The relationship between fatigue, psychological and immunological variables in acute infectious illness

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Objective: The aim of this paper is to explore the longitudinal relationships between physical and psychological symptoms and immunological factors following acute infective illnesses.

Method: Preliminary data from a prospective investigation of patients with serologically proven acute infectious illnesses due to Epstein-Barr virus (EBV), Ross River virus (RRV) or Q fever are reported. Patients were assessed within 4 weeks of onset of symptoms and then reviewed 2 and 4 weeks later. Physical illness data were collected at interview. Psychological and somatic symptom profiles were assessed by standardised self-report questionnaires. Cell-mediated immune (CMI) function was assessed by measurement of delayed-type hypersensitivity (DTH) skin responses.

Results: Thirty patients who had been assessed and followed over the 4-week period (including 17 patients with EBV, five with RRV and eight with Q fever) were included in this analysis. During the acute phase, profound fatigue and malaise were the most common symptoms. Classical depressive and anxiety symptoms were not prominent. Initially, 46% of cases had no DTH skin response (i.e. cutaneous anergy) indicative of impaired cellular immunity. Over the 4-week period, there was a marked improvement in both somatic and psychological symptoms, although fatigue remained a prominent feature in 63% of subjects. The reduction in reported fatigue was correlated with improvement in the DTH skin response ($p = 0.001$) and with improvement in General Health Questionnaire (GHQ) scores ($p < 0.01$).

Conclusions: Acute infectious illnesses are accompanied by a range of non-specific somatic and psychological symptoms, particularly fatigue and malaise rather than anxiety and depression. Although improvement in several symptoms occurs rapidly, fatigue commonly remains a prominent complaint at 4 weeks. Resolution of fatigue is associated with improvement in cell-mediated immunity.

Key words: cell-mediated immunity, depression, fatigue, viral illness.

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Individuals who are infected with a viral or bacterial pathogen develop a characteristic constellation of symptoms, including pyrexia, fatigue, myalgia, athralgia and headache. In both animals and humans, infections are also accompanied by increased slow wave sleep and stereotyped behavioural responses, including, reduced motor activity, social withdrawal and anorexia [1,2]. These characteristic physical and behavioural correlates of infection result primarily from the host immune response to the pathogen [3–5]. Infections and other inflammatory processes cause the synthesis and liberation of cytokines, such as interleukin-1 (IL-1), tumour necrosis factor (TNF) and the interferons, into the circulation. These cytokines initiate a cascade of events including altered thermoregulation, the release of leucocytes from the bone marrow into the circulation, an increase in skeletal muscle catabolism, an increase in slow wave sleep, and the hepatic production of acute-phase proteins. The cardinal symptoms of infection including fever, anorexia and somnolence are a consequence of these physiological changes [6]. The systemic administration of cytokines, such as α-interferon, produces symptoms similar to those of acute infection [7], while injection of IL-1 into the central nervous system (CNS) of animals produces the onset of sleep within minutes [3,4,8]. Patients receiving treatment with recombinant human interferon exhibit profound lethargy and increased slow wave activity on EEG [9]. In addition to these systemic effects, neuropsychological effects are frequently reported: typically impaired concentration and short-term memory. Subjects experimentally infected with influenza and those with other acute viral illnesses demonstrate similar cognitive impairments which are likely to represent an underlying attentional deficit [10]. These neurocognitive deficits are also found in subjects with chronic fatigue syndrome and major depression, hence the specificity of the symptoms is uncertain [11]. In addition to initiating this acute immunological response, certain pathogens, such as Epstein-Barr virus (EBV), Ross River virus (RRV), or the rickettsia *Coxiella burnetii* (which causes Q fever), sometimes appear to precipitate a prolonged fatigue syndrome.

Epstein-Barr virus, a human herpes virus, is the aetiological agent of infectious mononucleosis. Symptomatic infection with EBV is distributed equally between the sexes with a peak incidence in the 15–24-year-old age group of 45.2 cases per 100 000 population per year in developed countries. In its clinical form (subclinical infections occur frequently in young children), it is generally a self-limiting illness marked by fever, pharyngitis and lymphadenopathy lasting up to 3 weeks [12]. However, a recent prospective cohort study following individuals from acute EBV infection [13,14] identified a prolonged fatigue syndrome, which was independent of psychiatric diagnoses, 6 months after onset infection.

Epidemic polyarthritis, or Ross River fever [15] is an endemic, mosquito-borne, viral infection which is particularly prevalent in the summer months throughout Australia. In 1996, there were 7823 laboratory notified RRV cases, implying an incidence of at least 42.7 per 100 000 population with rates of greater than 150 per 100 000 in rural areas of New South Wales, Queensland and Western Australia [16]. Although subclinical infection is common, RRV typically causes an illness characterised by polyarthritis or arthralgia, rash and constitutional disturbance, which resolves over several weeks. Retrospective studies suggest that protracted of periods of joint pain and fatigue are common months or even years after the initial illness [17].

Q fever infection is caused by *Coxiella burnetti*, a rickettsial organism which is transmitted from infected livestock, including cattle, sheep and pigs. The illness is typically marked by high fever, prominent sweats, headache and severe prostration. Acute complications occur in the form of pneumonia, and chronic infection including endocarditis or osteomyelitis may follow. Antibiotic therapy with tetracyclines is the standard treatment approach. Most cases are reported in males aged 20–44 years as it is predominantly an occupational disease [18]. Protracted debility and fatigue, unassociated with the recognised chronic sequelae of endocarditis or hepatitis, have been reported from retrospective analyses of patients with adequately treated Q fever infection [19].

Such prolonged post-infective fatigue syndromes appear to represent a persistence of the fatigue and malaise typical of the acute phase of infections. However, the relevance of immunological and psychological processes to these syndromes is unclear [20]. The aim of this study was to examine the relationships between physical and psychological symptoms, and immunological measures during the peak illness and recovery phases of acute infections with EBV, RRV or *C. burnetti*.

Method

Subjects with serologically proven acute infections (caused by EBV, RRV or *C. burnetti*) are being

studied in a prospective cohort study seeking to identify immunological and psychological determinants of prolonged fatigue. Recruitment for this study is via the University Health Service at the University of New South Wales (for EBV infections) and the Macquarie Area Health Service in Dubbo, NSW (for EBV, RRV and Q fever infections). Recruitment in the larger catchment area surrounding the rural city of Dubbo relies on close collaboration between the pathology laboratories, general practitioners and our research team. Adult patients presenting to their general practitioner with symptoms suggestive of infection with EBV, RRV or Q fever are tested serologically according to standard clinical practice. Patients with serologically confirmed acute infection (based on the detection of specific IgM antibodies against EBV, RRV or *C. burnetti*) are identified and approached by a research nurse via their doctor. In order to 'capture' subjects who are still within the acute phase of the illness, patients whose symptoms have been present for longer than 4 weeks are excluded. Potential participants in the study are informed that the study is seeking to identify those physiological and psychological factors associated with prompt or delayed recovery, without discussion of any propensity of these infections to cause prolonged ill-health or the nature of persistent symptoms. All subjects provide written informed consent prior to their participation. The study has been approved by the institutional and regional ethics committees.

Patients were assessed by the research nurse as soon as possible after serological confirmation of the diagnosis (baseline), and then again at 2 and 4 weeks ('week-2' and 'week-4'). At the first assessment, a standardised interview was administered to obtain details of both the presenting illness and any past medical history. Patients were also screened for any history of depression, anxiety or somatisation disorder using the Composite International Diagnostic Interview (CIDI-Auto version 1.1d). This computerised program [21] formulates ICD-10 and DSM-III-R diagnoses and records current as well as pre-existing psychiatric morbidity.

At baseline, the subjects completed self-report questionnaires aimed at assessing both physical and psychological symptoms. The Schedule of Fatigue and Anergia (SOFA) has been devised to identify cases of chronic fatigue syndrome [22,23]. The subject rates 10 items (such as 'I feel tired for a long time after physical activity' and 'I get muscle pain even at rest') on a 4-point scale (0–3, 'none or a little', 'some of the time', 'a good part of the time' or 'most of the time'). Subjects who score three or more items as 'a good part of the time' or 'most of the time' are classified as cases of 'fatigue/neurasthenia'. The Profile of Mood States (POMS) was used to assess current mood states [24]. This instrument includes seven subscales: 'fatigue', 'depression', 'anxiety', 'vigour', 'anger', 'friendliness' and 'confusion'. The 12-item General Health Questionnaire (GHQ) [25] was used to detect current cases of psychiatric morbidity.

In vivo cell-mediated immune function was assessed at baseline using the *Multitest CMI* (Merieux, France), a standardised test of the delayed-type hypersensitivity (DTH) skin response [26]. A disposable kit that delivers intra-dermal doses of seven pre-loaded antigens and a glycerin control is applied to the volar aspect of the left forearm. The induration response at each site of antigen exposure reaches a maximum at 48 h after application and is read as the mean of two perpendicular diameters at this time. The cumulative induration diameter for the test is calculated as the sum of individual reactions at each site, provided the glycerin control is negative. In addition, the number of antigens which produced a significant induration response ($\geq$ 2 mm mean diameter) is recorded. Results are categorised according to previously determined reference ranges generated by the testing of healthy adult populations [27]. Our research group has used this measure extensively in earlier studies of immunity in healthy and diseased populations [23,28–30].

At week-2, subjects were reviewed by the research nurse for the presence or absence of symptoms and completed self-report forms (SOFA, GHQ, POMS). The week-4 assessment was similar but included a repeat of the DTH test of cellular immunity. In the prospective cohort study, patients who are symptomatic at the week-4 review (as reflected by a SOFA score $\geq$ 3) will be followed at regular intervals until symptoms resolve.

Data analysis

Changes in the self-report measures and DTH measures were assessed by comparison of baseline results with those recorded at 4 weeks using paired *t*-tests. The effect size was calculated for all self-report variables according to the following equation: effect size (ES) = (baseline result – 4-week result)/standard deviation (SD) of baseline result. Correlations were then calculated between the effect-size of measures

of fatigue (SOFA, POMS 'fatigue' and 'vigour' subscales), psychological state ($\log_{10}$ GHQ scores, POMS 'depression', 'anxiety' and 'anger' subscales), and the total DTH diameters.

Results

The first 30 subjects enrolled in the prospective cohort who have been followed for at least 4 weeks are reported here. The majority of the subjects were male (23/30, 82%), with a mean age of 29 years (range = 15–77 years). There were 17 serologically proven acute cases of EBV infection, eight of Q fever and five of RRV infection. During the period of enrolment, a similar number of subjects with serologically confirmed infections were excluded primarily because they had already been symptomatic for periods in excess of 4 weeks.

Table 1. Prevalence of physical symptoms during the resolution of acute infections evaluated by standardised interview (percentage of patients reporting each symptom, n=30)

Symptom	Baseline	Week-2	Week-4
Fatigue	100	73	63
Malaise	87	37	23
Fevers/chills	73	17	3
Headache	63	20	13
Myalgia/arthralgia	67	40	37

At enrolment, patients had been symptomatic for a mean of 18.9 days (SD = 9.9). All subjects reported fatigue as a predominant symptom in the standardised interview conducted at baseline. The other most frequently reported symptoms were: malaise, fevers and chills, headaches, as well as myalgias and arthralgias. Table 1 summarises the changes in the proportion of patients reporting these symptoms over the 4 weeks of follow-up.

At the initial assessment, 57% of patients were classified as cases of fatigue/neurasthenia on the basis of SOFA scores, and 69% as cases of psychological distress using GHQ scores. By four weeks, 27% of patients were still classified as SOFA cases, while 27% continued to meet the cut-off for GHQ caseness. The changes in self-report measures of fatigue (SOFA, POMS 'fatigue' and 'vigour' subscales), and psychological measures (GHQ, POMS 'depression' and 'anxiety' subscales) were compared over the 4-week period (Table 2). While most symptoms improved, it was notable that the significant changes were in somatic symptoms including fatigue and malaise, rather than the psychological constructs of anxiety and depression.

The relationships between changes in fatigue and psychological variables were examined by correlating the effect sizes (ES) of change. Significant correlations were seen between the ES of the GHQ, with the ES of the POMS 'fatigue' and 'vigour' subscales, respectively ($r = 0.482$ and $r = -0.449$), suggesting that the change in psychological caseness (as determined by the GHQ) may be attributable to changes in the central constructs of perceived fatigue and vigour. The 'fatigue' and 'vigour' subscales are

Table 2. Changes in self-reported fatigue and psychological variables following acute infection

	Baseline		Week-4		
Variable	Mean	SD	Mean	SD	t-test
SOFA[a]	3.17	2.02	1.63	1.87	4.17**
POMS					
'fatigue'	15.03	5.26	8.57	5.86	5.70**
'depression'	7.48	8.44	5.04	6.21	1.80 NS
'anxiety'	9.76	5.42	7.90	4.64	1.83 NS
'anger'	8.03	7.41	5.50	5.95	3.14*
'vigour'	8.97	5.2	14.72	6.15	-4.49**
GHQ[b]	4.21	2.96	1.72	2.58	4.65**

[a]Measure of somatic distress; [b]measure of psychological distress.
*$p < 0.01$; **$p < 0.001$; NS, non-significant.

thought to be relatively independent factors rather than simply opposite poles of a single factor [24].

At baseline, 46% of the patients were unable to mount a positive DTH response (i.e. cutaneous anergy), while at 4 weeks 50% of the patients were anergic. Correlations between the ES for the DTH measure and the ES of psychological and fatigue variables were significant for POMS 'fatigue' and the total diameter of the DTH skin responses ($r = -0.575$, $p = 0.001$), indicating a relationship between fatigue and immune responsiveness.

Discussion

This study describes a longitudinal analysis of changes in physical and psychological symptoms, and immunological parameters, during the acute and convalescent phases of three serologically documented acute infectious illnesses. Associations have been demonstrated between the resolution of physical and psychological symptoms, and a measure of immune competence over a 4-week period. Although preliminary, these findings lend support to the notion of an immunological basis for post-infective fatigue states.

All patients reported fatigue as a predominant presenting symptom. Many patients spontaneously defined the symptoms in practical terms, such as being unable to 'run up stairs', 'play their usual sport' or perform heavy manual work. For some patients, this was the key symptom that led them to seek appropriate medical attention. The physical symptoms most commonly reported at baseline (fever, chills and malaise) are consistent with symptoms linked to the release of cytokines into the circulation as a result of immune activation [3,4]. A central hypothesis of this ongoing research project is that the other cardinal symptoms in the acute phase, including fatigue, myalgia and arthralgia, are also likely to be immunologically mediated. Furthermore, as a high percentage of patients (63%) continued to report significant fatigue when assessed 4 weeks after enrolment, this persistent symptom complex may also have an immunological basis.

As expected, psychological symptoms were also common during the acute phase of these infections [11]. Changes in these symptoms were better measured by GHQ scores, rather than a standard depression or anxiety scale such as the POMS. The mean GHQ score was elevated at baseline and improved significantly by 4 weeks, whereas the depression and anxiety subscales of the POMS were not elevated at either timepoint. Consistent with these standardised records, although some patients reported feeling uncharacteristically 'miserable', 'weepy' or 'irritable' when first seen, the character of these mood changes were not those classically associated with clinical depression or anxiety disorders. Instead, they were essentially more low-grade and neurocognitive in nature with concentration difficulties being commonly reported. These complaints typically improved as the infection resolved, although some patients reported persistent concentration impairment.

The high prevalence of cutaneous anergy demonstrated on DTH testing performed at baseline is consistent with a previous report in acute infectious mononucleosis [31], although this is the first evaluation of this response in the other acute infections such as RRV or Q fever. The substantial number of patients who remained anergic at the 1-month follow-up is also consistent with the previous study in which DTH responses were not restored until 6 weeks after they were initially tested in the acute phase [31]. This delayed restoration of DTH responsiveness implies a slow recovery of normal cell-mediated immune function *in vivo*.

The preliminary evidence of a correlation between improvement in fatigue and immune responsiveness demonstrated here may indicate a shared mechanism underlying the symptom of fatigue and the phenomenon of cutaneous anergy. Our research group has previously documented a similar high prevalence of cutaneous anergy in patients with chronic fatigue syndrome, not seen in healthy control subjects or patients with major depression [28].

Epidemiological studies such as this one are susceptible to important sources of bias which may give rise to misleading or mistaken interpretations. As this study is primarily seeking to characterise the features and associations of the syndrome of persistent ill-health following acute infections, considerable effort has been made to portray the research in an open-ended manner without mention of possible symptoms such as fatigue. By definition, the recruitment is biased to the inclusion of individuals who are symptomatic, who attend their general practitioner, and who have the recent onset of symptoms. This selection process excludes those with mild or sub-clinical forms of these infections, and those who do not, or cannot, attend their local doctor. The nature of the DTH skin response could also lead to a reporting bias in the questionnaires; however, the skin responses are actually recorded 48 h after completion of the self-report instruments. Furthermore, subjects tend to

interpret the development of areas of induration which are visible and palpable on their forearms as indicative of abnormal immunity, whereas the converse is true. Thus, this potential bias operates against a spurious correlation between immunity and symptom report. Finally, the patients' knowledge and beliefs about the outcome of these infections may influence the reported duration of symptoms. In this regard, the patients were typically given the expectation of a short duration, self-limiting outcome by their doctor, and those with persistent symptoms expressed surprise and frustration at the delayed recovery. The majority of subjects with all three infections had taken relatively brief periods of sick leave and had returned to work despite ongoing symptoms.

This prospective investigation of fatigue, psychological symptoms and immune status is an essential step in resolving the controversy surrounding the pathophysiological basis of prolonged fatigue syndromes, particularly chronic fatigue syndrome (CFS) [6,18,20]. Continued recruitment into, and follow up of, this prospective cohort will include specific specialist medical and psychiatric evaluation of cases with prolonged fatigue after 6 months for caseness according to the diagnostic criteria for chronic fatigue syndrome [32,33]. In addition, detailed immunological studies will be performed to evaluate the role of cytokines in the pathogenesis of the prolonged fatigue states following acute infection.

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