Correspondence

Diverse Etiologies for Chronic Fatigue Syndrome

SIR—Koelle et al. [1] recently studied 22 pairs of identical twins discordant for chronic fatigue syndrome and concluded that there was no major contribution for viral infections in the perpetuation of chronic fatigue syndrome (CFS). The authors should be commended for their methodology and the use of well-matched control subjects. However, the study raised several issues.

First, similar to previous studies, the approach of Koelle et al. [1] was to look for statistical differences among the well-matched pairs with respect to the presence of viral antibodies and, more specifically, the presence of DNA of the viruses studied. Although these viruses were no more prevalent among the patients with CFS than among their healthy twins, one cannot conclude that these viruses are not the cause of CFS in a small subset of patients. CFS has been described in a small number of patients who had had well-documented acute Epstein-Barr virus (EBV), cytomegalovirus (CMV), and parvovirus B19 infections [2–4], and many of the patients responded to specific antiviral therapy. Of the first 200 patients with CFS who we evaluated for viral etiologies (table 1), only ~10% had etiologies that were attributed to the viruses studied by Koelle et al. [1]. *Chlamydia pneumoniae* infection, an uncommon, although treatable, cause of CFS, was also dismissed in a previous, smaller study [5].

Second, latent EBV DNA and EBV viruses were often found in the blood and saliva, respectively, of asymptomatic, seropositive individuals [6, 7], and, therefore, by themselves, are not ideal markers of active viral infection or the resultant symptoms of CFS. Would detection of virus-specific mRNA be more indicative of smoldering infection in the PBMCs, and would a positive response to antiviral therapy increase the specificity of the finding? Third, the tissue localization and persistence of viruses may be responsible for the symptoms of CFS, and viruses may not be detected by viral assay of PBMCs or plasma. We have seen 2 patients with CFS who, after acute viral infection, had urine samples positive for EBV DNA and urine cultures persistently positive for CMV growth during a period of 6 months, but whose blood samples tested negative for EBV DNA and CMV DNA, respectively. Both patients improved after receiving intravenous cidofovir therapy.

About one-half of our first 200 patients with CFS had significantly elevated levels of neutralizing antibodies to coxsackievirus B and echoviruses, compared with control subjects from the community. On repeat testing, ~39% of the patients tested positive for enteroviral RNA in PBMCs, as documented by 3 different PCR techniques [8, 9]. These results are similar to those reported by some investigators [10, 11]. Furthermore, results of a recent animal study and cell culture experiments clearly demonstrated the mechanism of enteroviral persistence [12, 13]. Although no less controversial, it would be interesting to test the twins who participated in the study of Koelle et al. [1] for the presence of enteroviral RNA and neutralizing antibody to enteroviruses.

After 2 decades of extensive research, it is clear that no single virus is responsible for this elusive syndrome. Perhaps we should approach the causes of CFS in the same way that we approach the causes of fever of unknown origin. Many diseases, infectious or noninfectious, can cause fever of unknown origin. There is no single diagnostic test for the entire spectrum of diseases, and the final etiology for each patient can only be ascertained after the meticulous use of reliable tests to eliminate known diseases as causes. We agree with Koelle and colleagues that early evaluation of patients for acute infectious etiology may help document or eliminate common viral infections as causes, perhaps when the fatigue persists for >3 months. Defining the spectrum of infectious and noninfectious causes of this disorder and the relative frequency of various diseases is important since no single treatment strategy will be uniformly effective for diverse infectious etiologies.

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Table 1. Probable causes of chronic fatigue syndrome in 200 patients.

Probable cause	Criteria for inclusion	No. of patients (n = 200)
Chlamydia pneumoniae infection	High antibody titer compared with control subjects from the community; response to macrolide therapy [5]	18
Epstein-Barr virus infection	Whole blood (at 1:1000 dilution) or urine sample positive for EBV DNA; response to Val or iv Cid therapy[a]	6
Cytomegalovirus infection	Surveillance of acute infection for a period >6 months; positive culture results; response to iv Cid or IVIG therapy	3
Recurrent VZV infection	Recurrent lesions; response to antiviral drugs	6
Recurrent HHV6-like disease	Recurrent roseola-like illness for a period of 3 years; response to iv Cid therapy	1
Parvovirus B19 infection	Test results positive for IgM or viral DNA	3
Hepatitis C	Resolution of symptoms after interferon/ribavirin therapy	3
Neurocardiogenic hypotension	Initial flulike illness; tilt test positive for NMS; response to midodrine therapy	2
Toxic mold exposure	Documented cultures of environmental samples positive for toxic mold; >1 household member was affected; symptoms improved after leaving the house	2
Postvaccination	Received pneumovax, MMR, or influenza vaccine	3
Enterovirus infection	Persistent, significantly elevated levels of neutralizing antibody for coxsackievirus B or high echovirus titer compared with controls from the community; PBMC sample positive for enteroviral RNA[b]	109
Unknown	—	44

NOTE. Cid, cidofovir; EBV, Epstein-Barr virus; HHV6, human herpesvirus 6; IVIG, intravenous immunoglobin; MMR, measles, mumps, and rubella; NMS, neurally mediated syncope; Val, valacyclovir; VZV, varicella-zoster virus.

[a] The EBV DNA assay of whole blood was performed by the University of Southern California (USC) reference laboratory. One urine sample positive for EBV DNA was confirmed by the USC reference laboratory, the Associate Regional University Pathologist's laboratory, and the Microbiology Reference Laboratory.

[b] There were 150 control subjects who visited the medical clinic for whom determination of neutralizing antibody for coxsackievirus B1-6 and echovirus 6, 7, 9, 11, and 30 was done. A significant elevation of antibody level was defined as a titer greater than 2× (mean level + 2 SDs) for control subjects.

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Reply

Sir—Chronic fatigue syndrome (CFS) is a clinical syndrome that potentially involves many organ systems. Determining that a syndrome is caused by an infectious agent requires the proverbial "compared to what." Our small study was directed at the detection of an association between common viral infections and CFS. To demonstrate such an association, appropriate controls are needed, but this feature is lacking, in either reference or data, in the letter from Drs. Chia and Chia [1].

We compared identical twins, one with CFS and one without CFS, to determine whether common viral infections were associated with CFS. This unique approach controlled perfectly for genetic influences, and, to a considerable degree, for environmental exposures, neither of which have been adjusted for in previous studies of the association between infectious agents and CFS. Our data clearly showed that neither the subjects with CFS nor their healthy twins had evidence of an active systemic viral infection. As is the case for all studies, there is a degree of uncertainty in our results, and we invite other