Concise report

Markers for work disability in anti-neutrophil cytoplasmic antibody-associated vasculitis

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Abstract

Objectives. ANCA-associated vasculitis (AAV) commonly affects those of working age. Since survival rates have been transformed by immunotherapeutics, the measurement of other outcomes has become increasingly relevant. Work disability is an important outcome for both patient and society that has yet to be fully evaluated in AAV. We aimed to assess employment status in AAV patients and identify putative predictors of their work disability.

Methods. A cross-sectional study was undertaken. AAV cases were recruited according to consecutive clinic attendance. Subjects completed a questionnaire that determined employment status and other psychosocial measures. Clinical factors were concurrently recorded by the attending physician. From the data of those subjects of working age, a multivariable model was developed using forward stepwise logistic regression to identify the independent associations of work disability, defined by those subjects reporting unemployment secondary to ill-health. Results are expressed as odds ratios (ORs) and 95% CIs.

Results. Of the 410 participants (84.4% response rate), 149 (36.7%) were employed, 197 (48.6%) retired and 54 (13.3%) unemployed secondary to ill health. Of those of working age, 26.0% were considered work disabled. Fatigue (OR 7.1, 95% CI 1.5, 33.1), depression (OR 4.4, 95% CI 1.8, 10.8), severe disease damage [Vasculitis Damage Index (VDI) > 4 (OR 3.9, 95% CI 1.01, 14.7)] and being overweight (OR 3.4, 95% CI 1.3, 8.9) were independently associated with their unemployment.

Conclusion. A quarter of working-age AAV subjects reported unemployment as a result of ill health and are characterized by high levels of fatigue, depression, disease damage and being overweight. These potentially modifiable factors may inform future multidisciplinary interventions aimed at alleviating work disability.

Key words: ANCA-associated vasculitis, work disability, fatigue.

Introduction

The multisystem autoimmune diseases of granulomatosis with polyangiitis (GPA, Wegener’s), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA) are collectively referred to as ANCA-associated vasculitis (AAV). In the recent past they were considered acute illnesses invariably associated with high rates of mortality. However, the application of well-tested immunotherapeutics have transformed their course such that they are now considered chronic diseases. Unfortunately, cure remains elusive and relapse rates are high despite maintenance therapies, which in themselves are associated with high rates of toxicity. As a
consequence, other outcomes such as morbidity [1] and quality of life [2] remain poor.

It is common for AAV to begin in those of working age and so it would not be surprising if work disability was one of the major consequences of illness. As with other chronic diseases, the impact of work disability on the individual may be sizeable due to lost income, reduced self-esteem and difficult shifts in social roles. Moreover, the broader societal economic costs are also well documented [3].

Studies of GPA cohorts have reported significant work disability of between 27% and 31% in patients of working age [4, 5]; however, these studies were single centre and small (each n = 60). Even less data have been reported regarding the predictors of work disability in this population. In other fields, such data have informed the development of multidisciplinary interventions with a view to alleviating this burden [6]. This study aimed to quantify work disability among a large cohort of AAV patients as well as identify potentially modifiable factors associated with this important outcome.

Methods

Information on employment status was collected as part of a multicentre observational study in the UK examining the health status of AAV patients, the methods of which have been reported elsewhere [2]. In brief, adult subjects fulfilling the European Medicines Agency classification algorithm for AAV were approached by rheumatologists and nephrologists from 10 hospital-based UK sites according to consecutive clinic attendance. This study received approval from the North of Scotland Ethics Committee (reference 09/S0801/83) and written informed consent was obtained from all participants.

Willing participants completed a questionnaire comprising self-report demographic information and a number of validated psychosocial measures including (i) the Hospital Anxiety and Depression Scale, (ii) the Jenkin’s Sleep Estimation Scale, (iii) the ACR definition of chronic widespread pain, (iv) the brief COPE measure of coping and (v) the Chalder Fatigue Scale. Significant work disability was informed by closed self-report questions on employment status and, for this study, was defined as not working due to ill health or disability. Subjects were considered to be of working age if they were not retired.

Concurrently, clinical information was recorded and included an assessment of disease activity (BVAS 3) and damage [Vasculitis Damage Index (VDI)] in addition to pre-diagnosis co-morbidity (Charlson Index), diagnostic status, history of system involvement, overweight [World Health Organization (WHO) definition, BMI > 25 kg/m²], therapy, ANCA status (past/present), estimated glomerular filtration rate (eGFR), haemoglobin, lymphocytes, albumin and CRP, disease duration and immunosuppressant exposure. For the purposes of analysis, and as reported previously, variables were categorized using established cut-offs where available or dichotomized according to the general population mean [2].

Results

Subject characteristics

Of the 486 subjects approached, 410 (84.4%) participated and employment data were available for 405 (88.8%). In total, 149 (36.7%) were employed (86 full time, 49 part time, 10 house persons, 4 students), 197 were retired (48.6%), 5 (1.2%) were unemployed—unrelated to health—and 54 (13.3%) were not working secondary to ill health or disability. After excluding retired subjects, 208 subjects remained, of whom 26.0% were considered significantly work disabled.

This working age sample was generally mature [mean age 51.1 years (s.d. 12.3)] and evenly split by gender (52.4% female). The majority (85.6%) were ANCA positive during the course of their disease, with 144 (69.9%) classified as GPA, 40 (19.4%) MPA and 22 (10.7%) EGPA. At the time of assessment, only 20.6% were considered to have active disease (BVAS > 0) and overall disease damage was moderate (median VDI 2 [interquartile range (IQR) 1–4]).

Factors associated with work disability

Univariable analysis identified a number of potentially modifiable factors. Psychosocial factors most strongly associated with work disability were fatigue, pain, anxiety, depression and sleep disturbances (P < 0.001). In terms of coping mechanisms, behavioural disengagement (OR 2.9, 95% CI 1.5, 5.6) and acceptance (OR 2.0, 95% CI 1.1, 2.8) were also individually associated. Clinical factors, i.e. disease activity, therapies, disease subtype and ANCA status, did not confer a greater risk of work disability, although raised CRP (OR 2.5, 95% CI 1.2, 4.9), being overweight (OR 2.1, 95% CI 1.1, 4.3) and severe disease damage (VDI > 4) (OR 4.7, 95% CI 1.2, 18.7) did.

In multivariable analysis (Table 1), fatigue (OR 7.1, 95% CI 1.5, 33.1), depression (OR 4.4, 95% CI 1.8, 10.8), severe disease damage (OR 3.9, 95% CI 1.01, 14.7) and

Statistical analysis

First, the population’s employment status was characterized and retired subjects were excluded from further analysis. All patients of working age were characterized by applying simple descriptive statistics and univariable associations of work disability were tested with each candidate psychosocial and clinical determinant using logistic regression. Those factors identified to be at least moderately associated (P < 0.2) were then offered to a forward stepwise multivariable logistic regression model. All variables significant at P < 0.1 were retained and those with P > 0.15 were excluded. The retained variables were then resubmitted to a standard logistic regression in order to diminish the consequences of missing data on the precision of the effect sizes [expressed as odds ratios (ORs) and 95% CIs]. Finally, the importance of each retained factor on a population level was quantified using population attributable risks (PARs). All analyses were conducted using STATA version 12.1 (StataCorp, College Station, TX, USA).
being overweight (OR 3.4, 95% CI 1.3, 8.9) were all retained within the final model. Positioning these independent associations according to PARs, fatigue ranked as the primary association of significant work disability (72.9%), followed by being overweight (39.3%), depression (29.5%) and severe disease damage (9.0%).

**Discussion**

Despite recent advances in therapy, more than one quarter of working-age patients with AAV report unemployment secondary to ill health. While disease factors, such as damage, certainly contribute to this poor outcome, it appears that fatigue, high BMI and depression may be more influential risk factors.

A number of methodological issues should be considered in the interpretation of these findings. First, the study is cross-sectional in design, so causal inferences cannot be made with certainty. This is especially applicable to the factors of fatigue, BMI and depression, which are most likely both causes and consequences of work disability. However, even if these were to be entirely consequential factors, their identification and modification would still be important in managing this outcome because diminution of these factors may allow reintroduction to work. Second, the study fails to evaluate other important dimensions of work disability. Even if subjects remain employed, they may still be constrained by their illness. For example, their working hours and career progression may be limited, with subsequent impact upon income and pension contributions. In addition, from the employer’s perspective, issues of absenteeism are of clear importance. Third, the study did not capture potentially important predictors such as education, so residual confounding may be a problem.

The prevalence of significant work disability reported here matches previous studies examining similar populations [4, 5]. Nevertheless, direct comparisons are limited by differing definitions. For the same reason, and because of significant demographic differences, it is difficult to contextualize these results with other chronic diseases, although comparable work disability rates are observed in RA (13–67% [7]), AS (13–31% [8, 9]) and SLE (20–40% [10]) cohorts.

Only Reinhold-Keller et al. [4] have previously sought to identify associations of work disability in an AAV population. In their study, females were more likely to be unemployed, but otherwise no clinically significant associations were reported. This likely reflects their small sample size and consequent underpowered analysis. In this current, much larger study, a positive individual association between female gender and work disability (OR 2.0, 95% CI 1.05, 3.8) was also observed, although this was not considered to be an independent association following multivariable analysis.

Of the independently associated factors identified in this study, only severe disease damage would be considered a traditional clinical factor. As a long-term marker of disease severity, it would be expected that those patients with the greatest problems would be less likely to maintain employment. This is mirrored in patients with SLE, another multisystem autoimmune disease, where cumulative organ damage is consistently identified as a predictor for work disability [11].

Increased BMI may be considered a clinical factor, augmented by standard AAV therapies such as corticosteroids, but it is also a recognized surrogate of socioeconomic class [12]. Thus the identified association in this study may be attributable to more than one mechanism. It is certainly evident from longitudinal studies of diseased and general populations that increased baseline BMI can predict longer-term work disability [13, 14].

The psychosocial symptoms of depression and fatigue appear to be very important determinants and/or consequences of work disability in AAV. Elsewhere, such variables are commonly considered as important and potentially modifiable in the context of work disability [9, 11], although they have not always been measured in studies looking to explain this outcome. Certainly poor mental health is now a public health priority because of its recognized impact on many outcomes, including work disability [15]. Qualitative studies have concluded that fatigue is the ‘main challenge’ to work ability in AS [9] and is ‘the aspect of inflammatory arthritis most limiting employment’ [16]. This message was reiterated by a recent UK RA patient group work survey where 80% of respondents cited fatigue as the main barrier to their remaining in employment [17].

Taken together, improved disease control remains a priority that the clinical and research community continue to target. In addition to optimizing traditional outcomes such

<table>
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<tr>
<th>Odds ratio</th>
<th>95% CI</th>
<th>PAR, %</th>
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<tbody>
<tr>
<td>Fatigue (CFS)</td>
<td>7.1</td>
<td>1.5</td>
</tr>
<tr>
<td>Overweight (BMI &gt; 25)</td>
<td>3.4</td>
<td>1.3</td>
</tr>
<tr>
<td>Depression (HADS)</td>
<td>4.4</td>
<td>1.8</td>
</tr>
<tr>
<td>Severe disease damage (VDI &gt; 4)</td>
<td>3.9</td>
<td>1.0</td>
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AAV: ANCA-associated vasculitis; PAR: population attributable risk; CFS: Chalder Fatigue Scale, dichotomized at the general population mean; HADS: Hospital Anxiety and Depression Scale; VDI: Vasculitis Damage Index.
as mortality and morbidity, it is likely to reduce work disability. That being said, greater gains in minimizing work disability may be achieved by employing multidisciplinary programmes targeting weight loss, fatigue and depression. These types of interventions are recommended and are being developed further in other rheumatic disorders [18] with an emphasis on earlier intervention [19].

This study is the largest ever to evaluate work disability in AAV and, despite some limitations, is an important first step to informing management of this key outcome. Future studies should seek to characterize early markers of work disability and use multidimensional measures with a view to developing a disease-specific intervention. In the interim, the apparent similarity in predictors from other chronic conditions supports the inclusion of AAV patients within existing multidisciplinary programmes or future studies that may have originally been developed for other disorders. Certainly such a generic approach is likely to be a more translatable option for most health care systems, where the reduction of work disability in patients with chronic disease has become increasingly important.

**References**