly with SF-36 providing a comprehensive alternative. Furthermore, its brevity reduces participant burden aiding participation rates. Identical norm-based scoring metrics are used, allowing both the instruments to be directly comparable. Scores range from 0 to 100, with higher scores corresponding to a higher QoL and a score of 50 representing the average US general population [20]. Pooling of questionnaire items allows calculation of the physical component summary (PCS) and mental component summary (MCS), both internationally valid estimates of physical and mental health, respectively [20]. Scores were divided into tertiles: low, medium and high.

ii. The Chalder Fatigue scale (CFS) is an 11-item instrument validated for use in population studies [21]. Each item has four possible responses, but for the purposes of analysis, these were dichotomized at the median. These individual scores were summed, providing a total score between 0 and 11. Fatigue was categorized according to previously proposed cut-offs: absent (0), mild (1–3) and moderate/severe (4–11) [22].

iii. The Beck Depression Inventory (BDI) is a 21-item instrument that has been demonstrated as a valid measure of depression. Initially developed as a measure of depression severity for research purposes, it is now routinely used as a clinical screening tool [23]. The four possible responses were scored 0, 1, 2 or 3 (Likert style) according to increasing severity. A score of ≥13 is recognized to distinguish significant mood disturbance [24].

iv. The General Health Questionnaire (GHQ) was developed as a measure of psychological distress and has also been demonstrated to be a valid screening tool for mental illness [25]. The 12-item version has been widely validated in population studies. Typically scored in a Likert style, for analysis the scores were dichotomized: low <22 and high ≥22.

v. The ACR definition of chronic widespread pain (CWP) used in the criteria for FM was employed as a measure of pain status [26]. These criteria require at least a 3-month history of widespread pain, which must include areas on both the left and right sides of the body, above and below the waist and the axial skeleton. To identify those who fulfilled these requirements, subjects were asked to mark areas of pain on a four-view blank body manikin and to subsequently quantify the duration of their reported symptoms.

Disease factor assessment

All cases were clinically assessed within a fortnight of questionnaire completion. The Birmingham Vasculitis Activity Score (BVAS) was used to measure disease activity [27], where inactive disease was defined as BVAS = 0. Disease damage was recorded using the Vasculitis Damage Index (VDI) [28], with damage described as absent (VDI = 0), mild/moderate (VDI 1–2) or severe (VDI > 2). Routine blood investigations (full blood count, urea and electrolytes, CRP and ANCA) were ordered and analysed.

Finally, case medical records were reviewed and clinical parameters which may impact on QoL were collected. Specifically, these included information on disease duration, cyclophosphamide exposure, organ involvement and previous ANCA status.

Statistical analysis

SF-8 mean scores from cases and controls were compared using *t*-tests (two-sided *P*-value). Proportions of psycho-social variables were compared between cases and controls using χ^2-test. Odds ratios (ORs) with 95% CI were estimated using logistic regression to examine differences in pain, fatigue and mood between cases and controls. In addition, this allowed adjustment for age and sex. Since many tables contained cells with very few entered numbers, Fisher's exact tests were employed for the within-case analysis (association of disease and psycho-social factors with physical health and fatigue severity, respectively). Analysis was conducted using STATA v10.1 (Stata, College Station, TX, USA) and QualityMetric Health Outcomes Scoring Software v2.0 (Lincoln, RI, USA).

Ethical approval

The study was reviewed and approved by the North of Scotland Research Ethics Service (Reference: 07/S0802/46). Written informed consent was obtained from all cases, while consent was assumed if controls completed and returned the questionnaire.

Results

Subjects

Database cross-referencing identified 90 AAV patients: 60 WG, 14 MPA and 16 CSS. Of these, 72 (80%) agreed to participate: 59% male, mean age 59 years [interquartile range (IQR) 48–69 years]. Of the 2000 controls invited, 781 (39%) participated: 46% male, mean age 50 years (IQR 40–60 years). Table 1 describes basic clinical features of the AAV cohort. Low levels of damage were recorded by the VDI (mean 1.7; IQR 0.5–2) and absent disease activity (BVAS = 0) noted in 85% of patients.

Comparison of cases and controls

There was no significant difference in mental health-related QoL between cases and controls, as measured by the SF-8 MCS (cases mean 49.3, controls mean 49.0, *t*-test: $P = 0.84$). Conversely, persons with AAV were more likely to report significantly impaired physical health-related QoL as measured by the SF-8 PCS (cases mean 50.9, controls mean 46.1, *t*-test: $P < 0.0001$). This association remained after adjusting for age and sex: cases were more than two and a half times as likely to report low physical health (OR 2.63; 95% CI 1.28, 4.43) compared with controls.

When comparing pain between cases and controls (Table 2), 13.9% of cases reported CWP, comparable with 11.3% within population controls ($\chi^2 = 0.45$; $P = 0.51$). Similarly, there was no significant difference in psychological distress (cases 8%, controls 6%, $\chi^2 = 0.47$; $P = 0.49$) or depression (cases 15%, controls 21%, $\chi^2 = 4.34$; $P = 0.50$) as measured by the GHQ-12 and BDI, respectively. However, persons with AAV were significantly more likely to report mild (30.1%) or moderate/severe fatigue (38.4%), compared with controls (22.8 and 26.1%, respectively) ($\chi^2 = 10.41$; $P = 0.005$). After adjusting for age and sex: cases were more than twice as likely to report mild/moderate fatigue (OR 2.0; 95% CI 1.1, 3.8) or severe fatigue (OR 2.5; 95% CI 1.4, 4.5) compared with controls. Based on the observed significant impairments in physical health status and fatigue, further analysis to identify respective determinants was undertaken.

Physical health severity associations

Among cases, we examined the distribution of physical health (using tertiles of the SF-8) according to patient pain, fatigue and mood. Cases reporting moderate/severe levels of fatigue and significant mood disturbance had poorer physical health ($P < 0.001$ and $P =$

0.021 respectively; Table 3). There were non-significant trends for those with psychological distress ($P = 0.06$) and CWP ($P = 0.058$) to report poor physical health. In contrast, there were no significant associations between measured disease-related factors and physical health: abnormal CRP ($P = 0.24$), long disease duration ($P = 0.21$), a history of renal involvement ($P = 0.22$), high VDI ($P = 0.27$), diagnosis ($P = 0.84$), a history of ANCA positivity ($P = 0.63$), high BVAS ($P = 0.60$), exposure to cyclophosphamide ($P = 0.38$), impaired estimated glomerular filtration rate (eGFR) ($P = 0.46$) or anaemia ($P = 0.52$).

Fatigue severity associations

As demonstrated in Table 4, increasing fatigue severity was associated with a history of renal involvement ($P = 0.012$). However, there was no evidence that current renal function, as measured by the eGFR, impacted on levels of fatigue ($P = 0.83$). Similarly, other laboratory markers failed to show any significant relationship with fatigue.

Psycho-social factors were closely related to fatigue (Table 5). There was a clear association between significant mood disturbance and increasing fatigue severity ($P < 0.0001$). However, depression did not account for fatigue in all subjects with 32 (74%) complaining of fatigue without significant depression. CWP and psychological distress were also associated with fatigue, the former significantly so ($P = 0.036$).

Discussion

We report the first population-based case–control study to examine QoL in AAV. When compared with the general population, physical but not mental health compromised QoL in this patient group. Specifically, fatigue was the most commonly reported symptom in this cohort. Furthermore, fatigue was identified as a major determinant of impaired QoL. Exploratory analysis examining associations of fatigue severity identified the psycho-social factors of depression and chronic pain as potential determinants. However, with the exception of a history of renal involvement, disease factors appeared to be unrelated.

A number of methodological issues require consideration in interpreting these results. First, although 80% of the AAV cases agreed to participate, only 39% of the general population returned their questionnaire. Case non-responders were similar in age and sex to responders; however, in common with other population studies, control non-responders were younger and more likely to be male. These specific demographic factors tend to improve a population's overall reported QoL. A significant introduction of non-response bias appears unlikely since the observed general population QoL measures are similarly distributed to those quoted in other population-based studies with higher response rates and more enhanced data [24, 29, 30]. However, the degree of QoL impairment in cases compared with controls may have been underestimated.

Secondly, none of the employed QoL measures have previously been validated within this specific patient cohort. They have, however, been widely validated in the general population and several other disease-specific cohort studies. Thus, any misclassification with respect to these tools is likely to be random and so, if anything, underestimate observed associates. In fact, we found all the measures performed well in stratifying symptoms. The mental health measures of GHQ-12, BDI and SF-8—MCS were consistent in failing to show any significant differences between cases and controls, thus demonstrating convergent validity. Equally, answers to the SF-8 vitality domain were strongly associated with the CFS ($\chi^2 = 34.61$; $P<0.0001$). Of note, the SF-8 vitality domain is calculated within the MCS, thus the identified impact of fatigue on the SF-8 physical component score has not been contaminated by reciprocal measurement.

Finally, although this study represents one of the largest undertaken in the area of QoL and AAV, this remains a small study which only has power to detect differences between cases and controls. While this places greater emphasis on our positive outcomes such as the impact of fatigue on physical health, we may have missed other clinically relevant associations. For this reason, the within-case analysis should be considered exploratory. Indeed the difficulty in producing adequately powered studies in such uncommon diseases has led to the historic practice of 'merging' WG, MPA and CSS under the umbrella term AAV. AAV subsets share some clinical features and aetiologies and so AAV is a commonly used case definition in the field of vasculitis research [31]. Ultimately, the three subgroups retain distinct clinical and pathological phenotypes, therefore, separate studies would improve homonogeneity and consequent validity. However, due to the very limited power for subset analyses, these were not comprehensively undertaken.

While there are no comparable population-based case–control studies available, previous studies have described QoL in AAV using the SF-36. In comparison with previously described general population values, an overall impairment of QoL has been described [10, 12], consistent with our observations. The specific domains of body pain and mental health generally rank among the less important sources of detriment. Again, this supports our present findings where non-significant relationships between CWP, depression and psychological distress were noted. In contrast, fatigue, as measured by the relevant SF-36 subscale, is reported to be a salient factor in all studies. Using a symptom-specific tool, we have confirmed fatigue to be a prevalent problem in AAV. Furthermore, we have identified fatigue as a principal determinant of impaired physical health. Other groups have also highlighted employment and physical function as key contributors [10, 11].

Publications using symptom-specific tools are limited in this field. Although their study was uncontrolled, Koutantji *et al.* [10] utilized the Hospital Anxiety and Depression Scale to show high levels of psychological distress in their cohort. Interestingly, this challenged their concurrently collected SF-36 mental health subscale data which did not identify significant problems. This contradiction highlights the importance of exploring the psychometric properties of both generic and symptom-specific tools in the measurement of QoL.

Until now, no published study has analysed potential clinical associates of impaired QoL in AAV using contemporaneously collected, validated measures of disease activity and damage. Similar correlates have, however, been studied in other chronic auto-immune diseases. Pollard *et al.* [7] found no significant relationship between fatigue and disease activity in RA, rather, identifying pain and depression as the principle associates. In a large SLE cohort, Da Costa *et al.* [32] recognized both disease activity and damage as important contributors to fatigue, but also highlighted the importance of psycho-social factors such as depression. Such observations demonstrate that these mechanisms are clearly complex and likely to be multifactorial.

It is perhaps no surprise that patients with chronic, potentially devastating disease incur poor QoL. Indeed, it would be reasonable to expect even greater impairments than those observed. The methodological issues raised may go some way to explaining this discrepancy. However, the relative stability of this cohort should also be noted. The vast majority (85%) are reported to have quiescent disease activity, and the levels of accumulated damage are generally less than those reported elsewhere [33, 34]. This may relate to the local clinical service structure where, as per international recommendations [35], all patients receive multidisciplinary input from specialists with a particular interest and experience in the field. High clinic capacities allow frequent review, and hence close monitoring of disease factors, but equally provide substantial support and reassurance to the patient. The

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patient–physician relationship has long been recognized as a determinant of health status outcome [36].

Our study suggests that fatigue may be a dominant problem for patients. Further analysis identified a number of factors which may play a role in its occurrence. Although the study was underpowered to test relationships with disease factors, a history of renal involvement was significantly associated with fatigue severity. It is reasonable to consider this variable as a marker for overall disease severity and extent, especially since the commonly recognized causes of fatigue in renal disease (reduced eGFR and haemoglobin) showed no association. This observation can also explain the trend towards increasing fatigue in patients with MPA, a disease typically dominated by renal disease (95% in this cohort). The impact of the reported psycho-social factors appears relatively impressive despite the sample size limiting our ability to quantify these associations. Certainly the strong association between symptoms such as fatigue, depression and pain is well recognized both in general and diseased populations [30, 37, 38]. It may even be that these psycho-social measures are part of the same construct. The concept of ‘symptom clusters’ has been propagated by oncology researchers and refers to symptoms that co-occur in response to a disease [39, 40]. It recognizes that many symptoms rarely occur in isolation and may share the same mechanism(s). For example, fatigue, depression and pain have previously been grouped into a ‘somatic symptom’ cluster. Their co-existence may support a central aetiology and/or identify patients at risk of poor long-term QoL outcomes. Equally, in certain scenarios, clustering may help explain symptom absence. For example, a greater prevalence of mental distress would seem understandable following exposure to chronic pain. Such associations are widely documented in many rheumatic diseases characterized by musculoskeletal pain [19, 41-43]. Pain, however, is not a key feature in AAV and this may go someway to explain the observed normal levels of mental health in this cohort. Ultimately, the mechanisms of fatigue in this patient group are likely to be a mixture of both disease and psycho-social factors, the balance of which may alter depending on the disease’s phase.

In conclusion, patients with AAV report suboptimal QoL. During clinical assessment, the health care team should take time to recognize and evaluate fatigue, a symptom that we have identified to be a principal contributor to impaired health status. Future investigation should attempt to define and quantify the specific mechanisms of fatigue in this patient group. A better understanding of the relationships involved will aid the development of optimal management plans for a new generation of AAV patients where long-term survival is considered the norm and issues related to QoL take precedence.

Rheumatology key messages

- Physical but not mental health determines impaired QoL in AAV.
- Fatigue is a common problem in AAV and a principal contributor to impaired QoL.

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References

1. Fauci AS, Haynes BF, Katz P, Wolff SM. Wegener's granulomatosis: prospective clinical and therapeutic experience with 85 patients for 21 years. Ann Intern Med. 1983; 98:76–85. [PubMed: 6336643]
2. Hoffman GS, Kerr GS, Leavitt RY, et al. Wegener granulomatosis: an analysis of 158 patients. Ann Intern Med. 1992; 116:488–98. [PubMed: 1739240]
3. Booth A, Almond M, Burns A, et al. Outcome of ANCA-associated renal vasculitis: a 5-year retrospective study. Am J Kidney Dis. 2003; 41:776–84. [PubMed: 12666064]
4. Brijker F, Magee CC, Tervaert JW, O'Neill S, Walshe JJ. Outcome analysis of patients with vasculitis associated with antineutrophil cytoplasmic antibodies. Clin Nephrol. 1999; 52:344–51. [PubMed: 10604641]
5. Dobkin PL, Da Costa D, Dritsa M, et al. Quality of life in systemic lupus erythematosus patients during more and less active disease states: differential contributors to mental and physical health. Arthritis Care Res. 1999; 12:401–10. [PubMed: 11081011]
6. Koutantji M, Pearce S, Harrold E. Psychological aspects of vasculitis. Rheumatology. 2000; 39:1173–9. [PubMed: 11085794]
7. Pollard LC, Choy EH, Gonzalez J, Khoshaba B, Scott DL. Fatigue in rheumatoid arthritis reflects pain, not disease activity. Rheumatology. 2006; 45:885–9. [PubMed: 16449363]
8. Suurmeijer TP, Reuvekamp MF, Aldenkamp BP. Social functioning, psychological functioning, and quality of life in epilepsy. Epilepsia. 2001; 42:1160–8. [PubMed: 11580765]
9. Reinhold-Keller E, Herlyn K, Wagner-Bastmeyer R, et al. Effect of Wegener's granulomatosis on work disability, need for medical care, and quality of life in patients younger than 40 years at diagnosis. Arthritis Rheum. 2002; 47:320–5. [PubMed: 12115163]
10. Koutantji M, Harrold E, Lane S, Pearce S, Watts R, Scott DGI. Investigation of quality of life, mood, pain, disability and disease status in primary systemic vasculitis. Arthritis Rheum. 2003; 49:826–37. [PubMed: 14673970]
11. Hoffman GS, Drucker Y, Cotch MF, Locker GA, Easley K, Kwoh K. Wegener's granulomatosis: patient-reported effects of disease on health, function and income. Arthritis Rheum. 1998; 41:2257–62. [PubMed: 9870883]
12. Carpenter D, Thorpe C, Lewis M, Devellis R, Hogan S. Health-related quality of life for patients with vasculitis and their spouses. Arthritis Rheum. 2009; 61:259–65. [PubMed: 19177525]
13. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. conceptual framework and item selection. Med Care. 1992; 30:473–83. [PubMed: 1593914]
14. Leavitt RY, Fauci AS, Bloch DA, et al. The American College of Rheumatology 1990 criteria for the classification of Wegener's granulomatosis. Arthritis Rheum. 1990; 33:1101–7. [PubMed: 2202308]
15. Masi AT, Hunder GG, Lie JT, et al. The American College of Rheumatology 1990 criteria for the classification of Churg-Strauss syndrome (allergic granulomatosis and angiitis). Arthritis Rheum. 1990; 33:1094–100. [PubMed: 2202307]
16. Jennette JC, Falk RJ, Andrassy K, et al. Nomenclature of systemic vasculitides. Proposal of an International Consensus Conference. Arthritis Rheum. 1994; 37:187–92. [PubMed: 8129773]
17. Register General For Scotland. 15 September 2009, date last accessedPopulation estimates and projections for Grampian. http://www.hinetgrampian.org/hinet/file/1424/PopulationEstimatesGrampianTables.pdf
18. Krug HE, Woods SR, Mahowald ML. The importance of identifying depression in patients with rheumatoid arthritis: evaluation of the beck depression inventory. J Clin Rheum. 1997; 3:248–57.
19. Omdal R, Husby G, Mellgren SI. Mental health status in systemic lupus erythematosus. Scand J Rheumatol. 1995; 24:142–5. [PubMed: 7777824]
20. Ware, JE.; Kosinski, M.; Dewey, JE.; Gandek, BG. A manual for users of the SF-8 Health™ Survey. 3rd edition. QualityMetric; Lincoln, RI: 2001.
21. Chalder T, Berelowitz G, Pawlikowska T, et al. Development of a fatigue scale. J Psychosom Res. 1993; 37:147–53. [PubMed: 8463991]

22. Halder SLS, McBeth J, Silman A, Thompson D, Macfarlane G. Psychosocial risk factors for the onset of abdominal pain. Results from a large prospective population-based study. Int J Epidemiol. 2002; 31:1219–25. [PubMed: 12540725]
23. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry. 1961; 4:561–71. [PubMed: 13688369]
24. Michalak E, Murray G, Wilkinson C, et al. Estimating depression prevalence from the beck depression inventory: is season of administration a moderator? Psychiatry Res. 2004; 129:99–106. [PubMed: 15572189]
25. Goldberg, D. General Health Questionnaire (GHQ-12). Nfer-Nelson; Windsor: 1992.
26. Wolfe F, Smythe HA, Yunus MB, et al. 1990 classification criteria of fibromyalgia from the American College of Rheumatology. Arthritis Rheum. 1990; 33:160–72. [PubMed: 2306288]
27. Mukhtyar C, Lee R, Brown D, et al. Modification and validation of the Birmingham Vasculitis Activity Score (version 3). Ann Rheum Dis. 2009; 68:1827–32. [PubMed: 19054820]
28. Exley AR, Bacon PA, Luqmani RA, et al. Development and initial validation of the vasculitis damage index for the standardized clinical assessment of damage in the systemic vasculitides. Arthritis Rheum. 1997; 40:371–80. [PubMed: 9041949]
29. Pevalin DJ. Multiple applications of the GHQ-12 in a general population sample: an investigation of long-term retest effects. Soc Psychiatry Psychiatr Epidemiol. 2000; 35:508–12. [PubMed: 11197926]
30. Croft P, Rigby AS, Boswell R, Schollum J, Silman A. The prevalence of chronic widespread pain in the general population. J Rheumatol. 1993; 20:710–3. [PubMed: 8496870]
31. Anonymous, European community study group on clinical trials in systemic vasculitis ECSYSVASTRIAL. European therapeutic trials in ANCA-associated systemic vasculitis: disease scoring, consensus regimens and proposed clinical trials. Clin Exp Immunol. 1995; 101(Suppl. 1): 29.
32. Da Costa D, Dritsa M, Bernatsky S, et al. Dimensions of fatigue in systemic lupus erythematosus: relationship to disease status and behavioral and psychosocial factors. J Rheumatol. 2006; 33:1282–8. [PubMed: 16758508]
33. Brijker F, Magee CC, Tervaert JW, O'Neill S, Walshe JJ. Outcome analysis of patients with vasculitis associated with antineutrophil cytoplasmic antibodies. Clin Nephrol. 1999; 52:344–51. [PubMed: 10604641]
34. Chen M, Yu F, Zhang Y, Zou W, Zhao M, Wang H. Characteristics of Chinese patients with Wegener's granulomatosis with anti-myeloperoxidase autoantibodies. Kidney Int. 2005; 68:2225–9. [PubMed: 16221222]
35. Mukhtyar C, Guillevin L, Cid MC, et al. EULAR recommendations for the management of primary small and medium vessel vasculitis. Ann Rheum Dis. 2009; 68:310–7. [PubMed: 18413444]
36. Ong LM, de Haes JC, Hoos AM, Lammes FB. Doctor-patient communication: a review of the literature. Soc Sci Med. 1995; 40:903–18. [PubMed: 7792630]
37. Fifield J, Tennen H, Reisine S, McQuillan J. Depression and the long-term risk of pain, fatigue, and disability in patients with rheumatoid arthritis. Arthritis Rheum. 1998; 41:1851–7. [PubMed: 9778227]
38. Gaston-Johansson F, Fall-Dickson JM, Bakos AB, Kennedy MJ. Fatigue, pain, and depression in pre-autotransplant breast cancer patients. Cancer Pract. 1999; 7:240–7. [PubMed: 10687593]
39. Cleeland C. Symptom burden: multiple symptoms and their impact as patient-reported outcomes. J Natl Cancer Inst Monogr. 2007; 37:16–21. [PubMed: 17951226]
40. Miaskowski C, Aouizerat B, Dodd M, Cooper B. Conceptual issues in symptom clusters research and their implications for quality-of-life assessment in patients with cancer. J Natl Cancer Inst Monogr. 2007; 37:39–46. [PubMed: 17951230]
41. Dickens C, McGowan L, Clark-Carter D, Creed F. Depression in rheumatoid arthritis: a systematic review of the literature with meta-analysis. Psychosom Med. 2002; 64:52–60. [PubMed: 11818586]
42. Frank R, Beck N, Parker J, et al. Depression in rheumatoid arthritis. J Rheum. 1988; 15:920–5. [PubMed: 3418641]

43. Smedstad LM, Vaglum P, Kvien TK, Moum T. The relationship between self-reported pain and sociodemographic variables, anxiety and depressive symptoms in rheumatoid arthritis. J Rheumatol. 1995; 22:514–20. [PubMed: 7783072]

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Table 1

Clinical features of AAV in Grampian, Scotland

AAV	*n* (%)	Age, mean, years	Male, *n* (%)	Disease duration, IQR, years	ANCA$^+$ ever, *n* (%)	VDI, mean
WG	45 (62)	58.3	24 (54)	7.7 (2.0–11.0)	43 (96)	1.8
MPA	12 (17)	64.2	7 (58)	3.5 (0.5–6.0)	12 (100)	1.3
CSS	15 (21)	55.5	11 (73)	4.5 (1.2–6.0)	8 (53)	1.5
Total	72	58.7	42 (58)	6.3 (1.1–9.0)	63 (88)	1.7

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Table 2

The comparison of pain, fatigue and mood between cases and controls[a]

Exposure	Cases, *n* (%)	Controls, *n* (%)	OR (95% CI)[b]
CFS (fatigue)			
Absent	22 (31)	390 (51)	1
Mild	22 (31)	174 (23)	2.1 (1.1, 4.0)
Moderate/severe	27 (38)	199 (26)	2.5 (1.4, 4.6)
BDI (depression)			
Non-significant mood disturbance	56 (85)	576 (79)	1
Significant mood disturbance	10 (15)	151 (21)	0.8 (0.4, 1.5)
GHQ (psychological distress)			
Low	63 (91)	722 (94)	1
High	6 (8)	49 (6)	1.7 (0.7, 4.3)
CWP (chronic pain)			
Absent	60 (86)	693 (89)	1
Present	10 (14)	88 (11)	1.2 (0.6, 2.6)

[a] Number of cases and controls do not total 72 and 781, respectively, because of exclusion of subjects with missing or incomplete data;

[b] adjusted for age and sex.

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Table 3

Associations between psycho-social factors and physical health severity amongst cases[a]

Disease factor	SF-8 PCS (tertiles), *n* (%)			*P*-value*
	Low	Medium	High	
BDI (depression)				**0.021**
Non-significant mood disturbance	23 (43)	21 (39)	10 (19)	
Significant mood disturbance	9 (90)	1 (10)	0 (0)	
GHQ (psychological distress)				0.06
Low	29 (46)	23 (37)	11 (17)	
High	6 (100)	0 (0)	0 (0)	
CFS (fatigue)				<**0.0001**
Absent	3 (14)	12 (55)	7 (32)	
Mild	9 (45)	8 (40)	3 (15)	
Moderate/severe	23 (85)	4 (15)	0 (0)	
CWP (chronic pain)				0.058
Absent	26 (43)	23 (38)	11 (18)	
Present	8 (89)	1 (11)	0 (0)	

Results in bold indicate statistically significant results at $P < 0.05$.

[a]Number of subjects does not total 72 because of exclusion of subjects with missing or incomplete data;

*Fisher's exact test.

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Table 4

Associations between disease factors and fatigue severity[a]

Disease factor	CFS, *n* (%)			*P*-value*
	Absent	Mild	Moderate/severe	
Disease				0.05
WG	13 (30)	15 (34)	16 (36)	
MPA	1 (8)	6 (50)	5 (42)	
CSS	8 (53)	1 (7)	6 (40)	
ANCA (ever)				0.74
Positive	18 (29)	20 (32)	24 (39)	
Negative	4 (44)	2 (22)	3 (33)	
Disease activity (BVAS3)				0.75
Inactive	19 (33)	17 (30)	21 (37)	
Active	3 (21)	5 (36)	6 (43)	
Disease damage (VDI)				0.98
Absent	6 (35)	5 (29)	6 (35)	
Mild/moderate	11 (28)	13 (33)	15 (39)	
Severe	5 (33)	4 (27)	6 (40)	
Disease duration, years				0.72
<1	3 (23)	6 (35)	8 (47)	
1–10	14 (36)	12 (31)	13 (33)	
>10	5 (33)	4 (37)	6 (40)	
Cyclophosphamide exposure, g				0.26
0	8 (53)	3 (20)	4 (37)	
≤15	9 (23)	15 (38)	16 (40)	
>15	6 (33)	4 (22)	8 (44)	
Renal involvement (ever)				**0.012**
No	14 (45)	4 (13)	13 (42)	
Yes	9 (21)	18 (43)	15 (36)	
Current eGFR				0.83
Normal	11 (29)	11 (29)	16 (42)	

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Disease factor	CFS, *n* (%)			*P*-value*
	Absent	Mild	Moderate/severe	
Abnormal	11 (34)	10 (31)	11 (34)	
CRP				0.19
Normal, ≤10 mg/l	18 (32)	20 (36)	18 (32)	
Abnormal, >10 mg/l	4 (29)	2 (14)	8 (57)	
Anaemia[b]				0.37
No	20 (35)	17 (30)	20 (35)	
Yes	2 (14)	5 (36)	7 (50)	

Results in bold indicate statistically significant results at $P < 0.05$.

[a]Number of subjects does not total 72 because of exclusion of subjects with missing or incomplete data;

[b]Haemoglobin <120 g/dl in females and 140 g/dl in males;

*Fisher's exact test.

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Table 5

Associations between psycho-social factors and fatigue severity[a]

Disease factor	CFS, *n* (%)			*P*-value*
	Absent	Mild	Moderate/severe	
BDI (depression)				**<0.0001**
Non-significant mood disturbance	21 (40)	19 (36)	13 (25)	
Significant mood disturbance	0 (0)	1 (9)	10 (91)	
GHQ (psychological distress)				0.056
Low	22 (34)	20 (31)	22 (34)	
High	0 (0)	1 (17)	5 (83)	
CWP (chronic pain)				**0.036**
Absent	22 (34)	19 (31)	20 (33)	
Present	0 (0)	3 (30)	7 (70)	

Results in bold indicate statistically significant results at $P < 0.05$.

[a]Number of subjects does not total 72 because of exclusion of subjects with missing or incomplete data;

*Fisher's exact test.