Antimuscle and anti-CNS circulating antibodies in chronic fatigue syndrome

Article abstract—Chronic fatigue syndrome (CFS) patients suffer from disabling physical and mental fatigue. Circulating autoimmune antibodies may produce symptoms of muscular fatigue by reacting with acetylcholine receptors or calcium binding channels. They can also produce mental status changes by reacting with central nervous system (CNS) antigens. We thoroughly investigated the presence of circulating antimuscle and anti-CNS antibodies in 10 CFS patients and 10 controls. We were unable to detect any pathogenic antibodies.

NEUROLOGY 1997;48:1717–1719

Audrius V. Plioplys, MD, FRCPC, FAAP, CMD

Profound muscle fatigue precipitated by minimal physical activity is one of the major symptoms in chronic fatigue syndrome (CFS) patients. In CFS, there have been reports of excessive intramuscular acidification and abnormal jitter with single fiber electromyography, suggestive of abnormal muscle membrane function.[1] Clinical muscular dysfunction and fatigue can be caused by autoantibodies recognizing the acetylcholine receptor or the calcium channels.[2,3]

Mental fatigue with memory impairment and psychiatric disturbance (depression and anxiety) are common complaints in CFS patients.[4] Similar mental status changes, along with other clinical findings, occur in limbic encephalitis,[5] one of the paraneoplastic syndromes which is caused by the presence of anti-neuronal nuclear antibodies type 1 (ANNA-1; also called anti-Hu).[6]

Because immune-mediated mechanisms may be a cause of CFS symptoms, a reasonable hypothesis is that circulating antimuscle and anti-CNS antibodies may be a pathogenic cause of CFS symptoms. There has been no investigation reported of the possible presence of these circulating autoimmune antibodies in CFS.

Methods. Ten patients (seven women and three men; age range 20 to 67 years, median age of 49 years) were evaluated for CFS. They all underwent detailed reviews of medical history and a thorough general physical and neurologic examination. All underwent routine blood tests, including complete blood count, chemistry screen (including glucose, electrolytes, calcium, magnesium, liver function tests, and renal function tests), erythrocyte sedimentation rate, rheumatoid factor, ANA, T3, T4, TSH, CK, HIV, hepatitis screen, RPR, B12, red blood cell folate, and serum carnitine determinations. All patients had a urinalysis, chest radiograph, and intradermal intermediate-strength purified protein derivative testing. When clinically indicated, selected patients underwent Lyme disease screen, head MRI, and polysomnography. All patients underwent detailed clinical evaluations including the Fatigue Severity Scale (FSS),[7] and the CFS Impairment Index (CFS-II), which consists of physical and mental subsets.[8] All patients met the previous Centers for Disease Control criteria for the diagnosis of CFS[9] and the newly revised criteria for CFS.[10] All patients gave informed consent prior to entry

into this study, which was approved by an Institutional Review Board.

Ten age- and sex-matched controls also participated in this study. Each control individual was matched with a patient. The controls included seven women and three men, with an age range of 20 to 59 years, and a median age of 44 years. They all underwent detailed reviews of their medical history, a thorough general physical and neurologic examination, and detailed clinical evaluations including the FSS and the CFS-II. All controls gave informed consent prior to entry into this study.

Blood samples were drawn from the antecubital fossa in all cases. The serum samples were immediately processed, aliquoted, and frozen at −80 °C. Once serum collection was completed, all the samples were courier delivered on dry ice to the Neuroimmunology Laboratory of the Mayo Medical Laboratories, under the direction of Dr. Vanda Lennon. Immunoprecipitation techniques were used to assay for acetylcholine receptor binding antibodies, P/Q-type calcium channel binding antibodies, and N-type calcium channel binding antibodies. Immunofluorescence techniques were used to assay for antineuronal nuclear antibodies type 1 (ANNA-1; also called anti-Hu), antineuronal nuclear antibodies type 2 (ANNA-2; also called anti-Ri), anti-Purkinje cell cytoplasmic antibodies type 1 (PCA-1; also called anti-Yo), gastric parietal cell antibodies, smooth muscle antibodies, and antimitochondrial antibodies. ELISA techniques were used to assay for striational antibodies. Terminologic issues and techniques are reviewed in reference 11.

Results. Fatigue Severity Scale scores range from 9 in totally asymptomatic individuals to a maximum of 63 in severely fatigued individuals. In all the controls, the obtained score was 9. In the CFS patients the scores ranged from 42 to 63 with a median of 60. In the CFS-II physical subset, the scores range from 25 in asymptomatic individuals to 0 in severely fatigued patients. In all the controls, the score was 25, whereas in the CFS patients the score ranged from 5 to 20 with a median of 12. The CFS-II mental subset scores likewise range from 25 in asymptomatic individuals to 0 in severely fatigued patients. In all the controls, the score was 25, whereas in the CFS patients the scores ranged from 7 to 16 with a median of 14. The CFS-II total score, a sum of the physical and mental scores, was 50 in all the controls and ranged from 12 to 35 in the CFS patients with a median of 25. All of these fatigue scales indicate that the CFS patients had moderate to severe degrees of fatigue (both physical and mental fatigue) at the time of phlebotomy. All the results of the autoantibody assays in the CFS patients and controls were normal. None of the assayed antibodies were detected in any patient.

Discussion. Immunologic abnormalities may be a cause of the symptoms seen in CFS patients (reviewed in reference 4). Subtle abnormalities in cell-mediated and humoral immunity have led to speculation that in CFS there may be a disordered immune system response resulting from exposure to an infectious agent.[12] Immunologic abnormalities are reported in CFS: decreased function in natural killer cells and macrophages; reduced mitogenic response of lymphocytes; B-cell subset changes, and activation of CD8 cells.[13-16] There have also been reports of IgG subclass deficiencies, the presence of circulating immune complexes, decreased complement, and the presence of anticardiolipin and antiphospholipid antibodies.[17] One study has shown evidence that individuals with two or more CD8 cell subset alterations (increased CD11b, CD38, and HLA-DR) have a high probability (90%) of having active CFS.[12] However, the reported immunologic abnormalities vary significantly among different studies and have yet to be reliably replicated.[18]

Our results do not confirm the hypothesis that circulating autoantibodies against muscle or CNS antigenic determinants may be a cause of CFS.

From the Chronic Fatigue Syndrome Center, Mercy Hospital, and Department of Neurology, University of Illinois.

Received June 12, 1996. Accepted in final form July 26, 1996.

Address correspondence and reprint requests to Dr. Audrius V. Plioplys, Chronic Fatigue Syndrome Center, Mercy Hospital and Medical Center, Stevenson Expressway at King Drive, Chicago, IL 60616.

References

1. Jamal GA, Hansen S. Post viral fatigue syndrome: evidence for underlying organic disturbance in the muscle fiber. Eur Neurol 1989;29:273–276.
2. Lennon VA. Serological diagnosis of myasthenia gravis and the Lambert-Eaton myasthenic syndrome. In: Lisak R, ed. Handbook of myasthenia gravis. New York: Marcel Dekker, 1994:149–164.
3. Lennon VA, Kryzer TJ, Griesmann MS, et al. Calcium-channel antibodies in the Lambert-Eaton Syndrome and other paraneoplastic syndromes. N Engl J Med 1995;332:1467–1474.
4. Plioplys S, Plioplys AV. Chronic fatigue syndrome (Myalgic Encephalopathy). South Med J 1995;88:993–1000.
5. Corsellis JAN, Goldberg GF, Norton AR. Limbic encephalitis and its association with carcinoma. Brain 1968;91:481–495.
6. Dalmau J, Graus F, Rosenblum MK, Posner JB. Anti-Hu-associated paraneoplastic encephalomyelitis/sensory neuronopathy: a clinical study of 71 patients. Medicine 1992;71:59–72.
7. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale: application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol 1989;46:1121–1123.
8. Plioplys AV, Plioplys S. Serum levels of carnitine in chronic fatigue syndrome: clinical correlates. Neuropsychobiology 1995;32:132–138.
9. Holmes GP, Kaplan JE, Gantz NM, et al. Chronic fatigue syndrome: a working case definition. Ann Intern Med 1988;108:387–389.
10. Fukuda K, Strauss SE, Hickie I, et al. The chronic fatigue syndrome: a comprehensive approach to its definition and study. Ann Intern Med 1994;121:953–959.
11. Lennon VA. Paraneoplastic autoantibodies: the case for a descriptive generic nomenclature. Neurology 1994;44:2236–2240.
12. Landay AL, Jessop C, Lennette ET, et al. Chronic fatigue syndrome: clinical condition associated with immune activation. Lancet 1991;338:707–712.
13. Kibler R, Lucas D, Hicks MJ, et al. Immune function in chronic active Epstein-Barr virus infection. J Clin Immunol 1985;5:46–54.
14. Tosato G, Straus S, Henle W, et al. Characteristic T cell dysfunction in patients with chronic active Epstein-Barr virus

infection (chronic infectious mononucleosis). J Immunol 1985; 134:3082–3088.
15. Lloyd AR, Wakefield D, Boughton CR, et al. Immunological abnormalities in the chronic fatigue syndrome. Med J Aust 1989;151:122.
16. Klimas NG, Salvato FR, Morgan R, et al. Immunologic abnormalities in chronic fatigue syndrome. J Clin Microbiol 1990; 28:1403–1410.
17. Komaroff AL, Geiger AM, Wormsley S. IgG subclass deficiencies in chronic fatigue syndrome. Lancet 1988;1:1288.
18. Holmes GP. Defining the chronic fatigue syndrome. Rev Inf Dis 1991;13(suppl):53–55.