Fatigue after infection: aetiology and pathophysiology

Individuals suffering from acute infections typically experience systemic symptoms, including fever and musculoskeletal pain, as well as fatigue. Acute infections are also accompanied by increased slow wave sleep and stereotyped behavioural responses, including reduced motor activity, social withdrawal and anorexia. These manifestations are collectively termed the ‘acute sickness response’. The action of pro-inflammatory cytokines, such as interleukin (IL)-1 and IL-6 on the central nervous system mediate the key features of the response. In the great majority of cases, these constitutional symptoms, including fatigue, resolve in parallel with the fever. However, in a minority, a disabling fatigue state may persist for weeks, months or (rarely) years. Many of the features of the acute sickness response remain evident in the prolonged fatigue state.

Following acute Q fever, Epstein–Barr virus (EBV) infection or Ross River virus (RRV) infection approximately 30% of individuals experience severe post-infective fatigue and other symptoms lasting 3 months, and 10% of cases meet diagnostic criteria for chronic fatigue syndrome (CFS) when evaluated by a physician and psychiatrist at 6 months following the infection. Infection with several other viral and non-viral pathogens have been linked to a subsequent prolonged fatigue state (i.e. lasting 1 month or more), including cytomegalovirus (CMV), influenza, toxoplasmosis, brucellosis and leptospirosis. In contrast, non-specific viral infections (upper respiratory tract infections and gastroenteritis) have been specifically shown not to be associated with an increased incidence of prolonged fatigue. In addition, inappropriate attribution of chronic fatigue to a coincidental preceding infection is common. For instance, reported prevalence rates of persistent fatigue obtained from surveys taken 12–24 months following RRV infection are considerably higher than those identified in prospective studies.

Evaluation of a patient with post-infective fatigue relies on a thorough history, careful physical examination and judicious laboratory investigations. The assessment should include a review of the accuracy of the original infective diagnosis, both on clinical and epidemiological grounds, and the laboratory investigations conducted at the time. A characteristic feature of the fatigue state is a prolonged exacerbation triggered by relatively minor physical or even cognitive activities. This should be differentiated from muscle weakness (neuromuscular disease), dyspnoea (cardiac or respiratory disease), somnolence (primary sleep disorders) and loss of motivation and anhedonia (major depression). This assessment is important as a documented infection might have triggered the onset, but other factors may perpetuate the illness, such as depression or sleep–wake cycle disorder.

The physical examination should include a careful assessment for signs of persisting infection with the triggering pathogen, as chronic infection might provide an alternative explanation for the fatigue state. The most important infections in this regard are the non-viral pathogens, such as Q fever, in which chronic, localised infection might occur in the form of endocarditis or hepatitis, which in turn might cause a prominent fatigue syndrome. The remainder of the physical examination is aimed at identifying signs indicative of an alternative medical diagnosis.

Laboratory investigations are primarily intended to exclude alternative medical diagnoses and rule out classical features of infection or inflammation. Further specific investigations might be warranted, such as: phase I anti-Q fever antibody testing and PCR for suspected Q fever endocarditis; sexually transmitted infection (STI) screening in those with sexual exposure; or computed tomography (CT) scan of the sinuses if chronic sinusitis is suspected.

Given the association with infection at onset, many studies have sought evidence of persistence of the pathogen as a driver for ongoing symptoms in post-infective fatigue, and in chronic fatigue syndrome. These investigations have been both comprehensive and uniformly negative. A notable recent example has been the flurry of interest in relation to the report in Science describing the detection of sequences of xenotropic murine leukemia virus-related virus.
subsequent studies failed to replicate the South Wales finding. No evidence of PCR of approximately 12,000 ticks collected in coastal areas of New Zealand. A thorough survey by microscopy, immunohistochemistry and serology failed to provide any positive findings, which was ultimately shown to be laboratory contamination with murine genomic DNA.

Similarly, in Australia there has been ongoing interest in the possibility of locally acquired Lyme borreliosis as a cause for both acute manifestations and protracted fatigue. However, these reports are largely based on serological testing, including western blot based on IgM positivity, which is recognised to largely reflect false positives when sampling is undertaken outside the acute phase, or IgG detection but with insufficient IgG bands to meet Centers for Disease Control criteria for a positive result. Very few cases in non-travellers have been supported by PCR evidence of Borrelia burgdorferi in blood cells of patients with chronic fatigue syndrome.

(XMRV), as well as putative infectious virus in the blood of the majority of patients with chronic fatigue syndrome (67%) compared with a small proportion (3.7%) of healthy individuals. Multiple subsequent studies failed to replicate the finding, which was ultimately shown to be laboratory contamination with murine genomic DNA.

In addition to the data arguing against the possibility of a unique pathogen or abnormal persistence of a recognised microbe, several studies have examined the possibility of an exaggerated or protracted immune response as a driver of post-infective fatigue, including excessive pro-inflammatory cytokine production. Although cytokine levels correlate with fatigue and other symptoms during the acute, febrile phase, case-control studies in the post-infective phase do not show a similar association with fatigue. In combination, these findings are consistent with the most widely accepted hypothesis for the pathogenesis of post-infective fatigue, which is a central nervous system disorder triggered by acute infection associated with sensitisation to normal physiological signals from the body, including fatigue and pain.

### Table 1. Recommended investigations for chronic fatigue after infection.

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<tr>
<th>Test</th>
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<td>Full blood count, differential white cell count and film</td>
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<tr>
<td>Erythrocyte sedimentation rate</td>
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<td>Urea, creatinine and electrolytes</td>
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<td>Calcium and phosphate levels</td>
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<td>Liver function tests</td>
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<td>Thyroid function tests</td>
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<td>Random blood glucose</td>
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<td>Midstream blood glucose</td>
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<td>Other tests to exclude active infection or autoimmune disorder, if indicated</td>
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### References


Do pathogens contribute to multiple sclerosis aetiology?

Multiple sclerosis (MS) is a common neurological disease characterised by sclerotic plaques of dead and dying oligodendrocytes and neurons in the central nervous system, usually with evidence of accompanying inflammatory activity. Infectious agents might cause or contribute to this cell death, but none have yet been established as doing so. Instead, MS is regarded as predominantly an autoimmune disease, responsive to immunomodulators. However, there is compelling epidemiological and empirical evidence implicating Epstein–Barr virus (EBV), with minor support for other viruses, as contributing to the pathogenic immune response in MS. Now the recent dramatic advances in identifying the genetic risk factors for MS have provided some tantalising leads to microbe involvement. If conclusive evidence is found, vaccines, antivirals/antibiotics or pathogens themselves might prove useful therapeutics.

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Do pathogens contribute to MS aetiology?

Multiple sclerosis is one of the most common neurological diseases of young adults. It is primarily an inflammatory disorder of the brain and spinal cord in which focal lymphocytic infiltration leads to damage of myelin and axons. It is triggered by environmental factors, especially in individuals with genetic susceptibility. Many of the genetic variants increasing risk have now been identified, and these point to variation in cell-mediated immunity as driving susceptibility. These genes also potentially point to specific pathogens.

There is empirical and epidemiological evidence that pathogens could be environmental triggers, but the distinction between association and causation is problematic. Two likely mechanisms for causation have been described: bystander activation, where self-reactive T cells are activated due to tissue damage by a pathogen; and molecular mimicry, where T cells that recognize pathogen epitopes are also self-reactive and are activated by the pathogens (Figure 1). Alternatively, pathogens might be protective in autoimmune disease, by inducing tolerance.

The sudden arrival and subsequent epidemics of MS in the Faroe Islands during and after WWII was most easily explained as facilitated by the arrival of British troops and accompanying pathogens in 1945. But if MS here and elsewhere was caused by an infection, the pathogen has remained elusive. From the geographic and ethnic distribution, the pathogen is likely to be ubiquitous in western