What Causes Prolonged Fatigue after Infectious Mononucleosis—and Does It Tell Us Anything about Chronic Fatigue Syndrome?

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(See the article by Cameron et al., on pages 56–66.)

Many doctors do not believe that chronic fatigue syndrome (CFS), sometimes called "myalgic encephalomyelitis," exists [1]. Some believe that it is no more than an atypical form of depressive illness. Some believe CFS to be a discrete condition, although recent evidence suggests that it is heterogeneous [2]. This makes discovering its pathophysiology extremely complex.

One successful way of sorting fact from fiction has been through the use of cohort studies of populations at high risk for developing prolonged fatigue. Perhaps one of the most fruitful areas of research has involved postinfectious cohorts, particularly following Epstein-Barr virus (EBV) infections presenting as infectious mononucleosis (IM) in adults. Five such cohort studies have been published [3–7]. These studies have demonstrated that a discrete postinfectious fatigue syndrome exists, one that is not a mood disorder [8, 9]. In fact, there seems to be not 1 but 2 postinfectious fatigue syndromes, one characterized by excessive sleep and the other characterized by insomnia associated with muscle and joint pain [8, 9]. Both syndromes also include poor concentration, irritability, and psychomotor retardation [8, 9].

The risk of either prolonged fatigue or CFS is ~5–6 times that of other common upper respiratory tract infections, such as *Streptococcus pyogenes* infection [3, 7], and there is a 10%–12% risk of CFS 6 months after infectious onset [3–5]. The risk of CFS is not specific to EBV alone; CFS has been shown to follow parvovirus infection [10], Q fever, and Ross River virus infection [5], among others.

It therefore seems that EBV infection, when it presents as IM, is a significant risk factor for CFS in adults, with the level of risk consistent with it playing some etiological role. But some 90% of patients recover from IM without developing CFS, suggesting that EBV may be a necessary but insufficient cause of CFS in these cases.

What cofactors make CFS happen after IM? A systematic review of all studies of prolonged fatigue found that physical inactivity was the most replicated predictor [11]. Of particular interest, the first reported cohort study showed that neither premorbid mood disorder nor recent stressful life events predicted post-IM CFS, once comorbid mood disorder had been controlled for [12]. By contrast, these same factors did predict depressive illness after IM, reinforcing the contrast with mood disorders. Predictiors of prolonged fatigue 6 months after onset were early positivity for heterophil antibody and evidence of physical deconditioning 4 months earlier. There were no significant associations with any other immune response to EBV [11, 12]. No other cohort has shown convincing associations with the immune response to EBV [5, 13].

Lloyd and colleagues in Australia have collaborated with Reeves and colleagues at the Centers for Disease Control and Prevention, and this has led to a cohort study of not 1 but 3 high-risk infections: IM, Q fever, and Ross River virus infection. The population was based around Dubbo, a rural area in Australia. This work has already shown that the risk of CFS is about the same in all 3 cohorts, with some 1 in 10 going on to develop CFS [5]. The group has also shown no association between CFS and EBV load in mouth washings [13]. The only significant predictor of CFS was the initial severity of acute IM at onset [5]. The to-date limited evidence base for significant predictors and associations is unlikely to be related to the apparent heterogeneity of CFS, because at most there are only 2 apparent phenotypic illnesses of prolonged fatigue after IM [8, 9]. It is

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more likely related to looking for the wrong risk factor over the wrong time scale. These problems may be overcome by the method used by Cameron et al. in their study of the same cohort presented in this issue of the *Journal* [14].

Cameron and colleagues used a nested case-control study from the Dubbo cohort of EBV-infected people to examine gene expression over time, seeking associations and predictions in those patients with prolonged fatigue. The study was innovative and may provide a means of understanding the pathophysiology of complex syndromes such as postinfectious fatigue syndrome.

The authors found 35 genes that were abnormally expressed over time in those with prolonged disabling fatigue. More genes were found to be associated with fatigue and separately with musculoskeletal pain. The genes identified had no obviously coherent pattern of functions, but some genes were related to signal transduction pathways, metal ion binding, and ion channel activity. No consistent target tissue was identified. Although cluster analysis was reasonably accurate in differentiating case from control subjects soon after infectious onset, no differentiation was possible 6 months after onset.

The strengths of the study include its longitudinal cohort design and repeated measures. Although none of the identified genes had previously been found in gene expression studies of CFS, this may be because of the heterogeneity of CFS [15]. The authors acknowledge this but point out that there was a pattern in the genes found in that they are important in immune response and neuronal function.

The weaknesses of the study include the small number of subjects (with type I errors likely), the lack of matching by sex, and the lack of validation by real-time polymerase chain reaction analysis of messenger RNA. We cannot be sure that gene expression in lymphocytes reflects gene expression in other tissues, such as the brain. Because gene expression changes rapidly and in response to behavioral changes, the lack of replication of the results of previous studies is no surprise.

What can we conclude from this study? Gene expression may perhaps help us identify pathways involved in the pathophysiology of complex syndromes such as CFS. Examining more homogeneous populations, such as individuals from high-risk infectious cohorts, is more likely to identify underlying pathology, but large cohorts are needed to make progress. This will require large, multicenter cohort studies with longitudinal measures of gene expression. The alternative is either to seek correlations with less changeable genetic variables, such as single-nucleotide polymorphisms, or to test hypotheses by directly measuring biological processes that are related to previously observed abnormalities, such as sleep architecture, interoception (visceral perception), inactivity, and the functional immune system.

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