Enterovirus Related Myopathy
in a Subset of Chronic Fatigue Syndrome?

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Enteroviruses are a group of viruses within the extensive Picornaviridae [Picornaviruses] family. As a whole, the Picornavirus family contains five genera: Enterovirus, Rhinovirus, Hepatovirus or hepatitis A virus, Aphthovirus or foot-and-mouth disease viruses, and Cardiovirus, of which the first three groups contain important human patho-
Enteroviruses are transient inhabitants of the human alimentary tract. The poliovirus is part of the enterovirus genus. Another enterovirus subgroup, namely the Coxsackieviruses, which are the topics of interest in the present manuscript (2). Coxsackieviruses are divided into two groups [A and B], and are capable of producing a wide variety of illnesses in humans. Although remaining asymptomatic in the majority of cases, group B serotypes may cause severe generalized disease, pleurodynia [epidemic myalgia], myocarditis, pericarditis, meningoencephalitis, and a variety of respiratory illnesses [including laryngotraceobronchitis, bronchiolitis, pneumonia] (1,3). In addition, Coxsackievirus type B infection of the pancreas triggers destruction of exocrine tissue by immune cells (4). Group B Coxsackieviruses contain at least six subtypes [Group B types 1 to 6]. Consistent with the broad range of diseases potentially caused by Coxsackieviruses is the diversity of the clinical manifestations of these infections. The human body defends itself against Coxsackieviruses by producing neutralizing and complement-fixing antibodies (1).

The report by Lane and colleagues described the detection and characterization of enteroviral RNA in muscle tissue originating from Chronic Fatigue Syndrome [CFS] patients who have myalgia (2). Furthermore, the authors tried to relate the presence of the enterovirus to an abnormal lactate response during exercise in CFS patients (2). They studied patients fulfilling the Oxford criteria for CFS (2), and presenting with myalgia. Reverse transcription, nested polymerase chain reaction was used to detect enterovirus RNA in quadriceps muscle [i.e., the vastus lateralis] biopsy samples of 48 CFS patients and 29 controls. The control sample consisted of patients with non-specific arm or leg pain, patients undergoing abdominal surgery or amputation, and subjects without known muscle disease. On the same day as the needle muscle biopsy, all patients performed a subanaerobic threshold exercise test [exercise at 90% of the predicted anaerobic threshold work rate; venous blood samples for lactate measurements were taken prior, immediately after, and 30 minutes after the exercise testing]. An abnormal response to exercise testing was defined by a plasma lactate level exceeding the upper 99% confidence limit for normal sedentary controls at two or more time points (2). These reference data were previously reported by the same group in the same Journal (5). The majority of the CFS patients [28 of 48] exhibited an abnormal exercise response, and 10 of 48 muscle biopsy samples were positive for enterovirus sequences. None of the control biopsy samples were positive for the enterovirus sequences. Furthermore, the ten positive samples were characterized by direct nu-
cleotide sequencing, revealing that the PCR products were most closely related to the Coxsackie B virus. Interestingly, nine of the ten positive enterovirus cases were among the CFS subgroup presenting with an abnormal exercise response.

These results are compelling, but should be interpreted cautiously when deriving conclusions. In the Results section of the manuscript, it is indicated that the results point to a significant association between CFS and the detection of enterovirus sequences in muscle tissue (2). First, given the fact that their CFS sample is unlikely to be representative of the CFS population in general [see comments below], this conclusion is somewhat premature. More importantly, the data presented in the manuscript [i.e., based on the Fisher’s exact test the statistically significant difference in positive enterovirus sequences in muscle biopsy samples in CFS patients compared to human tissue control samples] are unable to reveal an association between CFS and the detection of enterovirus sequences in muscle tissue. These data do indicate that the muscle biopsy samples of the studied CFS patients were more likely to be positive for enterovirus sequences, compared to the muscle biopsy samples of the 29 human tissue controls. However, a correlation analysis between measures capable of quantifying disease severity [for instance, symptom severity or functionality] and the enterovirus detection [real time polymerase chain reaction might be useful in quantifying the enterovirus related myopathy] is required to reveal an association. Likewise, the authors made a considerable assumption by stating that “there is an association between abnormal lactate response to exercise and the presence of enterovirus sequences in muscle in a proportion of CFS patients.” This is not substantiated by their data. What they did show is that in their sample of Oxford-defined CFS patients exhibiting myalgia the subjects who were positive for the enterovirus detection were more likely [odds ratio of 9.00; 95% CI 1.04 to 78.17] to present with an abnormal exercise response. It is tempting to speculate that these results point to an association between the enterovirus and the abnormal lactate response to exercise, but only preliminary evidence supporting this view is provided. In order to obtain strong evidence supporting an association between an abnormal exercise response and the enterovirus detection, one should perform a correlation analysis between the enterovirus detection and the exercise capacity parameters. Using the dataset presented in the manuscript, it would have been of interest to count the point biserial correlation coefficient (6) in order to reveal an association between the dichotomous variable [i.e., the presence or absence of an
enterovirus] and the continuous variable [the exercise capacity parameters].

Their sample consisted of 48 patients fulfilling the operational criteria for CFS as described by Sharpe et al. (7). As previously discussed in this section of the Journal (8), this in turn limits the generalization of their findings. Compared to the 1994 CDC [Center for Disease Control and Prevention] case definition for CFS (9), Sharpe and colleagues (7) describe a much broader definition of CFS. British CFS researchers have chosen not to include symptoms of depressive illness and anxiety disorders as exclusion factors, for they consider these symptoms to be central and debilitating aspects of the syndrome (7). Additionally, they used fewer symptom criteria for it has been argued that no symptoms have been shown to be specific for CFS (10). Previous research has shown the prevalence of CFS among chronically fatigued patients to vary according to the criteria used (11). In addition, the 1994 CDC criteria for CFS (9) includes ‘postexertional malaise lasting more than 24 hours’ as a minor criterion [4 of more of the minor criteria should be present to comply with these criteria], and this might have been of interest to the present investigation. Consequently, extrapolation of research results addressing Sharpe et al. (7) defined CFS patients to Fukuda et al. (9) defined subjects may be inappropriate.

In the Discussion section of the manuscript, the authors themselves indicated that their CFS patients might not be representative of the CFS patient population (2). Indeed, they studied a subgroup of CFS who exhibit myalgia. Nishikai et al. found that 85 of the 114 [74.6 percent] patients with CFS reported muscle pain, and 74 [64.9 percent] had multi-joint pain (12). In another study, twenty-four of the 44 [54.5 percent] subjects examined reported widespread muscle and joint pain (13). There is a growing international consensus that the CFS population should be subclassified, because more homogeneous subgroups are less likely to reveal conflicting data among investigators (14). Chronic fatigue with musculoskeletal system disorders such as widespread muscle and joint pain has been suggested as an important subclass of CFS (14). The etiology of widespread pain in patients with CFS, however, remains to be clarified. The present report suggests that an enterovirus related myopathy may be at the basis of muscle pain in at least a subset of CFS patients. Furthermore, the 48 CFS patients studied by Lane et al. (2) comprised of 26 men and 22 women. Although their sample was randomly allocated from consecutive referrals, the gender distribution does not comply with previously published epidemiological data of CFS patients. In fact, women appear to be more likely to develop the
disease than men and children (15,16). Klimas (17) indicated that approximately 80% of the CFS population is female, while Clauw and Chrousos (18) suggested that 70% of the patients are female. The distribution of the sexes appears to be more equal in young children, but girls outnumber boys after puberty (19).

Still, these data provided new evidence supporting an enterovirus related myopathy in at least a significant subgroup of CFS patients [i.e., those presenting with myalgia and fulfilling the Oxford diagnostic criteria]. Previous reports on enteroviruses or myopathies in CFS patients were scarce. Ten years ago this same group reported a high prevalence [41 of 158] of enteroviral RNA in muscle biopsy samples from patients with postviral fatigue syndrome, and they concluded that postviral fatigue syndrome might be a consequence of a previous inflammatory viral myopathy (20). Galbraith and colleagues (21) found evidence for enteroviral sequences, related to the Coxsackie B-like viruses, in eight patients with CFS, while Nairn et al. (22) studied 100 CFS patients and 100 matched controls and found that 42% of the patients were positive for enteroviral sequences by PCR, compared to only 9% in the healthy control sample. However, a Coxsackie B antibody neutralization assay was unable to differentiate the two groups (22). Smith et al. (23) found little evidence for Coxsackie B viruses in 15 adolescents with chronic fatigue. Another study reported the lack of IgM antibodies to Coxsackie B viruses in any of the studied chronic fatigue patients, and significant levels of neutralizing antibodies to Coxsackie B viruses in 6 of 19 patients (24). Remarkably, in the 1998 edition of Jawetz, Melnick, & Adelberg’s Medical Microbiology handbook it is indicated that “there is accumulating evidence of a possible association between CFS and infection with enteroviruses, particularly coxsackie B viruses” (1). Based on our own clinical observations, Coxsackie B infected CFS patients exhibit a high number of both natural killer and activated T cells, and an increased creatine phosphokinase. Interestingly, a recent report indicates a marked protective effect of the interferon inducer ‘Ampligen’ [Poly(I)-Poly(C12U)] on the development of Coxsackie B3 virus-induced myocarditis in mice (25). A quick literature search indicated that little is known about the immunopathology of Coxsackie B viruses, making it impossible to speculate whether or not these types of infections fit into our current understanding of immunopathology in CFS patients. Based on the compelling results of the Lane et al.’s study (2), these are important questions for future research.
REFERENCES


