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Gulf War syndrome: Proposed causes

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ABSTRACT

Many veterans of the Persian Gulf War suffer from vague symptoms that have collectively become known as the Gulf War syndrome. Potential explanations include infectious disease, chemical exposure, and psychological stress. To date, no single etiology has been identified to explain Gulf War syndrome conclusively. It may be that multiple illnesses with overlapping symptoms and causes are responsible.

BETWEEN AUGUST 1990 and July 1991 approximately 700,000 American military personnel participated in the Persian Gulf crisis. Five years after the war, 5,000 to 80,000 veterans were estimated to suffer from various poorly characterized symptoms that have collectively become known as the Gulf War syndrome.[1] To date, no single etiology has been conclusively identified to explain these illnesses.

WAR-RELATED ILLNESS NOT UNIQUE TO THE PERSIAN GULF EXPERIENCE

Poorly characterized sickness following participation in armed conflicts has been documented among veterans of the Vietnam and Korean wars, World Wars I and II, and the United States Civil War.[2] Although the symptoms cited are remarkably consistent among each veteran group, no unique war-related disease or unifying etiological factor unrelated to psychological stress has been demonstrated. Given this historical precedent, the report of a post Gulf War syndrome is not surprising.

TABLE 1

Symptoms often cited by Gulf War veterans

Fatigue
Headache
Joint pain and stiffness
Muscle pain
Rash
Difficulty remembering or concentrating
Irritability
Depression
Sleep disturbance
Diarrhea, gas, abdominal cramps
Shortness of breath
Cough
Choking sensation
Sinus congestion

HEALTH OF GULF WAR VETERANS

Comparison of postwar mortality rates among Gulf War participants and nonparticipants has failed to demonstrate a difference in deaths due to disease-related causes. Furthermore, when specifically compared to the general population of the United States, Gulf War veterans have significantly lower cause-specific standardized mortality ratios.[3]

In regard to morbidity, review of Department of Defense hospital records for 25 months following the war found that Gulf War veterans were not at increased risk for unexplained hospitalization during this time period.[4]

Despite these findings, data from case series and population-based surveys[5–8] suggest that Gulf War veterans more frequently suffer from a variety of complaints than nonparticipants. The symptoms most frequently cited are listed in TABLE 1. Despite similar

No single cause has been conclusively identified

TABLE 2

Possible causes of Gulf War syndrome

Infectious exposure
- Pathogens endemic to the Middle East
- Biological warfare agents
- Predeployment vaccination

Chemical exposure
- Chemical warfare agents
- Pyridostigmine used as prophylaxis against chemical weapons
- Pesticides and rodenticides
- Petroleum products
- Depleted uranium used in munitions
- Chemical agent resistant paint
- Desert sand

Psychological stress
- Posttraumatic stress disorder
- Depression
- Anxiety
- Somatization
- Adjustment reaction

Viscerotropic leishmaniasis can present years later

symptom reporting from several investigators, examination of these complaints has failed to reveal a consistent physical examination or laboratory abnormality, nor conclusively implicated a distinct exposure, geographic risk factor, or demographic except for the observation that National Guard and reserve personnel are more frequently affected. Exploratory factor analysis[9,10] has attempted to better characterize these symptoms as a distinct illness, but a confirmatory factor analytic model[11] failed to support the existence of a unique disease.

PROPOSED ETIOLOGIES

Potential explanations for the Gulf War syndrome can be divided into three categories (TABLE 2):

- Infectious disease
- Chemical exposures
- Psychological stress.

The more popular of these hypotheses will be discussed in further detail.

INFECTIOUS DISEASE: VISCEROTROPIC LEISHMANIASIS

Historically, infectious disease has had a significant impact on military operations in the Middle East, with the most common illnesses being diarrhea, hepatitis, sandfly fever, cutaneous leishmaniasis, and schistosomiasis.[12] In addition to being exposed to endemic pathogens, Gulf War participants were potentially exposed to agents of biological warfare.

Surprising though is the apparent minimal impact on morbidity caused by infection during the Gulf War. Among 226 non-combat deaths, none were infectious disease-related. Furthermore, the disease non-battle injury rate was lower than any other major American war. There were no reported cases of cholera, typhoid fever, amoebic dysentery, giardiasis, schistosomiasis, echinococcosis, brucellosis, sandfly fever, anthrax, or botulism. Only a handful of cases of cutaneous leishmaniasis, malaria, Q fever, West Nile fever, meningococcosis, and hepatitis were reported.[13]

Despite the paucity of infectious disease during the war, the report of a variant form of visceral leishmaniasis presenting months to years after return from the Gulf War has stimulated interest in a link to Gulf War syndrome.[14] This illness (termed viscerotropic leishmaniasis) was originally reported in eight veterans who suffered with vague symptoms manifesting up to 2 years after the war's end. Symptoms reported included various combinations of arthralgia, fever, malaise, abdominal pain, diarrhea, nausea, chronic fatigue, rigors, weight loss, coryza, nonproductive cough, and headache. Physical examination findings were waxing and waning in nature and ran a spectrum from none to hepatomegaly, splenomegaly, adenopathy, and abdominal tenderness. Laboratory findings demonstrated mild anemia and elevated transaminases in some, but others had no abnormalities. Definitive diagnosis often required repeated microbiologic testing, presumably due to lower organism burdens in this variant form of visceral disease. The potential relationship to Gulf War syndrome is intriguing as the protean nonspecific nature of viscerotropic leishmaniasis closely mimics the vague, poorly

characterized illness of the Gulf War syndrome. It is thus a diagnosis that should be entertained in all Gulf War veterans presenting with perplexing illness.

CHEMICAL EXPOSURE: ORGANOPHOSPHATE INJURY

Troops may have been exposed to organophosphate chemicals in the form of pesticides and chemical weapons that were released during destruction of Iraqi ammunition bunkers. Organophosphates are acetylcholinesterase inhibitors that damage the nervous system by two mechanisms: first, an acute injury resulting from a functional excess of acetylcholine leading to the classic cholinergic toxidrome, and second, a delayed, chronic neurotoxic injury known as "organophosphate-induced delayed polyneuropathy" (OPIDP) resulting from inactivation of the neural tissue enzyme neurotoxic esterase. Classically, OPIDP affects the peripheral nervous system, resulting in paresthesias, numbness, and flaccid paralysis. The spinal cord, brainstem, and subcortex can also be involved, leading to hyperreflexia, bowel and bladder incontinence, autonomic dysfunction, spasticity, fatigue, ataxia, depression, and cognitive impairments. As many of these symptoms have been observed among Gulf War veterans, it has been suggested that Gulf War syndrome is a variant of OPIDP.[15]

The use of pyridostigmine as prophylaxis against possible chemical weapons attack increases the attractiveness of this hypothesis. Troops were ordered to take pyridostigmine during the air and ground wars. By reversibly and transiently binding to acetylcholinesterase, pyridostigmine theoretically protects a proportion of acetylcholinesterase from binding irreversibly to the organophosphate in the chemical weapon, thus providing an opportunity to survive a chemical warfare attack. The problem is that in the doses prescribed, pyridostigmine does not penetrate the blood-brain barrier and therefore provides no protection against chemical nerve agent binding to neurotoxic esterase in the central nervous system. Furthermore, by competing with the chemical weapon for peripheral binding to acetylcholinesterase, pyridostigmine may cause a relative increase in the peripheral pool of chemical weapon available to enter the central nervous system, increasing the potential to develop OPIDP.[15,16]

In an attempt to link the OPIDP hypothesis to Gulf War syndrome, exposure of chickens to various combinations of organophosphate chemicals and pyridostigmine in doses likely encountered during the Gulf War resulted in both clinical and histological evidence of nervous system injury.[17] Several studies have been conducted in humans to look for objective evidence of neurological damage among sick veterans.[18–20] Interesting trends suggestive of neurological injury have been reported, yet the small sample sizes and methodological shortcomings of many of these experiments limit the ability to draw more convincing conclusions.

PSYCHOLOGICAL STRESS

The observation that National Guard and reserve personnel appear to be more frequently afflicted may suggest a psychological etiology. These people were in general older than regular military personnel, more likely to have had civilian jobs and dependents back home, and less prepared for combat and therefore may have been psychologically more susceptible to the stresses of war. There is no doubt that many veterans have suffered psychological illness as evidenced by increased prevalence of adjustment reactions, depression, anxiety, somatization, alcohol and drug dependence, and post-traumatic stress disorder.

Oranophosphate-induced delayed polyneuropathy can affect the peripheral nervous system, spinal cord, brainstem, and subcortex

DIAGNOSIS

Few guidelines are available to assist the clinician in diagnosis and workup. Suspicion of infection should lead to microbiological and serological testing, with the understanding that diseases such as viscerotropic leishmaniasis are often difficult to objectively confirm. All patients should have careful and complete neurological examinations. If OPIDP is suspected, patients should be referred for neurological testing such as evoked potentials, nerve conduction measurements, electromyography, sural nerve biopsy, and neuropsychological questionnaires. Finally, the possibility of primary psychiatric disease must be ruled out.

PUTTING GULF WAR SYNDROME IN PERSPECTIVE

Unexplainable postwar illness is not unique to the Persian Gulf experience. Retrospective analysis of the Gulf War veteran cohort has failed to demonstrate an increased disease-specific mortality or morbidity from illness that might necessitate hospitalization. Case series and population survey data suggest that Gulf War veterans complain of more vaguely characterized symptoms than do control populations, with National Guard and reserve personnel more frequently affected. Numerous theories have been advanced including infectious or chemical exposures and psychological trauma. As of this date the symptoms cannot be localized to one organ system, and no single etiology has been conclusively identified. It may be that multiple illnesses with overlapping symptoms and causes are responsible.

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