Rheumatic Findings in Gulf War Veterans

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Background: Rheumatic symptoms were commonly described among soldiers who served in previous wars.

Objective: To describe the frequency of rheumatology consultations, along with the diagnoses, and abnormal results on serologic testing in Gulf War veterans evaluated for Gulf War syndrome.

Methods: The medical records of the first 250 consecutive Gulf War veterans referred to the comprehensive clinical evaluation program at Wilford Hall Air Force Medical Center and Brooke Army Medical Center, San Antonio, Tex, were reviewed for demographic characteristics and frequency of subspecialty consultations. A retrospective review of rheumatic diagnoses and the frequency of abnormal serologic test results was recorded.

Results: Of the 250 Gulf War veterans evaluated in the comprehensive clinical evaluation program, 139 (56%) were referred for rheumatology consultation, which was the most common elective subspecialty referral. Of the patients evaluated, 82 (59%) had soft tissue syndromes, 19 (14%) had rheumatic disease, and 38 (27%) had no rheumatic disease. The most common soft tissue syndromes were patellofemoral syndrome (33 patients [25%]), mechanical low back pain (23 patients [18%]), and fibromyalgia (22 patients [17%]). Of the 19 patients with rheumatic disease, 10 had osteoarthritis, 2 had rheumatoid arthritis, 2 had gout, and 1 each had systemic lupus erythematosus, Behcet disease, parvovirus arthritis, psoriatic arthritis, and hypothyroid arthropathy. Abnormal serologic test results were common among the Gulf War patients regardless of the presence or absence of rheumatic disease.

Conclusions: The rheumatic manifestations in Gulf War veterans are similar to symptoms and diagnoses described in previous wars and are not unique to active duty soldiers. Overall, the results of serologic screening were poor predictors of the presence of rheumatic disease.

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Approximately 700,000 United States troops were deployed to the Persian Gulf to liberate Kuwait from Iraqi occupation during operations Desert Shield and Desert Storm between August 1990 and April 1991.1 While most veterans with illnesses after returning from the Gulf have had diagnosable conditions, thousands of veterans are seeking medical care for unexplained symptoms of chronic fatigue, rash, headache, arthralgia, myalgia, diarrhea, impaired concentration, forgetfulness, irritability, and sleep disturbance.1,4 This complex of symptoms has been referred to as Gulf War syndrome or Gulf War illness. Although the cause of these symptoms remains unclear, many troops were exposed to potentially adverse substances in the hostile wartime environment, including chemical toxins, infectious agents, and multiple simultaneous immunizations.3,5 In response to the symptoms of the Gulf War veterans, the Department of Defense (DoD) and the Department of Veterans Affairs developed similar, comprehensive clinical evaluation programs for the evaluation and treatment of the veterans’ illnesses.1 The DoD comprehensive clinical evaluation program (CCEP) provides a systematic, extensive evaluation for DoD beneficiaries. Potential DoD beneficiaries include Gulf War veterans on active duty or retired, members of the full-time National Guard who were Gulf War veterans, Gulf War veterans from the reserve components, and eligible family members of such personnel.

Rheumatic symptoms are common among soldiers in war and peace.9,13 The goal of this study was to retrospectively describe the specific rheumatic diagnoses and the frequency of abnormal serologic test results in the first 250 Gulf War veterans evaluated in CCEP at Wilford Hall Medical Center and Brooke Army Medical Center, San Antonio, Tex, between November 1994 and April 1995.
PATIENTS AND METHODS

The medical records of the first 250 consecutive Gulf War veterans who were referred to the CCEP at Wilford Hall Medical Center or Brooke Army Medical Center were reviewed for demographic characteristics. The number and frequency of all subspecialty consultations and the results of standard CCEP screening tests for each patient were documented.

The CCEP is a voluntary program available for DoD beneficiaries, initiated in June 1994, and consists of 2 clinical phases. After January 1995, the CCEP evaluations were redefined. The first phase consisted of a comprehensive history and physical examination along with complete blood cell count, urinalysis, and chemistry profile. Further testing and consultation were carried out at the discretion of the examiner. Rheumatology consultation could be recommended at any time during the CCEP evaluations. The second phase, if clinically indicated, included determinations of erythrocyte sedimentation rate, C-reactive protein, rheumatoid factor (RF), antinuclear antibody (ANA), liver-associated enzyme (LAEn), creatine kinase, purified protein derivative, vitamin B12, and folate; serologic testing for human immunodeficiency virus and hepatitis A, B, and C; a VDRL test; thyrotropin and thyroid function tests; and chest radiographs. Dental, infectious disease, and psychiatry evaluations were also included in the second phase.

The presence of RF was determined at Brooke Army Medical Center by latex agglutination, with a seropositive result reported as a titer greater than or equal to 1:160. The presence of RF was determined at Wilford Hall Medical Center by fluorescent immunoassay, with a seropositive result reported as greater than 15 IU/mL. The ANA was determined at both medical centers by indirect fluorescent antibody using human epithelioid tissue (Hep 2) cell line with a positive titer reported as greater than or equal to 1:160. The level of creatine kinase was determined by an enzyme calorimetric procedure at Brooke Army Medical Center (Kodak Ektachem) (normal level, 20-323 U/L for males and females) and at Wilford Hall Medical Center (Hitachi 747, Boehringer Mannheim method) (normal level, 24-170 U/L for females and 24-195 U/L for males).

The rheumatic diagnoses were obtained from a review of the rheumatology consultations performed by 7 board-certified rheumatologists from Wilford Hall and Brooke Army medical centers. Patients’ conditions as evaluated by rheumatology were categorized as noninflammatory and/or soft tissue syndromes, rheumatic disease, or no rheumatic diagnosis.

RESULTS

A total of 250 completed CCEP evaluations were reviewed. The demographic information is given in Table 1. Patients referred for rheumatology evaluation were similar in demographic characteristics to those not evaluated by a rheumatologist.

Of the 250 Gulf War patients evaluated, 139 (56%) were referred for rheumatology consultation. Rheumatology was the most common elective subspecialty referral followed by gastroenterology (111 [44%]), pulmonary (104 [42%]), and dermatology (100 [40%]).

Of the 139 Gulf War patients evaluated by rheumatology, 82 (59%) had soft tissue syndromes, 19 (14%) had rheumatic disease, and 38 (27%) had no rheumatic diagnosis. There were a total of 130 soft tissue syndromes diagnosed among the 139 rheumatology evaluations (Table 2). The most common soft tissue condi-
tions seen were patellofemoral syndrome (33 patients [25%]), mechanical low back pain (23 patients [18%]), fibromyalgia (22 patients [17%]), and shoulder tendinitis and/or bursitis (12 [9%]). Nineteen patients (14%) were diagnosed as having a rheumatic disease according to the American College of Rheumatology diagnostic criteria for each disease (Table 3). They included 10 with osteoarthritis, 2 with rheumatoid arthritis, 2 with gout, and 1 each with systemic lupus erythematosus, Behçet disease, parvovirus arthritis, psoriatic arthritis, and hypothyroid arthropathy. Thirty-eight patients (27%) were placed into the category of no rheumatic diagnosis. This subset of patients had no evidence of an underlying inflammatory rheumatic or connective tissue disease and had no definable mechanical or soft tissue syndrome. The majority of the patients with no rheumatic disease were given the diagnosis of arthralgia and/or myalgia or pain syndrome of undetermined cause.

There were a total of 22 patients diagnosed as having fibromyalgia (15 men and 7 women). Two patients were positive for hepatitis C, and 1 patient was positive for ANA at a titer of 1:160 without evidence of connective tissue disease. The rest of the patients with fibromyalgia had normal laboratory test results. Of the 22 patients with fibromyalgia, 16 underwent psychiatric evaluations, with a total of 28 diagnoses (7 depression, 5 posttraumatic stress disorder, 3 cognitive disorder, 3 hypochondriasis, 2 somatization disorder, 2 history of alcohol dependency, 2 anxiety disorder, 1 dysthymic disorder, and 3 nonspecific diagnoses). Fifteen of the 22 patients underwent neuropsychological testing and were given a total of 17 diagnoses (5 cognitive disorder, 4 adjustment disorder, 3 posttraumatic stress disorder, 1 somatization disorder, and 4 nonspecific findings). There was significant variability between the psychiatric and the neuropsychiatric diagnoses.

The frequency of individual laboratory abnormalities was similar between patients referred to rheumatology and those not referred (Table 4). Abnormal serologic test results were relatively common among the 250 patients. The denominator for each laboratory test varied depending on the time of patient enrollment in the CCEP program.

Abnormal results on serum protein electrophoresis (SPEP) was the most common laboratory finding. Of the patients referred to rheumatology, 31 (31%) of 94 had abnormal screening SPEP results: 15 hypergammaglobulinemia (12 nonspecific, 1 systemic lupus erythematosus, 1 anti–hepatitis B core with urticaria, and 1 anti–hepatitis B core), 9 elevated α or γ fraction (5 nonspecific, 1 rheumatoid arthritis, 1 hepatic steatosis, 1 sickle cell trait, and 1 metastatic adenocarcinoma), 5 decreased β-globulin (4 nonspecific, 1 anti–hepatitis B core), 1 monoclonal spike associated with anti–hepatitis A virus, and 1 with hyperproteinemia for nonspecific reason. Eleven of the 15 patients with hypergammaglobulinemia had a coexistent positive autoantibody result (RF in 6, ANA in 2, antinuclear antibodies in 2, and Lyme disease on enzyme-linked immunosorbent assay in 1). Ten of the 15 were diagnosed as having a soft tissue syndrome, 4 had no definable rheumatic disease, and 1 had systemic lupus erythematosus. The SPEP results were abnormal in 29 (45%) of 64 patients not evaluated by rheumatology: 21 hypergammaglobulinemia (18 nonspecific, 2 hypothyroidism, 1 hepatitis B surface antigen), 7 elevated α,γ-globulin level for nonspecific reasons, 2 decreased β-globulin level (1 hepatitis C, 1 hepatitis B surface antigen), and 3 other nonspecific abnormalities (1 α,γ-globulin, 1 monoclonal spike, and 1 hyperproteinemia). Associated seropositive results associated with hypergammaglobulinemia in this subset included RF in 2 patients, ANA in 3, and VDRL in 2.

Twenty-one (9%) of 228 patients were positive for RF, but only 2 patients were diagnosed as having rheumatoid arthritis. The ANA titer was abnormal in 14 (6%) of 232 patients, with only 1 patient diagnosed as having systemic lupus erythematosus. An elevated creatine kinase level was noted in 23 (10%) of 230 patients; 22 of the 23 were male and 15 were African American. One patient with an elevated creatine kinase level evaluated by rheumatology had hypothyroid arthropathy and none of the other patients were diagnosed as having myositis. A total of 3 muscle biopsies were performed, the findings of which were all normal. Serologic tests were positive for hepatitis in 10 (5%) of 217 patients: hepatitis C in 3 patients evaluated by rheumatol-
ogy and hepatitis B and hepatitis C in 4 and 3 patients, respectively, not evaluated by rheumatology.

Enzyme-linked immunosorbent assay was positive for Lyme disease in 11 patients, and 5 were negative for Lyme disease on Western blots. None of the patients had any risks for Lyme disease, nor were they from endemic areas. Of the remaining 6 patients, 1 was positive for ANA; 1, for *Giardia lamblia*; 1, for *Enterobius vermicularis*; 1, for antibodies to hepatitis B surface antigen; and 1, for antibodies to hepatitis B core antigen.

**COMMENT**

It is estimated that 15% to 33% of adult Americans suffer from a musculoskeletal disorder. Musculoskeletal complaints are the second most common symptom for which patients seek medical attention and the third leading diagnosis made by internists, resulting in a significant number of outpatient visits for primary care physicians. Musculoskeletal disorders are extremely common among active-duty soldiers and can be a major cause of disability. Furthermore, rheumatic complaints have been frequently described in war-related syndromes from the US Civil War to the Gulf War.9,10,13

A high frequency of rheumatic symptoms and diagnoses was observed in our Gulf War patients, a finding that supports the previous observations described in the literature. In fact, the rheumatic diagnoses established in our patients after the Gulf War were not different from those diagnosed by West during Operation Desert Storm. Rheumatic diseases were seen in 19 (14%) of the Gulf War patients in our study population, with more than half having osteoarthritis. The incidence of individual rheumatic diseases reflected that which would be expected in the general population. Soft tissue syndromes were the most common rheumatic diagnoses (59%) among our Gulf War patients. The most frequently diagnosed soft tissue diagnoses were patellofemoral syndrome, mechanical low back pain, and fibromyalgia. In 2 previous studies of rheumatic disease in the military population, mechanical low back pain and patellofemoral syndrome were also the most commonly diagnosed conditions. However, we observed a much higher incidence of fibromyalgia than was seen previously. In our study, 17% of patients referred to rheumatology were diagnosed as having fibromyalgia, compared with 8% diagnosed at an evacuation hospital during Operation Desert Storm and 8% of Air Force recruits who have to be medically discharged for fibromyalgia. Both of these studies were large; therefore, the difference may simply be a reflection of study size or could have represented a manifestation of posttraumatic stress disorder after the Gulf War. However, the 22 patients with fibromyalgia in our study demonstrated a wide variety of psychiatric diagnoses, and only 5 patients were diagnosed as having posttraumatic stress disorder by formal psychiatric evaluation and 3 by neuropsychological testing.

Although we can conclude that the rheumatic diagnoses are not unique to Gulf War veterans, the high percentage of unexplained symptoms of arthralgia and/or myalgia is still a challenging clinical question. Twenty-five percent to 50% of all primary care visits are made by patients who do not have a serious medical cause for their presenting symptom. Musculoskeletal symptoms are common and nonspecific in patients who may have functional impairment or underlying psychiatric disorders. Thirty-eight patients (27%) in our study had musculoskeletal symptoms without a definable rheumatic diagnosis. When these patients were compared with those who had a definable rheumatic diagnosis and with those who were not referred to rheumatology, there was no difference in any single demographic factor or type of abnormal laboratory test result. The patients in this ill-defined subset of Gulf War veterans have recently been referred to as having the “arthromyoneuropathy” syndrome, which is characterized by joint and muscle pains, muscle fatigue, difficulty in lifting, and extremity paresthesias, and have frequently been labeled or diagnosed as having the Gulf War syndrome. Physicians must resist the pressure to diagnose a disease in these patients for which scientific evidence is lacking. In general, clinical psychiatric diagnoses and/or abnormal findings on neuropsychiatric testing were more commonly described among this patient subset in our study, although this observation was not statistically significant in those patients who were studied. These Gulf War patients may have to be followed up for many years to better clarify the cause of their symptoms.

In an effort to detect diseases accounting for the Gulf War syndrome, mandatory serologic testing was performed for an extended period during the CCEP evaluations. The diagnostic utility of serologic screening in Gulf War patients is debatable, since multiple serologic tests have been analyzed for their sensitivity, specificity, and predictive value, and the accepted consensus is that serologic testing is most useful when there is clinical suspicion of disease. Abnormal results on serologic testing were common among all our Gulf War patients who were reviewed, regardless of the presence or absence of rheumatic disease. The SPEP was the most common serologic test with abnormal results in our patient population. Patients referred to rheumatology had a slightly higher incidence of positivity for RF and ANA or of an elevated creatine kinase level than patients not seen by a rheumatologist, although this is most likely a referral bias. A false-positive result on enzyme-linked immunosorbent assay for Lyme disease was common, even in the absence of risk factors for, or clinical evidence of, Lyme disease. All of the rheumatic diagnoses were established using diagnostic criteria, and no diagnosis was made on the basis of positive serologic test results alone. Our serologic observations support the medical literature in that the test results were most useful when they were negative, and the overall results of serologic screening were poor predictors of the presence of disease.

There are several limitations to our study. First, all the patients in our study did not undergo the same CCEP screening evaluation. Some patients underwent mandatory evaluations when they were screened before January 1995, and patient evaluations after this time were determined using clinically selected tests and consultations. This significant evaluation bias does not allow us to compare patients with each other, nor does it allow us to accurately determine the sensitivity or specificity of sero-
logic screening tests in our patient population. Second, we did not include environmental exposures during the Gulf War that varied among our patients and that may have influenced symptoms, medical conditions, and abnormal serologic test results, but this was beyond the scope or intent of this descriptive clinical study. Third, interpretations based on comparisons with other patient populations should be made with caution and only with the explicit recognition of the limitations of the CCEP as a selected case series.4

In conclusion, many Gulf War veterans fear they are suffering from a chronic disabling disease, although there is no evidence of a previously unknown disease among Gulf War veterans.1,4 Also, there is no excess of unexplained hospitalizations among Gulf War veterans who have remained on active duty since the end of the war.33 The presence and frequency of rheumatic manifestations of the Gulf War appear to be similar to symptoms and diagnoses described in previous wars,9,10,12,13 and they are not unique to active-duty soldiers.14,15,22

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