Spatial analysis of the etiology of amyotrophic lateral sclerosis among 1991 Gulf War veterans

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A B S T R A C T

Background: Veterans of the 1991 Gulf War have an increased risk of amyotrophic lateral sclerosis (ALS), but the etiology is unknown.
Objectives: This study sought to identify geographic areas with elevated risk for the later development of ALS among military personnel who served in the first Gulf War.
Methods: A unified geographic information system (GIS) was constructed to allow analysis of secondary data on troop movements in the 1991 Gulf War theatre in the Persian Gulf region including Iraq, northern Saudi Arabia, and Kuwait. We fit Bayesian Poisson regression models to adjust for potential risk factors, including one relatively discrete environmental exposure, and to identify areas associated with elevated risk of ALS.
Results: We found that service in particular locations of the Gulf was associated with an elevated risk for later developing ALS, both before and after adjustment for branch of service and potential of exposure to chemical warfare agents in and around Khamisiyah, Iraq.
Conclusions: Specific geographic locations of troop units within the 1991 Gulf War theatre are associated with an increased risk for the subsequent development of ALS among members of those units. The identified spatial locations represent the logical starting points in the search for potential etiologic factors of ALS among Gulf War veterans. Of note, for locations where the relative odds of subsequently developing ALS are among the highest, specific risk factors, whether environmental or occupationally related, have not been identified. The results of spatial models can be used to subsequently look for risk factors that follow the spatial pattern of elevated risk.

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1. Introduction

Although controversial, recent reports document an approximately twofold increase in the risk of amyotrophic lateral sclerosis (ALS) – a fatal neurological condition – among veterans of the 1991 Gulf War over the subsequent 10 years (Horner et al., 2003; Coffman et al., 2005). This elevated risk was evident among deployed military personnel who were on active duty as well as in the Reserves and National Guard, and across all branches of service, with statistically significant elevations especially notable among those in the Air Force and Army. A second, independent study involving only Gulf War veterans under the age of 45 also found an elevated risk of ALS among this population (Haley, 2003). However, other earlier reports failed to identify an association between deployment and ALS among Gulf War veterans (Kang and Bullman, 1996, 2001; Smith et al., 2000; Sharief et al., 2002; Kelsall et al., 2005).

There are no reports on the occurrence of ALS among veterans of other conflicts, although the newly created Department of Veterans Affairs National ALS Registry may ultimately allow such investigation (Kasarskis et al., 2004; Allen et al., 2008). There is

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Abbreviations: ALS, amyotrophic lateral sclerosis; GIS, geographic information system; UIC, unit identification code; USACHPPM, US Army Center for Health Promotion And Preventive Medicine; NOAA, National Oceanic and Atmospheric Administration; PGVR, Persian Gulf Veterans Registry.

only a single report that suggests ALS may arise from environmental exposures associated with military service, *per se* (Weisskopf et al., 2005). A comprehensive review of the evidence on neurological disorders among veterans of the 1991 Gulf War reported no association between service in the Persian Gulf and the occurrence of neurological disorders, whether clinical syndrome or clinically defined disease, other than ALS (Rose and Brix, 2006). For diseases of unknown etiology such as sporadic ALS, the occurrence of a cluster of cases, especially among individuals who are expected to be at low risk (here, a majority of cases were under the age of 45 years) presents an opportunity to explore an environmental cause.

The relatively young age of the veterans who developed this condition is an infrequent occurrence, suggesting the possibility of an environmental or occupationally related cause, either alone or in interaction with a genetic predisposition or stress-mediated responses. In the 1-year period of military operations, deployed military personnel experienced numerous exposures to multiple, potentially neurotoxic agents (Spencer et al., 1998). If the array of possible candidate environmental exposures could be reduced, it may be possible to identify or at least focus inquiry on specific potential causative agent(s).

Geographic information systems (GIS) analysis is an analytic tool that has potential to achieve this objective through spatial characterization of military unit movements in the war zone. An example of this approach is demonstrated by Proctor et al. (2005) in an analysis of troop movement data and reported chronic multisymptom illness. By identifying those areas with elevated risk for the later development of particular health outcomes, more informed analysis of relevant risk factors can be performed. This paper directly considers the locations where troops were deployed in the theatre of war to determine whether there is any systematic pattern to the spatial locations of persons who eventually developed ALS. A GIS was established for the Southwest Asia area and then used as the basis for undertaking the spatial analysis. While relevant data were relatively limited, data on branch of service and potential of exposure to chemical warfare agents in and around Khamisiyah, Iraq, were available. These explanatory variables were incorporated into the analysis both separately and in combination.

2. Materials and methods

2.1. Study design

This is a secondary analysis of data from a nation-wide case ascertainment study of all new occurrences of ALS among veterans of the 1991 Gulf War from initial deployment in August 1990 through December 2001. This ascertainment period includes the additional year of surveillance for cases that was conducted after the original study ended. The Institutional Review Board at each performance site approved the study design and data collection protocols. The methodology of the original study is briefly summarized below; methodological details are available elsewhere (Horner et al., 2003).

2.2. Study population

For this investigation, the unit of analysis was the individual soldier, nested in a troop unit uniquely identified by a unit identification code (UIC). Fifty verified cases of ALS were identified among the military personnel who were deployed to Southwest Asia at any time during the period of 2 August 1990 through 31 July 1991. These cases were linked to their units based on their UIC as reported by the Defense Manpower Data Center.

Case identification occurred through nation-wide passive and active case ascertainment methods. Passive ascertainment involved a nationally publicized toll-free telephone number that individuals could call if they believed they were eligible for the study. Active case ascertainment involved screening extant Veteran's Administration (VA) and Department of Defense (DoD) inpatient, outpatient, and pharmacy databases using the International Classification of Diseases (9th Revision, Clinical Modification) diagnostic code for ALS (335.20) or use of riluzole, a drug indicated for the treatment of ALS. VA and DoD benefit files, and TriCare (a military health insurance plan) were also searched for individuals with a diagnosis of ALS. Potential participants were sent a letter describing the study and then telephoned to confirm their eligibility and determine their willingness to participate in the study. No financial incentives were offered for study participation.

Disease status was determined according to the most recent World Federation of Neurology El Escorial criteria for ALS (Brooks, 1994; Brooks et al., 1998). A case was defined broadly as any subject who met the criteria for clinically definite, probable, probable with supporting laboratory evidence, possible or suspected ALS (i.e., either lower or upper motor neuron signs and symptoms only). ALS was verified by medical record review for living subjects. If the subject was deceased, disease status was confirmed by either medical record review or, in the absence of medical records, by the underlying cause of death on the death certificate. Each subject's medical record was randomly assigned to two of five study neurologists who were specialists in ALS. Disagreements in the diagnosis (three occurrences) were resolved by consensus among the reviewing neurologists. In three additional cases, the reviewing neurologists agreed that further information was required, and the subject underwent a neurological examination to determine the diagnosis.

2.3. Military unit data

The US Army Center for Health Promotion and Preventive Medicine (USACHPPM) provided data on military troop unit movement, branch of service, and potential exposure to chemical warfare agents near Khamisiyah, Iraq. Military troop unit movement data, developed by the US Armed Services Center for Unit Records Research, tracked daily unit locations from the time of deployment into the Gulf War theatre through withdrawal from the region. The Defense Manpower Data Center's Persian Gulf Veterans Registry (PGVR) used these data to track individual service members' troop unit assignments during Operation Desert Storm, as well as their dates of entry and exit from the theatre. Among the 50 cases, 41 (82%) had records in the PGVR and could be linked to a specific troop unit.

The military troop unit data were originally provided in three tables, including:

- Location of all UICs, containing 705,246 records and described as having "distinct, daily locations of all troop units" in theatre including administrative UICs, which had person counts of 0.
- Locations of UICs that had at least one case.
- Locations of UICs with one or more cases but only for the days each case was actually in theatre.

All locations of administrative UICs were excluded from analysis. Because a UIC ($n = 3327$) could be in multiple locations on any given day or its location data could be missing, a table (667,452 records) was created that contained at least one location for each UIC on each day the UIC was in theatre. In addition, each record includes a count of total ALS cases at that location for each