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Cytokine expression provides clues to the pathophysiology of Gulf War illness and myalgic encephalomyelitis

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ABSTRACT

Gulf War illness (GWI) is a chronic disease of unknown etiology characterized by persistent symptoms such as cognitive impairment, unexplained fatigue, pervasive pain, headaches, and gastrointestinal abnormalities. Current reports suggest that as many as 200,000 veterans who served in the 1990–1991 Persian Gulf War were afflicted. Several potential triggers of GWI have been proposed including chemical exposure, toxins, vaccines, and unknown infectious agents. However, a definitive cause of GWI has not been identified and a specific biological marker that can consistently delineate the disease has not been defined. Myalgic encephalomyelitis (ME) is a disease with similar and overlapping symptomology, and subjects diagnosed with GWI typically fit the diagnostic criteria for ME. For these reasons, GWI is often considered a subgroup of ME. To explore this possibility and identify immune parameters that may help to understand GWI pathophysiology, we measured 77 serum cytokines in subjects with GWI and compared these data to that of subjects with ME as well as healthy controls. Our analysis identified a group of cytokines that identified ME and GWI cases with sensitivities of 92.5% and 64.9%, respectively. The five most significant cytokines in decreasing order of importance were IL-7, IL-4, TNF-α, IL-13, and IL-17F. When delineating GWI and ME cases from healthy controls, the observed specificity was only 33.3%, suggesting that with respect to cytokine expression, GWI cases resemble control subjects to a greater extent than ME cases across a number of parameters. These results imply that serum cytokines are representative of ME pathology to a greater extent than GWI and further suggest that the two diseases have distinct immune profiles despite their overlapping symptomology.

1. Introduction

Gulf War illness (GWI) and myalgic encephalomyelitis (ME) are complex diseases of unknown etiology. They are often characterized by a constellation of unexplained and overlapping symptoms, which include widespread inflammation, fatigue, multisystemic neuropathology, joint and muscle pain and gastrointestinal pathology [1–3]. Although the two diseases are similar with overlapping symptoms, GWI is a specific term given to returning military veterans and civilian workers of the Persian Gulf War that took place from August 2, 1990 to February 28, 1991. ME is frequently associated with acute flu-like onset as well as noninfectious environmental triggers [4]; whereas, multiple factors including environmental exposure, toxins, vaccines, and unknown infectious agents have been evaluated as potential triggers for GWI [5,6]. Indeed, GWI and ME have many clinical symptoms in common including long-term and severe fatigue that is not relieved by rest, gastrointestinal disorders, and neurological impairments [2]. Accordingly, it has been suggested that GWI cases meet the diagnostic criteria for ME and, therefore, represent discrete subsets of ME. Currently, there is no pathognomonic marker for either disease as well as no clinical diagnostic test available; for these reasons, diagnosis is mainly based on clinical observation, epidemiological evaluation, and medical anamnesis.

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