Post-infective and chronic fatigue syndromes precipitated by viral and non-viral pathogens: prospective cohort study

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Abstract

Objective To delineate the risk factors, symptom patterns, and longitudinal course of prolonged illnesses after a variety of acute infections.
Design Prospective cohort study following patients from the time of acute infection with Epstein-Barr virus (glandular fever), *Coxiella burnetii* (Q fever), or Ross River virus (epidemic polyarthritis).
Setting The region surrounding the township of Dubbo in rural Australia, encompassing a 200 km geographical radius and 104 400 residents.
Participants 253 patients enrolled and followed at regular intervals over 12 months by self report, structured interview, and clinical assessment.
Outcome measures Detailed medical, psychiatric, and laboratory evaluations at six months to apply diagnostic criteria for chronic fatigue syndrome. Premorbid and intercurrent illness characteristics recorded to define risk factors for chronic fatigue syndrome. Self reported illness phenotypes compared between infective groups.
Results Prolonged illness characterised by disabling fatigue, musculoskeletal pain, neurocognitive difficulties, and mood disturbance was evident in 29 (12%) of 253 participants at six months, of whom 28 (11%) met the diagnostic criteria for chronic fatigue syndrome. This post-infective fatigue syndrome phenotype was stereotyped and occurred at a similar incidence after each infection. The syndrome was predicted largely by the severity of the acute illness rather than by demographic, psychological, or microbiological factors.
Conclusions A relatively uniform post-infective fatigue syndrome persists in a significant minority of patients for six months or more after clinical infection with several different viral and non-viral micro-organisms. Post-infective fatigue syndrome is a valid illness model for investigating one pathophysiological pathway to chronic fatigue syndrome.

Introduction

Although chronic fatigue syndrome is commonly reported to develop after an acute infective illness,[1 2] many case-control studies have failed to find consistent associations between chronic fatigue syndrome and infectious agents.[3–5] Nevertheless, post-infective fatigue states have been linked to a diverse spectrum of severe infections.[6–11] A comprehensive prospective study of clinical outcomes after other minor viral infections found no association with prolonged fatigue.[12] Population based prospective studies are needed to delineate the key symptoms and longitudinal course of the post-infective fatigue syndrome; to identify demographic, microbial, immunological, and psychological risk factors; and to determine whether disparate pathogens can precipitate chronic fatigue syndrome.

Methods

Study site and participants

The study is centred on the township of Dubbo in a rural region of southwestern Australia, with 104 400 residents. The 94 family practitioners and four diagnostic pathology laboratories that serve the region provided coded reports of all IgM positive serological results indicating acute Epstein-Barr virus, Q fever, or Ross River virus infections. Enrolled patients were aged 16 years or over. We excluded patients who had symptoms present for more than six weeks or reported pre-existing medical disorders or drug use likely to be associated with prolonged fatigue. After baseline assessment, we followed up participants at three weeks, six weeks, three months, and 12 months.

Interview schedules and self report instruments

At enrolment we recorded the clinical, medical, psychiatric, and family history.[13] At each visit, we recorded self report assessments of physical and psychological health on the somatic and psychological health report (SPHERE) questionnaire and collected a blood sample. An empirically derived subscale recording somatic symptoms (the SOMA) identified the key clinical features of prolonged fatigue states.[14] We also monitored mood state and functional impairment and risk factors for anxiety and depression.[15]

Case definitions

We classified participants as provisional cases of post-infective fatigue syndrome if their SOMA scores at all time points up to three months exceeded the threshold score of three (out of the possible 12).[14] We invited these cases, and control participants matched by age and sex who had recovered promptly from the same infection, at six months for a medical interview, examination by a physician and a psychiatrist, and laboratory investigation. The physician and psychiatrist diagnosed chronic fatigue syndrome at six months after the onset of symptoms.[16] We confirmed the initial serological diagnoses by testing acute and convalescent sera.[17 18]

Statistical analysis

To describe the clinical phenotypes and to assign values to the severity of each symptom domain, we did

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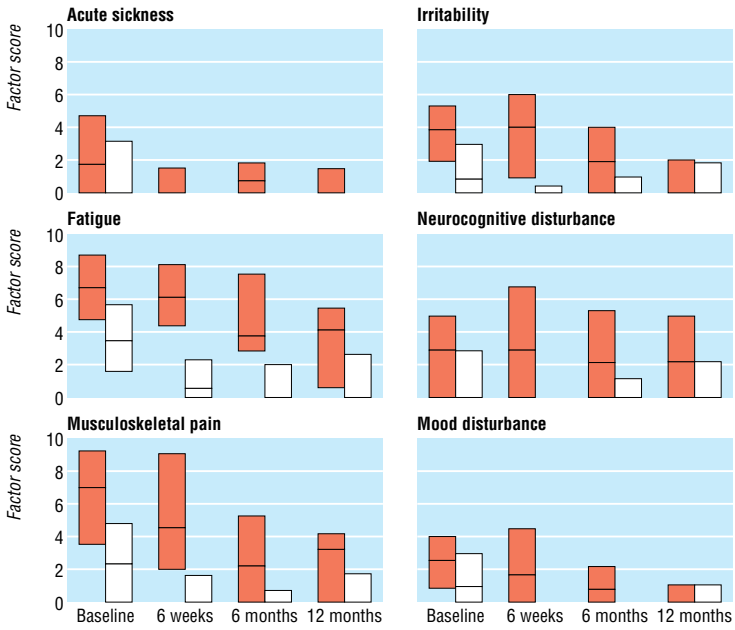

Pattern of change in individual symptom factors in participants with and without post-infective fatigue syndrome. Median (horizontal bar) and 25th/75th centiles (box extremities) of normalised factor scores for six symptom domains in confirmed cases of post-infective fatigue syndrome (orange boxes; n=28) and those who recovered more promptly (white boxes; n=225)

factor analysis of the somatic and psychological health report data from the 229 participants assessed four to eight weeks after the onset of acute illness. We assessed associations between symptom factor scores and disability measures. We assessed risk factors for caseness at each time point with regression analyses. To understand the patterns of resolution of the symptom domains, we calculated change in mean factor scores per unit of time and compared these data across the infective subgroups of participants.

Results

Demographic characteristics

We received laboratory notifications of 855 potential participants over a five year period. We contacted 430 of these, and 253 (59%) of them agreed to longitudinal assessments. The demographic and illness characteristics of these 253 participants were not significantly different from those who declined enrolment or those who agreed to be followed by self report only (n = 177).

The demographic features of the main cohort were consistent with the expected patterns of exposure to these pathogens.[19-21] In all three infection groups, approximately 25% of the original serological diagnoses were not confirmed by more stringent laboratory criteria applied to the longitudinally collected samples.

Factor analysis of symptoms

We derived six symptom domains. Two factors captured the physical and mental distress of acute illness ("acute sickness" and "irritability"). We identified four other factors—"fatigue," "musculoskeletal pain," "mood disturbance," and "neurocognitive disturbance." Scores on the fatigue factor showed the strongest and most consistent correlations with functional impairment: "days out of role in the past month" (baseline $r = 0.22$, $P < 0.01$; three months $r = 0.37$, $P < 0.01$; six months $r = 0.25$, $P < 0.01$).

Incidence of post-infective fatigue syndrome

The case rate for provisional post-infective fatigue syndrome was 35% (87/250) at six weeks, 27% (67/250) at three months, 12% (29/250) at six months, and 9% (22/250) at 12 months. No difference in these case rates existed between the initial infective agents. After one exclusion, the 28 cases of confirmed post-infective fatigue syndrome included 14 men and 14 women with a mean age of 37 (range 17-63) years. The rates of premorbid psychiatric diagnoses in the confirmed cases of post-infective fatigue syndrome and the matched control participants determined by formal psychiatric assessment at six months were comparable—21% versus 17%, difference = 5% (−18% to 27%)—as were the rates of intercurrent psychiatric disorders—21% versus 10%, difference = 11% (−10% to 33%).

Characteristics of post-infective fatigue syndrome

If the same pathophysiology underpinned all the clinical aspects of the acute infective illness and the post-infective fatigue state, we would predict that the individual symptom factors would resolve in a uniform manner across time. We found substantial variation. In the group of 28 confirmed cases of post-infective fatigue syndrome, the median score on the acute sickness factor rapidly dropped to zero, whereas the median scores for fatigue, musculoskeletal pain, and neurocognitive disturbance remained high (figure). For the group as a whole, acute sickness and irritability factors showed the greatest initial speed of resolution. By contrast, the fatigue and neurocognitive disturbance factors showed significant reductions only late in the course of the illness (see bmj.com). These differences were most significant in the period between baseline and three months, when planned contrasts showed that the key construct of fatigue differed from all other factors (all $P < 0.05$), with the exception of neurocognitive disturbance. When we compared the gradients between three and six months, significant differences no longer existed, suggesting that the symptom domains had become more uniform and stable over time.

These symptom patterns were also highly stereotyped, regardless of the original infective trigger. Planned contrasts of the patterns of resolution of the six symptom factors by infective subcohorts revealed that only musculoskeletal pain showed significant differences in prevalence and natural history in the early post-infective period (baseline to three months: Ross River virus *v* Epstein-Barr virus, $P < 0.001$; Ross River virus *v* not confirmed, $P < 0.01$; Ross River virus *v* Q fever, $P < 0.01$). The central symptom domains of post-infective fatigue syndrome did not differ between the infection groups at later time points.

Risk factors for acute sickness and post-infective fatigue syndrome

Demographic characteristics did not generally predict the scores on the six symptom factors recorded at baseline (see bmj.com). The predictors of post-infective fatigue syndrome over the 12 months after acute infection were largely limited to the factor scores that reflect

severity of acute illness (table). Premorbid and intercurrent psychiatric disorder did not show predictive power for post-infective fatigue syndrome at any time point.

Discussion

Prolonged fatigue states after infections are common and disabling and may persist for 12 months or longer. Although the acute phase of the infections varied, the post-infective fatigue illnesses shared a similar clinical phenotype. Severity of the acute illness, and not demographic or psychological factors, was predictive of post-infective fatigue syndrome.

Strengths and weaknesses

The application of the chronic fatigue syndrome case definition to designate incident cases in the post-infective setting described here provides strong evidence for a causative role of these infections in triggering chronic fatigue syndrome. The rate of post-infective fatigue syndrome detected at six months (11%) is comparable to those in previous cohort studies.[22-27] These findings confirm that chronic fatigue syndrome is a relatively common sequel of several different infections—now documented to include Epstein-Barr virus, Ross River virus, and Q fever—but not minor upper respiratory tract or gastrointestinal infections.[16] Nevertheless, the case rate for post-infective fatigue syndrome in the group who were followed from the serologically unconfirmed infections was similar, suggesting that severity of the acute illness rather than the specific pathogen may be the major determinant of post-infective fatigue syndrome.

Risk factors for post-infective fatigue syndrome (n=229). Values are standardised β coefficients from regression analysis

	3 months	6 months†	12 months
Demographic factors			
Age (years)	0.03	0.17	0.08
Sex (female=1)	0.04	–0.07	0.002
Education (secondary=1)	–0.07	0.12	0.03
Education (tertiary=1)	0.06	0.27	0.29
Baseline symptom factor scores			
Acute sickness	0.06	–0.11	–0.002
Irritability	0.24*	0.23	0.08
Musculoskeletal pain	0.27*	0.30*	0.13
Mood disturbance	0.23	0.07	–0.05
Neurocognitive disturbance	0.24*	0.20	0.14
Fatigue	0.50**	0.35**	0.27*
Psychological factors			
Premorbid psychiatric disorder (DSM-IV)	0.13	0.12	0.08
Intercurrent psychiatric disorder (DSM-IV)	–0.24	–0.05	–0.08
Neuroticism score	0.04	0.07	0.20
Locus of control score	–0.004	0.17	0.11
Microbiological factors			
EBV confirmed‡	0.13	0.05	–0.01
RRV confirmed‡	0.11	–0.05	0.07
Q fever confirmed‡	0.12	–0.15	–0.06

DSM-IV=*Diagnostic and Statistical Manual of Mental Disorders*, fourth edition; EBV=Epstein-Barr virus; RRV=Ross River virus.
*P<0.05.
**P<0.001.
†Caseness for chronic fatigue syndrome designated at six months after medical, psychiatric, and laboratory evaluation.[1]
‡Acute infection confirmed by testing of longitudinally collected sera.

What is already known on this topic

A post-infective fatigue syndrome that meets diagnostic criteria for chronic fatigue syndrome may follow Epstein-Barr virus infection but not common, minor viral infections

What this study adds

Post-infective fatigue syndrome represents a common and stereotyped outcome from several viral and non-viral infections

The key risk factor for post-infective fatigue syndrome is the severity of the acute illness and not age, sex, or psychological factors

Unlike in previous reports, we required the cases to have serological confirmation of Epstein-Barr virus infection, continuity of the prolonged fatigue state, and strict application of the diagnostic criteria for chronic fatigue syndrome with exclusion of alternative medical and psychiatric disorders. White and colleagues also identified the importance of the specific pathogen and of severity of the acute illness.[24] In addition, premorbid and intercurrent mood disorders were not associated with an increased likelihood of post-infective fatigue syndrome.

A weakness of our study is that the sample size did not allow exclusion of risk factors for post-infective fatigue syndrome with small effect sizes. The participant group enrolled in the cohort was likely to be biased by factors influencing presentation to the general practitioner, including illness severity.

Meaning of the study

Examination of outcomes after the acute infections reported here implicates aspects of the host response to infection as the likely determinant of post-infective fatigue syndrome, as the case rates after infection were comparable and the symptom characteristics progressively merged over time. Patients with post-infective fatigue syndrome constitute a distinguishable subset within the broad diagnostic category of chronic fatigue syndrome.

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Diagnostic accuracy of clinical examination for detection of non-cephalic presentation in late pregnancy: cross sectional analytic study

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Abstract

Objective To examine the diagnostic accuracy of clinical examination to determine fetal presentation in late pregnancy.
Design Cross sectional analytic study with index test of clinical examination and reference standard of ultrasonography.
Setting Antenatal clinic in tertiary obstetric hospital in Sydney, Australia.
Participants 1633 women with a singleton pregnancy between 35 and 37 weeks' gestation attending antenatal clinics.
Intervention Fetal presentation assessed by clinical examination during routine antenatal care, followed by ultrasonography to confirm the diagnosis.
Main outcome measures Sensitivity, specificity, and positive and negative predictive values of clinical examination compared with ultrasonography. Diagnostic rates by maternal characteristics.
Results Ultrasonography identified non-cephalic presentation in 130 (8%) women, comprising 103 (6.3%) with breech and 27 (1.7%) with transverse or oblique lie. Sensitivity of clinical examination for detecting non-cephalic presentation was 70% (95% confidence interval 62% to 78%) and specificity was 95% (94% to 96%). The positive predictive value and negative predictive value were55% and 97%, respectively.
Conclusions Clinical examination is not sensitive enough for detection and timely management of non-cephalic presentation.

Introduction

Antenatal detection of non-cephalic presentation—comprising breech presentation and transverse or oblique lie—in late pregnancy is important for timely management and clinical decision making. For breech presentation, women and their clinicians must decide whether to try external cephalic version to increase the likelihood of vaginal birth or plan a caesarean section, with optimal gestation being 37 and 39 weeks, respectively.[1] Diagnosis of non-cephalic presentation after the onset of labour is associated with increased maternal and infant morbidity and mortality.[2]

Fetal presentation is generally assessed by palpating the abdomen (clinical examination), though we do

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