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The temporal stability and co-morbidity of prolonged fatigue: a longitudinal study in primary care

I. HICKIE,[1] A. KOSCHERA, D. HADZI-PAVLOVIC, B. BENNETT AND A. LLOYD

From the School of Psychiatry and Inflammation Research Unit, School of Pathology, University of New South Wales; Academic Department of Psychiatry, St George Hospital and Community Health Service; and Mood Disorders Unit, Prince Henry Hospital, Sydney, New South Wales, Australia

ABSTRACT

Background. Depression, anxiety and fatigue are among the most common symptoms presented in primary care. Whether such symptoms indicate discrete psychological syndromes or whether they result from a common vulnerability is not clear. This study examined longitudinally the patterns of co-morbidity between prolonged fatigue and other forms of psychological distress in patients attending general practitioners.

Methods. Adults attending primary care completed questionnaires designed to detect cases of prolonged fatigue and psychological distress at presentation and 12 months later.

Results. Of 652 patients, the prevalence rates of 'prolonged fatigue' alone, 'psychological distress' alone, 'prolonged fatigue + psychological distress' and 'no disorder' were 7%, 19%, 15% and 59% respectively at initial assessment. Of those patients with any prolonged fatigue syndrome initially, 58% still reported fatigue 12 months later (representing 13% of the total sample). Most importantly, the risk of developing prolonged fatigue was not increased in patients who initially had psychological distress (OR = 0·95; 95% CI 0·2–3·6), neither was the risk of developing psychological distress increased in patients who initially had prolonged fatigue (OR = 1·4; 95% CI 0·6–3·4).

Conclusions. This study indicates that prolonged fatigue is a persistent diagnosis over time. The longitudinal patterns of co-morbidity with psychological distress do not support an aetiological model that proposes a common vulnerability factor for these disorders. Psychiatric classification systems may be better served by treating prolonged fatigue and psychological distress as independent disorders.

INTRODUCTION

Prolonged fatigue states (PF), which are characterized by disabling fatigue, hypersomnia, musculoskeletal pain, headaches, neurocognitive symptoms and irritable mood (Hickie *et al.* 1990, 1995; Lloyd *et al.* 1990; Angst & Koch, 1991; Sharpe *et al.* 1991; Katon & Russo, 1992; Fukuda *et al.* 1994), are reported by 10–25% of patients attending primary care (Kroenke *et al.* 1988; Bates *et al.* 1993; Katon & Walker, 1993; Pawlikowska *et al.* 1994; Hickie *et al.* 1996). Duration criteria for 'caseness' vary from 2 weeks for PF (Hickie *et al.* 1996, 1997), to 3 months for the ICD-10 diagnosis of neurasthenia (WHO, 1992) and 6 months for the specific diagnosis of chronic fatigue syndrome (CFS; Fukuda *et al.* 1994).

The importance of PF has been well demonstrated by the WHO multi-centre study of primary care (Sartorius *et al.* 1993; Üstün *et al.* 1995). In that study, neurasthenia was the third most common psychiatric disorder with a prevalence ranging from 1·5–10·5%. Though the impact of 'neurasthenia/prolonged fatigue' syndromes on health care utilization is clear (Gureje *et al.* 1997; Kroenke *et al.* 1997; Hickie *et al.* 1998), as a diagnostic category it has had a chequered history (Wessely, 1990, 1994; Shorter, 1992). This has been a consequence largley of syndromal overlap with major de-

[1] Address for correspondence: Professor Ian Hickie, Academic Department of Psychiatry, St George Hospital and Community Health Service, 7 Chapel Street, Kogarah, NSW 2217, Australia.

pression (Manu *et al*. 1989; Wessely & Powell, 1989; Goldberg & Bridges, 1991; Goldberg, 1996; Kessler *et al*. 1996; Wessely *et al*. 1996) and limited other longitudinal, family, neurobiological or treatment data to support its validity. This study used 12-month longitudinal data in primary care to examine the temporal pattern of co-morbidity between PF and the other common forms (anxiety/depression) of psychological distress (PSYCH).

METHOD

Use of longitudinal data to assess aetiological mechanisms

When two disorders are truly co-morbid (as appears to be the case with PF and PSYCH) either one disorder is a cause of the other or both share a common risk factor(s). While the merits of these competing explanations cannot be determined in cross-sectional studies, they can be tested in longitudinal and family data sets. If the relationship is causal, then patients who originally had disorder 'A', will have an increased rate at later examinations not only of 'A' (and of the combination of the two syndromes 'A + B'), but also an increased rate of 'B'. Furthermore, we do not expect to find an increased rate of 'A' alone in patients who initially had the pure form of 'B'. By contrast, if the two disorders are due to a common risk factor, patients who present with pure forms of 'A' or 'B' initially will both have increased rates of 'B' and 'A' respectively at later examinations.

Recruitment of subjects

Consecutive adult attenders at selected family practices were asked to participate in a longitudinal study of medical and psychological symptoms (Hickie *et al*. 1996). The initial sample of 1593 patients was first interviewed in 1993/4 and was predominantly female (75%), middle-aged (mean = 37·8 years, range = 18 to 89 years) and of Anglo–Celtic background (88%). The subjects of this report are the 652 subjects who completed both the initial and follow-up questionnaires (approximately 12 months later).

Evaluation of psychological distress

The 30-item General Health Questionnaire (GHQ) has been used extensively in community and general medical settings to detect cases of psychological disorder (Goldberg *et al*. 1988). A score of five or more symptoms is used to define patients as 'psychological' cases (Goldberg & Williams, 1988, p. 22). The factor structure of the GHQ-30 suggests that it is underpinned essentially by the two highly-correlated constructs of anxiety and depression (Goldberg, 1996).

Evaluation of fatigue

The Schedule of Fatigue and Anergia (SOFA) – Community Version is a 10-item self-report scale developed to identify cases of PF in community and general practice settings (SOFA/GP; Hickie *et al*. 1996). The initial version of the scale (SOFA-CFS) was developed to identify cases of chronic fatigue syndrome in patients attending specialist medical clinics (Lloyd *et al*. 1990). To adapt the scale for use in primary care, anchor points were simplified and the period referred to was shortened to the 'last few weeks'. An individual symptom is scored as positive if the subject has experienced it a 'good part of the time' or 'most of the time'. This scale (SOFA/GP) was then validated against appropriate latent class solutions in 1593 general practice attenders (Hickie *et al*. 1996). A cut-off score of $\geqslant 3$ for identifying cases of prolonged fatigue was preferred as it excludes all 'non-fatigued' cases (sensitivity = 81%, specificity = 100%). Of the fatigue cases identified by the SOFA in primary care, two-thirds will also be identifed as psychological cases by the GHQ-30 (Hickie *et al*. 1996). Of 275 patients with PF (alone or co-morbid with PSYCH) 4% had a duration of less than 4 weeks and 96% of patients had had symptoms between 4 weeks and 25 years (median 2·2 years). Patients with PF have levels of disability comparable with patients with ICD-10 defined neurasthenia and greater than those with major depression (Koschera *et al*. 1998).

Factor analysis of the SOFA and GHQ (Koschera *et al*. 1999) demonstrated a clear separation between fatigue-related items and those recording anxiety or depression in primary care. Essentially, GHQ-items combined into a single construct (Cronach's $\alpha = 0{\cdot}95$), while a second factor consisted of all SOFA items (Cronbach's $\alpha = 0{\cdot}81$). Similar separation of SOFA and GHQ items have been demonstrated in a community-based sample of 2703 Australian

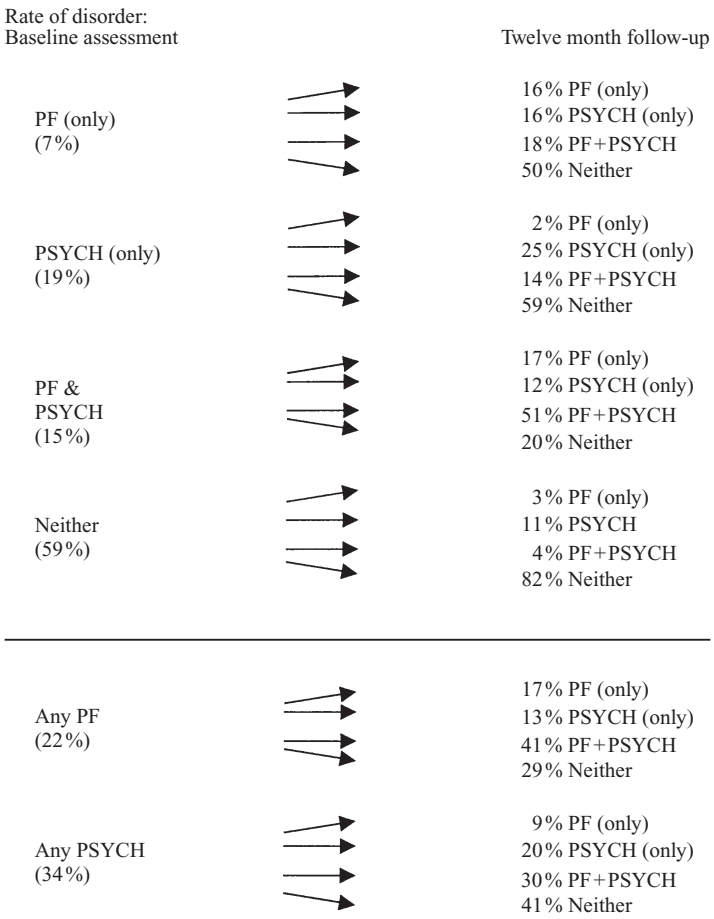

FIG. 1. Twelve month follow-up of prolonged fatigue syndromes, groups with and without psychological co-morbidity ($N = 652$). PF, only (SOFA, cut-off > 2 and GHQ, cut-off < 5); PSYCH only (GHQ-30, cut-off > 4 and SOFA, cut-off < 3).

twins (Kirk *et al.* 1999) and or original clinic-based sample of CFS (Hickie *et al.* 1995).

Statistical analyses

Data were analysed using the Statistical Package for Social Sciences (SPSS, 1998). Logistic regression analyses were employed to achieve adjusted (for age, sex and total years of education) odds ratios (or with 95% confidence intervals, CI) for each of the associations examined longitudinally. Our aetiological concept requires the comparison (ratio) of the odds of becoming a case of disorder (i.e. PF, PSYCH, PF+PSYCH) between the mutually exclusive morbid groups an the non-morbid group. The definitions for each group were as follows: 'PF' only includes 'pure' fatigue cases (SOFA > 2 and GHQ < 5); 'PSYCH' only includes 'pure' psychological distress cases (GHQ > 4 and SOFA < 3); 'PF+PSYCH' includes co-morbid cases (SOFA > 2 and GHQ > 4); and 'Neither' includes all non-symptomatic cases (SOFA < 3 and GHQ < 5).

RESULTS

Sample characteristics

Of the original 1593 patients, 789 returned the follow-up questionnaires (approximately 12 months later). Of these, 652 patients had complete SOFA and GHQ questionnaires at both assessments. 'Non-responders' were contacted twice in writing. Of the remaining 804 non-responders 162 had changed address, 2 had

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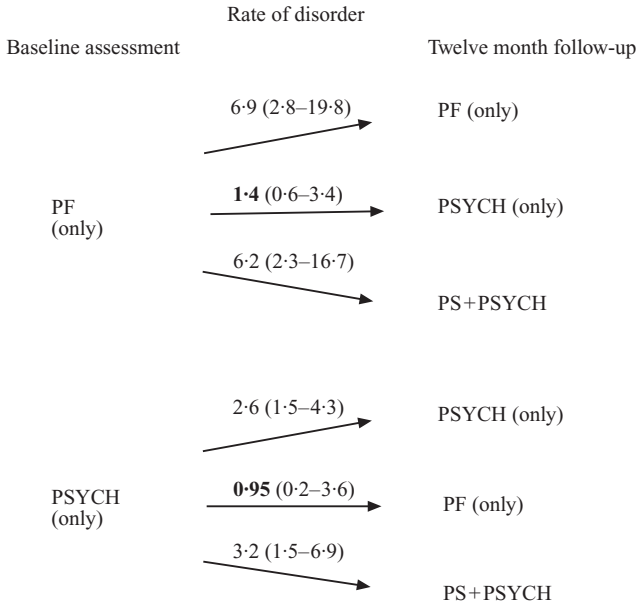

FIG. 2. Results of logistic regression (adjusted* odds ratios). PF only (SOFA, cut-off > 2 and GHQ, cut-off < 5); PSYCH only (GHQ-30, cut-off > 4 and SOFA, cut-off < 3). *Odds ratios adjusted for age, sex and total years of education.

died, 1 was overseas and 5 returned blank questionnaires. Compared with the original sample (Hickie *et al.* 1996) this cohort was also predominantly female (75% *v.* 78%, $\chi^2 = 3{\cdot}0$, NS), of Anglo–Celtic background (88% *v.* 88%, $\chi^2 = 0{\cdot}06$, NS), but somewhat older (39·8 *v.* 37·8 years, $t = 2{\cdot}8$, $P < 0{\cdot}01$) in age. Most of the sociodemographic (sex (OR = 1·1), age (OR = 1·0), years of education (OR = 0·95), social status (OR = 1·0)), and psychological characteristics (SOFA-caseness: OR = 0·85, NS; GHQ-caseness: OR = 0·85, NS) of the subjects had no effect on the likelihood of returning the questionnaire. Patients with more children living at home did return questionnaires more often (OR = 1·3, $P = 0{\cdot}02$).

Pattern of diagnostic change over 12 months

The prevalence rates for the four subject groups (PF, PSYCH, PF + PSYCH, Neither) (see Fig. 1) in this study at initial assessment were no different to those recorded in the whole cohort (7%, 19%, 15%, 59% *v.* 7%, 19%, 18%, 56% respectively, $\chi^2 = 2{\cdot}6$, NS). The pattern of diagnostic change over 12 months is shown in Fig. 1. Although the incidence of any new disorder in initially asymptomatic persons was 18%, this group was four times more likely to develop PSYCH only than PF only (i.e. 11·5% *v.* 2·6%). The patients with co-morbid disorders ('PF + PSYCH') were the most likely to remain symptomatic longitudinally (81% still 'cases' after 12 months), compared with the PF only group (50% still 'cases', $\chi^2 = 13{\cdot}9$, df = 1, $P < 0{\cdot}001$) and the PSYCH only group (41% still 'cases'; $\chi^2 = 35{\cdot}1$, df = 1, $P < 0{\cdot}001$). The pure PF and PSYCH groups were not significantly different in terms of remission rates (50% *v.* 59%, $\chi^2 = 1{\cdot}01$, NS). Of those with any fatigue syndrome initially (PF ± PSYCH, $N = 142$), 71% were still symptomatic at 12 months, while 58% still reported prolonged fatigue. That is, 82 cases (13%) had PF (alone or co-morbid with PSYCH) at both time points.

Contrary to the predictions of the common vulnerability model (see Fig. 2), neither the PF group was at increased risk of developing PSYCH (OR, 1·4, 95% CI 0·6–3·4), nor was the PSYCH group at increased risk of developing PF (OR, 0·95, 95% CI 0·2–3·6). That is, over time, patients with either PF or PSYCH are at increased risk of reporting both the same state and the co-morbid PF + PSYCH syndrome, but not the other discrete disorder. However, the

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pattern of ORs, provides only weak support for the alternative 'causal' model, with PF only slightly increasing the risk to PSYCH over time. There is no indication that PSYCH is a risk factor for PF longitudinally.

Adjustment for instrumentation effects

As the clinical syndromes of PSYCH and PF overlap, some degree of 'co-morbidity' will occur simply as a consequence of instruments including similar items. We tested for possible distortions due to this effect by examining the change in ORs after removal of common symptom items. Importantly, there was no change in the overall patterns of ORs (for PF to PSYCH, adjusted OR = 1·39; 95% CI 0·5–3·8; and, for PSYCH to PF, adjusted OR = 1·2; 95% CI 0·2–6·0). As the comparisons described may be influenced by threshold effects for 'caseness', we compared the percentage of patients who were just 'subthreshold' and found that they were comparable (34% PSYCH cases in the PF group *versus* 33% PF cases in the PSYCH group). Similarly, if we increased the threshold to more closely resemble overt clinical syndromes (i.e. GHQ > 10 items), a similar pattern of ORs was again observed.

DISCUSSION

When followed longitudinally, 13% of patients presenting to general practice had fatigue syndromes (with or without concurrent psychological distress) persist for at least 12 months. The prospective risk analyses indicated that while PF and PSYCH commonly co-occur (odds ratio of 6·26; Hickie *et al.* 1996), it is unlikely that they represent clinical variants of a common underlying vulnerability. However, asymptomatic persons were unlikely to develop PF over the longitudinal phase (incidence of only 2·6% per year). Once patients had PF they preferentially maintained that profile either alone or in combination with later PSYCH. Half of the patients with pure PF are still symptomatic 12 months later, with a third still reporting fatigue syndromes.

By contrast, asymptomatic individuals were four times more likely to develop PSYCH (incidence of 11·5% incidence per year). Those with overt PSYCH also tended to maintain their form of disorder over time (alone or in combination with fatigue), with no evidence that they were more likely to develop PF alone. Those with PSYCH alone initially also had the highest rate of remission over 12 months (59%). The more severe co-morbid syndromes (PF + PSYCH) do not commonly develop in previously asymptomatic individuals (incidence of 4% per year), and they are the most likely to result in chronic symptoms (i.e. only 19% remission over 12 months).

PF appears to behave in a 'trait-like' fashion, being present at initial evaluation and stable in form longitudinally. By contrast, the common forms of PSYCH (anxiety/depression) appear to behave in a more 'state-like' pattern, occurring more frequently in individuals who were asymptomatic initially, and being more likely to remit over the course of the study. The results of our study support a previous longitudinal study of neurasthenia (Merikangas & Angst, 1994), which emphasized the temporal stability of that diagnosis. The results of this study, however, do not provide a clear reason for the observed co-morbidity between PF and PSYCH. The most apparent explanation is that genuinely overlapping phenotypes result in the apparent co-morbidity between the syndromes. Additionally, a weak causative effect may be operative with PF increasing the risk of developing PSYCH over time. This interpretation is consistent with the aetiological model we derived from twin studies (Hickie *et al.* 1999*a*, *b*). That is, while one genetic factor appeared to contribute to the development of both PF and PSYCH, a second genetic factor was specific for PF alone. Additionally, there appeared to be differential environmental factors contributing to the aetiology of PF and PSYCH.

Longitudinal studies of somatoform disorders tend to emphasize their persistence over time (Merikangas & Angst, 1994; Clark *et al.* 1995; Garcia-Campayo *et al.* 1996, 1997). These studies are also consistent with the notion of a vulnerability to somatic forms of distress being expressed at an early age, and being persistent over time. Somatoform disorders are not simply restricted to particular cultural groups, being prevalent in all populations studied (Kleinman, 1982; Swartz *et al.* 1986; Escobar, 1989; Fuhrer & Wessely, 1995; Samuels, 1995; Lobo *et al.* 1996; Minowa & Jiamo, 1996; Lawrie *et al.* 1997). In English-speaking countries tradition-

ally such disorders are either classified as part of the affective disorder spectrum or are omitted from epidemiological study (e.g. Kessler *et al*. 1994). Recognition of prolonged fatigue syndromes by specialist psychiatrists, however, may assist with the elucidation of aetiological mechanisms, the development of specific treatment interventions and the education of primary care practitioners (Hickie *et al*. 1997, 1998; Hickie, 1999).

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