

NAVAL HEALTH RESEARCH CENTER

OCCURRENCE OF AMYOTROPHIC LATERAL SCLEROSIS AMONG GULF WAR VETERANS

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Report No. 02-08

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20040105 028

REPORT DOCUMENTATION PAGE

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| 1. Report Date (DD MM YY) 22 April 2002 | 2. Report Type New | 3. DATES COVERED (from - to) August 2,1990-July 31, 1991 |
|--|-----------------------|---|

| | |
|--|---|
| 4. TITLE AND SUBTITLE Occurrence of Amyotrophic Lateral Sclerosis Among Gulf War Veterans | 5a. Contract Number: 5b. Grant Number: 5c. Program Element: 5d. Project Number: 5e. Task Number: 5f. Work Unit Number: OH8095 5g. IRB Protocol Number: MOU Only |
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| 6. AUTHORS Ronnie D. Horner, Ph.D., Kimberly Gray Kamins, Ph.D., John R. Feussner, M.D., M.P.H., Steven C. Grambow, Ph.D., Jennifer Hoff-Lindquist, M.Stat., Yadollah Harati, M.D., Hiroshi Mitsumoto, M.D., D.Sci., Robert Pascuzzi, M.D., Peter S. Spencer, Ph.D., Richard Tim, M.D., Dawn Howard M.S.P.H., Tyler C. Smith, M.S., Margaret A.K. Ryan, M.D., M.P.H. and Edward J. Kasarskis, M.D., Ph.D. |
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| 7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Naval Health Research Center P.O. Box 85122 San Diego, CA 92186-5122 | 9. PERFORMING ORGANIZATION REPORT NUMBER Report No. 02-08 |
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| 8. SPONSORING/MONITORING AGENCY NAMES(S) AND ADDRESS(ES) Chief, Bureau of Medicine and Surgery MED-02 2600 E St NW Washington DC 20372-5300 | 10. Sponsor/Monitor's Acronyms(s) BUMED & VA |
| | 11. Sponsor/Monitor's Report Number(s) |

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| 12 DISTRIBUTION/AVAILABILITY STATEMENT Approved for public release; distribution unlimited. |
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| 13. SUPPLEMENTARY NOTES Published in: <u>Neurology</u> , 2003, 61(Sep), 742-749 |
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14. ABSTRACT (maximum 200 words) Context. A nation wide epidemiological investigation was undertaken in response to Gulf War Veterans' concerns of high rates of amyotrophic lateral sclerosis (ALS). **Objective.** To determine if Gulf War veterans have an elevated rate of ALS. **Design.** A field epidemiological study to ascertain all occurrences of ALS for the 10-year period since August, 1990. Target group: military personnel deployed to S.W. Asia during the Gulf War; comparison group: Gulf-era non-deployed military personnel. **Participants.** All active duty military and mobilized Reserves, including National Guard, who served during the time (August 2, 1190-July 31, 1991) defined as the Gulf War period. **Outcome measure.** A diagnosis of ALS was confirmed by medical record review and, as necessary, neurological examination. Risk was assessed by the age-adjusted, average, annual 10-year cumulative incidence rate. **Results.** Among approximately 2.5 million eligible military personnel, 107 confirmed cases of ALS were identified for an overall occurrence of 0.43 per 100,000 persons per year. A statistically significant elevated risk of ALS occurred among all deployed personnel (RR=1.29; 95% CL=1.29,2.84) and deployed active duty military (RR=2.15, 95%CL=1.38,3.36) but not among deployed Reserves and National Guard (RR=2.50; 95%CL=0.88,7.07). Among service branches, a statistically significant elevated risk was observed for deployed personnel in the Air Force (RR=2.38, 95%CL=1.24,5.78) and Army (RR=2.04%;95%CL=1.10,3.77) but not Navy (RR=1.48,95%CL=0.62,3.57) OR marine Corps (RR=1.13;95%CL=0.27,4.79). Overall, the attribute risk associated with deployment was 18% (95%CL=4.9%,29.4%). **Conclusion.** Military personnel, especially Air Force and Army personnel, who were deployed to SW Asia during the Gulf War period experienced a greater post-war risk of ALS than those who were not deployed. Factors associated with elevated risk remain to be determined.

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| 15. SUBJECT TERMS |
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|---------------------------------|---------------------|----------------------|------------------------------------|--------------------------|---|
| 16. SECURITY CLASSIFICATION OF: | | | 17. LIMITATION OF ABSTRACT UNCL | 18. NUMBER OF PAGES 8 | 19a. NAME OF RESPONSIBLE PERSON Commanding Officer |
| a. REPORT UNCL | b. ABSTRACT UNCL | c. THIS PAGE UNCL | | | 19b. TELEPHONE NUMBER (INCLUDING AREA CODE) COMM/DSN: (619) 553-8429 |

Occurrence of amyotrophic lateral sclerosis among Gulf War veterans

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Abstract—Background: In response to Gulf War veterans' concerns of high rates of ALS, this investigation sought to determine if Gulf War veterans have an elevated rate of ALS. **Methods:** A nationwide epidemiologic case ascertainment study design was used to ascertain all occurrences of ALS for the 10-year period since August 1990 among active duty military and mobilized Reserves, including National Guard, who served during the Gulf War (August 2, 1990, through July 31, 1991). The diagnosis of ALS was confirmed by medical record review. Risk was assessed by the age-adjusted, average, annual 10-year cumulative incidence rate. **Results:** Among approximately 2.5 million eligible military personnel, 107 confirmed cases of ALS were identified for an overall occurrence of 0.43 per 100,000 persons per year. A significant elevated risk of ALS occurred among all deployed personnel (RR = 1.92; 95% CL = 1.29, 2.84), deployed active duty military (RR = 2.15, 95% CL = 1.38, 3.36), deployed Air Force (RR = 2.68, 95% CL = 1.24, 5.78), and deployed Army (RR = 2.04; 95% CL = 1.10, 3.77) personnel. Elevated, but nonsignificant, risks were observed for deployed Reserves and National Guard (RR = 2.50; 95% CL = 0.88, 7.07), deployed Navy (RR = 1.48, 95% CL = 0.62, 3.57), and deployed Marine Corps (RR = 1.13; 95% CL = 0.27, 4.79) personnel. Overall, the attributable risk associated with deployment was 18% (95% CL = 4.9%, 29.4%). **Conclusions:** Military personnel who were deployed to the Gulf Region during the Gulf War period experienced a greater post-war risk of ALS than those who were deployed to the Gulf.

NEUROLOGY 2003;61:742-749

Shortly after the end of the Gulf War, military personnel who had been deployed to the Gulf Region began reporting a variety of symptoms, such as memory loss, headaches, joint pains, chronic fatigue, and nervous system disorders. Diagnoses among these Gulf War veterans ranged from undiagnosed illness to ALS, a progressive degenerative neurologic disorder that is generally fatal within 5 years of diagnosis.

In early 1999, representatives of Gulf War veterans expressed their concern to the Chief Research and Development Officer of the Department of Veterans Affairs (VA) that ALS was occurring at a higher than expected rate among Gulf War veterans. They requested an investigation of the situation. During

the spring and summer of 1999, a series of expert panels met and reviewed the ad hoc evidence on the occurrence of ALS among Gulf War veterans. Evidence from a limited mortality study indicated that Gulf War veterans were not experiencing a greater than expected mortality rate from ALS.¹ Unpublished internal studies based on small case series yielded a similar conclusion.^{2,3} However, the panel members expressed concern about the number of cases occurring among relatively young individuals for a rare disease that is very unusual among persons under 45 years of age.

Following the standard epidemiologic approach to investigating a report of an unusual disease occurrence, the first step was to document that the occur-

See also pages 730 and 750

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Supported by the Department of Defense and the Department of Veterans Affairs through a grant from the VA Cooperative Studies Program, VA CSP #500. Received September 4, 2002. Accepted in final form March 18, 2003.

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rence of ALS among Gulf War veterans was truly above expected levels.⁴ Documentation of an elevated occurrence could result in service-connected benefits for those Gulf War veterans who were afflicted. It would also present an opportunity for an etiologic investigation of a disease that, in most cases, has an uncertain etiology; knowledge of etiology or risk factors could be useful in designing effective disease prevention efforts. Accordingly, we conducted an epidemiologic investigation to determine if a higher than expected rate of ALS occurred among military personnel who were deployed to the Gulf Region during the Gulf War, as compared to those who were not deployed. We specified a priori that both the significance and magnitude of the relative risk (i.e., an elevation in the range of twofold) were important considerations in interpreting the results. This report presents the findings of the investigation.

Methods. Study design. A nationwide, epidemiologic case ascertainment study design was used to identify all new occurrences of ALS among Gulf War veterans since the initial deployment in August 1990. The study activities included nationwide case ascertainment, neurologic examinations when required, and in-home interviews of veterans with ALS, their representatives, or both regarding various exposures. The study design and protocols were reviewed and approved by the Institutional Review Board at each performance site, including the Durham VA Medical Center, Durham, NC; Lexington VA Medical Center and the University of Kentucky, Lexington, KY; and the Portland VA Medical Center and the Oregon Health and Science University, Portland, OR.

Study population. The study population was defined as all active duty military and mobilized Reserves and National Guard who served for at least 1 month at any time during the period of August 2, 1990, through July 31, 1991, defined as the Gulf War period. Mobilized Reservists and members of the National Guard were those who were activated and called up, being either deployed to the Gulf Region or back-filling positions of military personnel who were deployed.

The deployed military personnel were the exposed population, with the referent population being Gulf-era military personnel not deployed to the Gulf Region during the Gulf War period. Military personnel were defined as deployed if they served in the Gulf Region theater during Operations Desert Shield and Desert Storm or in the period immediately after Desert Storm (i.e., clean-up).⁵ Although the geographic region that constituted being in-theater varied somewhat among the service branches, the ultimate defining characteristic used by the military was whether the individual received hazardous duty pay. Thus, military personnel were considered in-theater (i.e., deployed) if they were in the Gulf Region (Saudi Arabia, Kuwait and the other Arab Emirates, Turkey, Diego Garcia, or on the Red Sea) or received hazardous duty pay during the Gulf War. All other individuals in the study population were defined as nondeployed, although they may have been stationed outside the United States.

Study eligibility criteria. All eligible subjects had to be in the study population as defined above and have had a diagnosis of ALS made by a health care provider after August 1, 1990.

Case ascertainment. Both passive and active case ascertainment was employed to identify eligible subjects nationwide. Passive ascertainment involved a toll-free telephone number that individuals could call if they believed they were eligible for the study. The telephone number and the criteria for inclusion were publicized in military and nonmilitary media, primarily press releases to newspapers nationally. Subjects were also solicited through notices published on relevant Internet sites (such as that of the ALS Association) and mass mailings of study brochures to practicing neurologists who were members of the American Academy of Neurology, all neurologists at VA medical centers, and members of Veteran Service Organizations. All individuals who called the toll-free number were screened for eligibility and willingness to participate in the study.

Active case ascertainment involved screening extant VA and Department of Defense (DoD) inpatient, outpatient, and pharmacy medical 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. Subjects identified through the screening of the extant databases were first sent a letter describing the study and then telephoned to confirm their eligibility and determine their willingness to participate in the study. If a telephone number was unavailable, the individual was requested to call the toll-free number, if interested in participating. No financial incentives were offered for study participation. However, individuals may have self-identified in anticipation of financial gain either through litigation or service-connected benefits, although at the time of the study, benefits were not available for Gulf War veterans with ALS who were diagnosed more than 1 year after separation from service (i.e., the period for determining service-connected disease eligibility).

Eligible subjects were sent an enrollment packet that consisted of a written consent form and release of medical record information form. The subject completed and returned the forms to the investigative team in Durham, NC. If the veteran was deceased, written consent to participate and release of medical record information was sought from his or her legally authorized representative whenever possible.

Case definition and verification. For all enrolled subjects, disease status was determined according to the most recent World Federation of Neurology (WFN) El Escorial criteria for ALS.^{6,7} These criteria include the presence of lower motor neuron degeneration (by clinical, electrophysiologic, or neuropathologic evidence), upper motor neuron degeneration (by clinical evidence), and progressive spread of signs or symptoms within or beyond the affected regions by history or clinical examination. Moreover, there had to be an absence of electrophysiologic, pathologic, or neuroimaging evidence of other diseases that might explain the signs or symptoms. 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). As an alternative, more conservative definition, cases were excluded if defined as suspected ALS.

Disease status of ALS was verified by medical record review. If the subject was deceased, disease status was confirmed by medical record review whenever possible; in the absence of medical records, confirmation of disease status was by the underlying cause of death on the death certificate. Medical records were obtained from the subjects' medical providers. Each subject's medical record was randomly assigned to two of the five study neurologists, who were specialists in ALS. Disagreements in the diagnosis were resolved by consensus among the reviewing neurologists through discussions of the medical record data. Disagreements regarding the diagnosis being ALS occurred in only three cases; however, in three additional cases, the reviewing neurologists agreed that further information was required and the subject underwent a neurologic examination to determine the diagnosis.

For known deceased subjects, consent to obtain medical records and a copy of the death certificate was requested from the subject's legal representative. If medical records were incomplete or unobtainable, but primary cause of death was listed as ALS on the death certificate, the subject was classified as ALS definite. In the case of known deceased subjects for whom we were unable to locate next of kin, a copy of their death certificate was requested through the National Death Index (NDI), which was current through December 31, 1999. If we were unable to contact the next of kin for any deceased subject who died after December 31, 1999, the death certificate data were requested from the Veterans Benefits Administration.

Deployment status and service branch during the Gulf War period were based on data from the DoD Defense Manpower Data Center (DMDC). In 15 instances there was disagreement between the subject's (or the legal representative's) report of his or her deployment status during the Gulf War and the data from the DMDC. These discrepancies included 12 subjects who indicated they were deployed to the Gulf Region during the Gulf War period and 3 who indicated that they had not been deployed. Because the

Table 1 Demographic and military service characteristics of military personnel during the Gulf War, by DMDC-based deployment status and disease status (%)

| Characteristics | Deployed personnel | | Nondeployed personnel | |
|-------------------------|-----------------------|----------------|-------------------------|----------------|
| | Total* n = 696,118 | ALS* n = 40 | Total* n = 1,786,215 | ALS* n = 67 |
| Age in 1990, y | | | | |
| 24 or younger | 50.2 | 15.0 | 43.4 | 9.0 |
| 25-34 | 34.8 | 42.5 | 36.4 | 34.3 |
| 35-44 | 13.0 | 27.5 | 17.4 | 38.8 |
| 45-54 | 1.8 | 15.0 | 2.6 | 16.4 |
| 55 or older | 0.1 | 0.0 | 0.2 | 1.5 |
| Missing | 0.1 | 0.0 | 0.1 | 0.0 |
| Race/ethnicity | | | | |
| White | 70.7 | 77.5 | 75.2 | 67.2 |
| Black | 22.8 | 10.0 | 19.3 | 14.9 |
| Other | 6.3 | 10.0 | 5.4 | 11.9 |
| Unreported | 0.1 | 2.5 | 0.1 | 6.0 |
| Male sex | 92.8 | 95.0 | 86.8 | 100.0 |
| Unit | | | | |
| Active | 84.4 | 77.5 | 92.2 | 91.0 |
| Reserves/National Guard | 15.6 | 22.5 | 7.8 | 9.0 |
| Service branch | | | | |
| Air Force | 11.9 | 22.5 | 29.3 | 35.8 |
| Army | 50.4 | 52.5 | 33.0 | 29.8 |
| Marine Corps | 14.9 | 7.5 | 8.2 | 7.5 |
| Navy | 22.8 | 17.5 | 29.5 | 26.9 |

* Source: US Department of Defense Manpower Data Center (DMDC).

DMDC records are recognized to have a 5% error rate for deployment identification data from the Gulf War era, deployment status was also based on the subject's self-report as an alternative approach to defining this key variable.⁸

Data analysis. The fundamental measure of disease occurrence was the 10-year cumulative incidence rate that was calculated as the number of cases identified divided by the population at risk. The cumulative incidence was expressed as an average, annual rate per 100,000 persons. Age-adjusted rates were computed by direct adjustment using the total study population as the standard and were based on the earliest noted age at onset of the disease as determined by the medical record review; when unknown, age at onset was imputed by regression using data from deceased subjects for whom age at onset was known.⁹⁻¹¹ The risks among the deployed and nondeployed populations were compared using the age-adjusted risk ratio; 95% confidence limits (CL) were calculated based on the methods outlined by Rothman and Greenland.¹² To assess the absolute impact of deployment on the occurrence of ALS and the proportion of occurrence attributable to deployment, we calculated the risk difference and age-adjusted attributable risk (expressed as a percentage) and 95% CL per Rothman and Greenland.¹²

Results. Study population. There were 2,482,333 individuals who were on active duty or activated Reserve status during the Gulf War, of whom 696,118 were deployed to the Gulf Region. Table 1 presents the demographic and military service characteristics of these individuals at the time of the Gulf War according to

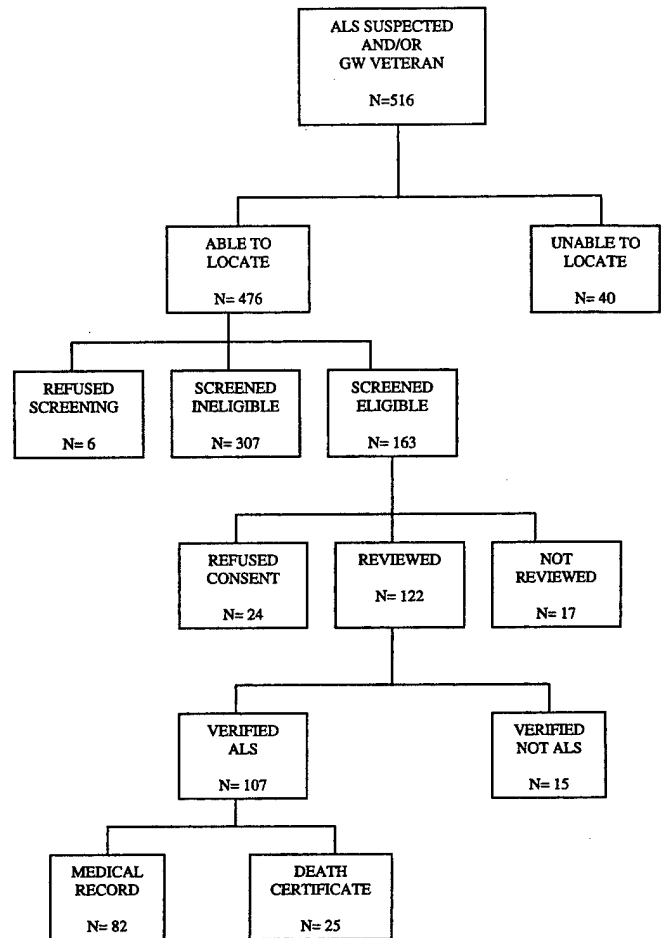


Figure. Study recruitment flow. GW = Gulf War.

their DMDC-based deployment status. Relative to nondeployed Gulf-era personnel, deployed personnel were younger and slightly more likely to be nonwhite and to be men. Deployed forces also were comprised of a greater proportion of mobilized Reserves and National Guard, Army, and Marine Corps personnel.

Case ascertainment. From the initial passive and active case ascertainment phase, 516 potentially eligible cases of ALS were identified (figure). Of these individuals, 476 (92.2%) were successfully contacted; a valid address or working telephone number was not available for the remaining 7.8%. Among the 476 potential cases who were contacted, 307 (64.5%) were ineligible for the study. For 279 (91%) of the 307 individuals, the diagnosis of ALS was unlikely based on the subjects' reported diagnosis or their description of their disease—i.e., they either indicated they were not diagnosed with ALS or reported that they were not having symptoms of ALS such as progressive difficulty walking; progressive weakness in their legs, arms, or hands; progressive difficulty in hand or arm movement; or difficulty chewing or speaking. The remaining 28 (9%) of the 307 individuals had a diagnosis date before August 2, 1990, had not been on active duty, or had not been activated and called up during the Gulf War period. Of the 476 contacted potential cases, 6 (1.3%) refused to be screened for eligibility. Thus, from among the 476 potential cases, the number of cases who were eligible for the study and progressed to case verification was 163 (34.2%). Only 23 (14.1%) of these 163 eligible cases were identified solely by passive methods, with the balance having been identified by active case ascertainment methods; 65% of all eligible cases were identified in two or more data sources. Deployed and nondeployed cases were similar in the proportions identified by the various methods: passive methods alone, active methods alone, or a combination of both active and passive methods, with approximately 17% of deployed and 12% of nondeployed identified by passive means alone.

Table 2 Age-adjusted, average, annual 10-year cumulative incidence of ALS among military personnel by DMDC-reported deployment status during the Gulf War

| Population | Defense Manpower Data Center (DMDC)-reported deployment status | | | | | | |
|-------------------------|--|-------|-------------------|----------------------------|-------|-------------------|----------------------|
| | Deployed, n = 696,118 | | | Nondeployed, n = 1,786,215 | | | Risk ratio† (95% CL) |
| | Population | Cases | Rate* | Population | Cases | Rate* | |
| Total | 696,118 | 40 | 0.67 (0.46, 0.88) | 1,786,215 | 67 | 0.35 (0.27, 0.44) | 1.92 (1.29, 2.84) |
| Unit | | | | | | | |
| Active duty | 587,426 | 31 | 0.73 (0.46, 0.99) | 1,646,926 | 61 | 0.34 (0.25, 0.42) | 2.15 (1.38, 3.36) |
| Reserves/National Guard | 108,692 | 9 | 0.94 (0.32, 1.56) | 139,289 | 6 | 0.38 (0.07, 0.68) | 2.50 (0.88, 7.07) |
| Service branch | | | | | | | |
| Air Force | 82,639 | 9 | 1.21 (0.42, 2.01) | 523,763 | 24 | 0.45 (0.27, 0.63) | 2.68 (1.24, 5.78) |
| Army | 351,046 | 21 | 0.66 (0.37, 0.94) | 588,740 | 20 | 0.32 (0.18, 0.46) | 2.04 (1.10, 3.77) |
| Marine Corps | 103,612 | 3 | 0.33 (0.00, 0.71) | 146,294 | 5 | 0.29 (0.03, 0.55) | 1.13 (0.27, 4.79) |
| Navy | 157,969 | 7 | 0.53 (0.13, 0.92) | 486,559 | 18 | 0.35 (0.19, 0.52) | 1.48 (0.62, 3.57) |

* Average annual rate per 100,000 persons during the 10-year period beginning August 2, 1990. Total study population used as the standard.

† Risk ratio: Risk of patients with ALS given deployment to the Gulf Region during the Gulf War; nondeployed Gulf-era military personnel are the referent population.

CL = confidence limits.

Case verification. Among the 163 eligible cases, 24 (14.7%) who initially indicated willingness to participate in the study subsequently refused; of these, 10 (41.7%) had been deployed to the Gulf Region. An additional 17 (10.4%) subjects had not provided authorization for medical record access by the end of the study. Medical record reviews or death certificates were obtained for 122 (74.8%) subjects. Those who refused to participate or who never provided written authorization for record review were similar to those who participated in terms of age, race/ethnicity, sex, service unit status (active or Reserves/National Guard), service branch, and deployment status.

The diagnosis of ALS, including all levels of certainty from definite to suspected, was confirmed for 107 (87.7%) of the 122 participating potential cases; level of diagnostic certainty was suspected ALS for 11 of these individuals, of whom 5 had been deployed to the Gulf Region during the Gulf War period. A familial history of ALS was present for six cases, two of whom had been deployed. The diagnosis for 13 (10.6%) individuals was based on NDI data alone because sufficient medical record data could not be obtained. A total of 15 (12.3%) of the 122 potential cases were determined not to have ALS per the study criteria; 10 of these 15 subjects had been deployed to the Gulf Region during the Gulf War period. The diagnoses of these individuals included demyelinating disease, spinocerebellar degeneration, post-traumatic stress syndrome, multiphasic motor neuron disease, various neuropathies (ulnar, diabetic, sensorimotor), familial spastic paraparesis, MS, and radiculopathy.

Among cases, those who had been deployed differed from those who had not been deployed in a number of characteristics (see table 1). As compared to nondeployed cases, deployed cases were younger at the time of the Gulf War, and a greater proportion was white, from the Reserves or National Guard, or in the Army, whereas lower proportions were in the Air Force or Navy.

Incidence and relative risk of ALS. The average, annual cumulative incidence of verified ALS among the entire study population was 0.43 per 100,000 persons (over the 10-year period beginning August 2, 1990). Average annual age-specific rates (per 100,000 persons) were 0.03 for those aged under 25 years at time of onset, 0.31 for those aged 25 to 34 years, 1.02 for those aged 35 to 44 years, 4.99 for those aged 45 to 55 years, and 13.84 for those aged 55 to 64 years. Those individuals who had been deployed to the Gulf Region during the Gulf War period had almost a twofold greater risk of ALS relative to those who were not deployed (table 2). Among deployed personnel, a significantly elevated relative risk occurred for those who were active duty military, Air Force,

and Army. Elevated, but nonsignificant, relative risks were found for deployed Reserves/National Guard, Marine Corps, and Navy personnel.

Risk difference and attributable risk. The risk difference (excess risk) associated with deployment to the Gulf Region during the Gulf War period was 0.32 per 100,000 persons per year. The attributable risk of ALS associated with deployment was 18% (95% CL = 4.9%, 29.4%). For Air Force and Army personnel, the attributable risk of ALS associated with deployment was 19% (95% CL = 0.0%, 36.6%) and 31% (95% CL = 0.0%, 54.2%).

Further analyses. Additional analyses were conducted to determine the robustness of the findings; these analyses employed the alternative definitions of deployment and case status. Also, to minimize any bias from cases who were potentially ill before the Gulf War, the set of cases was restricted to those who had disease onset after July 31, 1991; that is, after the Gulf War period. To assess the impact of sex differences between the deployed and nondeployed populations, an analysis restricted to men only was also performed. We also conducted an analysis restricted to cases without a family history of ALS.

When the case's self-report of deployment status was used instead of DMDC-reported status, the relative risk increased for all deployed military personnel, for those within each unit type (i.e., active vs Reserves/National Guard), and for those within service branches except for Army, which decreased slightly (table 3). Significantly elevated risks were found for deployed Navy personnel and Reserves/National Guard in addition to all active duty military and Air Force personnel; for deployed Army personnel, the relative risk was of borderline significance with the lower 95% CL being 1.002.

When the definition of case status was restricted in terms of diagnostic certainty, date of onset, sex, or family history of ALS, a significant elevation of risk was found uniformly for all deployed military personnel and deployed personnel who were active duty and, with a few exceptions, elevated risks were also found for deployed military personnel in the Reserves/National Guard, Air Force, and Army (table 4). Analyses involving various subsets (e.g., men only with strict criteria or men only with onset post-1991) yielded similar findings. As an additional analysis, those who had refused to participate (n = 24) and those who had not provided authorization for medical record access (n = 17) were assumed to be confirmed cases and their ages at onset were assumed to follow the distribution of the 107 confirmed cases. Again, deployment to the Gulf Region was associated with a significantly elevated risk of ALS whether DMDC-based deployment status

Table 3 Age-adjusted, average, annual 10-year cumulative incidence of ALS among military personnel by self-reported deployment status during the Gulf War

| Population | Self-reported deployment status | | | | | | Risk ratio† (95% CL) |
|-------------------------|---------------------------------|-------|-------------------|----------------------------|-------|-------------------|----------------------|
| | Deployed, n = 696,118 | | | Nondeployed, n = 1,786,215 | | | |
| | Population | Cases | Rate* | Population | Cases | Rate* | |
| Total | 696,118 | 49 | 0.84 (0.60, 1.07) | 1,786,215 | 58 | 0.31 (0.23, 0.38) | 2.74 (1.87, 4.01) |
| Unit | | | | | | | |
| Active duty | 587,426 | 40 | 0.99 (0.67, 1.31) | 1,646,926 | 53 | 0.29 (0.21, 0.37) | 3.37 (2.21, 5.14) |
| Reserves/National Guard | 108,692 | 9 | 0.99 (0.33, 1.65) | 139,289 | 5 | 0.33 (0.04, 0.61) | 3.05 (1.01, 9.16) |
| Service branch | | | | | | | |
| Air Force | 82,639 | 14 | 1.82 (0.86, 2.78) | 523,763 | 18 | 0.34 (0.18, 0.49) | 5.38 (2.67, 10.85) |
| Army | 351,046 | 20 | 0.63 (0.35, 0.90) | 588,740 | 21 | 0.34 (0.19, 0.48) | 1.85 (1.00, 3.43) |
| Marine Corps | 103,612 | 4 | 0.52 (0.00, 1.04) | 146,294 | 5 | 0.29 (0.03, 0.55) | 1.77 (0.46, 6.76) |
| Navy | 157,969 | 11 | 0.83 (0.33, 1.32) | 486,559 | 14 | 0.28 (0.13, 0.42) | 2.99 (1.35, 6.61) |

* Average annual rate per 100,000 persons during the 10-year period beginning August 2, 1990. Total study population used as the standard.

† Risk ratio: Risk of patients with ALS given deployment to the Gulf Region during the Gulf War; nondeployed Gulf-era military personnel are the referent population.

CL = confidence limits.

(RR = 1.90; 95% CL = 1.36, 2.65) or self-reported deployment status (RR = 2.91; 95% CL = 2.11, 4.03) was used.

To assess the potential magnitude and impact of underascertainment of deployed and nondeployed cases on the overall relative risk associated with deployment, a capture-recapture analysis was conducted. Capture-recapture analysis generates an estimate of the total number of cases in a population based on the overlap in the lists of identified cases derived from multiple data sources; the method was previously used in a study of ALS in France.^{13,14} This analysis indicated possibly 45 cases among deployed military personnel vs the 40 identified and possibly 89 cases among the nondeployed military personnel vs the 67 identified. The resulting

age-adjusted relative risk was 1.62 (95% CI = 1.13, 2.33), indicating a significantly elevated risk of ALS among the deployed. Moreover, as an alternative approach to adjusting for possible underascertainment of cases among the nondeployed, cases identified by passive ascertainment methods only were excluded. This resulted in an increase in the age-adjusted relative risk associated with deployment overall (RR = 2.16; 95% CL = 1.43, 3.24), for active duty military (RR = 2.41; 95% CL = 1.52, 3.82), Reserves/National Guard (RR = 3.01; 95% CL = 1.00, 9.06), Air Force (RR = 2.69; 95% CL = 1.19, 6.08), Army (RR = 2.27; 95% CL = 1.21, 4.27), Marine Corps (RR = 1.47; 95% CL = 0.33, 6.61), and Navy (RR = 1.79; 95% CL = 0.73, 4.40).

Table 4 Age-adjusted risk ratios* of ALS among military personnel according to alternative definitions of deployment status during the Gulf War and of an eligible case

| Population | DMDC-reported Deployment Status: | | | Self-reported Deployment Status: | | |
|-------------------------|--------------------------------------|-------------------------------|--------------------|--------------------------------------|-------------------------------|---------------------|
| | Strict Diagnostic Criteria† (n = 86) | Onset Post-July 1991 (n = 91) | Men Only (n = 105) | Strict Diagnostic Criteria† (n = 86) | Onset Post-July 1991 (n = 91) | Men Only (n = 105) |
| Total | 2.07‡ (1.34, 3.19) | 1.84‡ (1.20, 2.83) | 1.75‡ (1.17, 2.61) | 2.53‡ (1.65, 3.87) | 2.67‡ (1.77, 4.05) | 2.54‡ (1.72, 3.73) |
| Unit | | | | | | |
| Active | 2.22‡ (1.36, 3.63) | 2.01‡ (1.23, 3.28) | 1.99‡ (1.26, 3.13) | 2.54‡ (1.57, 4.12) | 3.14‡ (1.97, 5.00) | 2.93‡ (1.90, 4.51) |
| Reserves/National Guard | 3.37‡ (1.01, 11.27) | 2.73 (0.89, 8.40) | 2.17 (0.75, 6.31) | 8.55‡ (1.85, 39.44) | 3.89‡ (1.19, 12.71) | 4.14‡ (1.29, 13.31) |
| Service branch | | | | | | |
| Air Force | 3.06‡ (1.40, 6.70) | 2.11 (0.91, 4.91) | 2.60‡ (1.20, 5.62) | 4.64‡ (2.23, 9.67) | 4.39‡ (2.12, 9.05) | 4.97‡ (2.48, 9.94) |
| Army | 2.14‡ (1.07, 4.30) | 2.69‡ (1.35, 5.38) | 1.78 (0.95, 3.35) | 2.15‡ (1.07, 4.33) | 2.38‡ (1.20, 4.74) | 1.79 (0.95, 3.37) |
| Marine Corps | 0.90 (0.16, 4.93) | 1.13 (0.27, 4.79) | 1.09 (0.26, 4.59) | 0.90 (0.16, 4.93) | 1.13 (0.27, 4.79) | 1.09 (0.26, 4.59) |
| Navy | 1.92 (0.72, 5.15) | 0.99 (0.33, 3.00) | 1.41 (0.59, 3.40) | 2.42 (0.93, 6.27) | 2.71‡ (1.09, 6.77) | 2.84‡ (1.28, 6.29) |

* Risk ratios are based on the age-adjusted, average annual cumulative incidence rate per 100,000 persons during the 10-year period beginning August 2, 1990 among deployed and nondeployed military personnel. Total study population used as the standard. Ratios indicate the relative risk of ALS among military personnel deployed to the Gulf Region during the Gulf War. Nondeployed military Gulf-era personnel are the referent population.

† Strict diagnostic criteria are defined as the following World Federation of Neurology criteria of diagnostic certainty: definite, probable, and probable with laboratory evidence. Deceased cases with ALS as an underlying cause of death are considered definite ALS.

‡ Risk ratios are significantly elevated ($p < 0.05$).

DMDC = Defense Manpower Data.

Discussion. An almost twofold greater risk of ALS was found among military personnel who had been deployed to the Gulf Region during the Gulf War period. The attributable risk, or proportion of the occurrence, associated with deployment to the Gulf Region was 18%. Deployed personnel in the Air Force and Army also experienced a significantly elevated relative risk of ALS of approximately two or greater. The attributable risk was 19% and 31% for Air Force and Army. This implies that, perhaps, 7 of the 40 occurrences among the deployed overall, 1 of 9 occurrences among deployed Air Force, and 6 of 21 occurrences among deployed Army personnel are associated with deployment. The relative risks were similar when cases were restricted to those without a familial history of ALS, those who met more stringent WFN criteria: definite or probable ALS, those with a date of onset after the Gulf War period, those who were men, or combinations of these characteristics. The relative risks were generally higher when deployment status was based on self-report rather than on DMDC records.

It should be noted that the risk ratios were elevated in all subgroups, including Reserves and National Guard, Navy, and Marine Corps, but these risk ratios lacked significance. This is a likely consequence of low statistical power owing to the relatively small number of cases within these groups. As an epidemiologic investigation of disease occurrence in a specific population, the size of the population and its subgroups were predetermined and could not be modified by the study design. Thus, the sample sizes within some subgroups may have been suboptimal statistically for a study of a rare disease. However, the inability to definitively assess statistically the risk within some subgroups does not, per se, invalidate the significant risk ratio that we found for all deployed military personnel, and deployed active duty military, Air Force, and Army personnel. Low statistical power affects primarily the precision of the point estimate, widening the CL. With continued surveillance, additional cases may be identified that may yield more statistically precise rates within subgroups.

Previous published and unpublished studies report findings of equivocal interpretation regarding the occurrence of ALS among Gulf War veterans.^{1,3,13,14} A mortality study and its more recent update indicated a relative risk of 0.59 (95% CI = 0.21, 1.66), whereas a study of hospitalized patients estimated a relative risk of 1.66 (95% CI = 0.62, 4.44).^{1,15,16} These studies had 6 years of follow-up for a disease that may have an incubation period of 10 years or longer. Moreover, the study populations did not include all at-risk military personnel; the hospital-based study included only active duty military personnel and the mortality study used a sample of nondeployed military personnel. Thus, the observed differences in findings may be attributable to the longer follow-up or the inclusion of the entire at-risk population used in this study. Surveillance continues for veterans who de-

veloped ALS during the study period, as well as for those who develop the disease after the study period.

The current investigation sought to identify all occurrences of ALS from the entire population at risk, using both passive and active case ascertainment strategies and multiple sources. The majority of cases were found by active rather than passive ascertainment methods and appeared in multiple sources. Among those sources was the DoD medical retirement database where nondeployed cases were likely to be recorded before separation from service. Of the 107 verified cases, only 1 (2.5%) deployed case, but 9 (13.4%) nondeployed cases, were identified solely through passive ascertainment; if we use the larger group of verified and unverified cases, approximately 10% of both deployed and nondeployed cases were identified by passive methods exclusively. Exclusion of these cases—an approach to adjusting for underascertainment among the nondeployed military personnel—yielded higher risk ratios, but did not alter the significance. Because active ascertainment was restricted to VA and DoD medical databases, those cases who were using the private health sector exclusively would not be identified by this approach.

We were able to screen for eligibility the majority of the identified potential cases. Only 40 of the identified 516 potential cases could not be contacted and only 5 of the remaining 476 individuals refused to have their eligibility verified. Given the rarity of the disease and the high percentage of potential cases who had an unlikely diagnosis of ALS among those who were screened, there is a low probability that all or even most of these 46 individuals represent missed bona fide cases of ALS.

Underascertainment is a potential bias for any epidemiologic investigation; this is most serious when it differentially affects the groups of interest, namely, the deployed and nondeployed military personnel. Individuals who were deployed may have been more highly motivated to be identified because of the potential of monetary gain either through litigation or service-connected benefits. However, at the time of this investigation, veterans who developed ALS after the allowable separation period (1 year) were not eligible for veteran benefits on the basis of their disease. Thus, cases receiving benefits for undiagnosed illness and who were subsequently diagnosed with ALS more than 1 year after separation from service could potentially lose some compensation benefits. This potential risk was indicated in our consent form, a requirement of the involved Institutional Review Boards that we list all potential risks associated with participating, including the risk of possible loss of benefits if a diagnosis of ALS could change eligibility for benefits. In several instances ($n = 5$), eligible potential cases refused to participate in the study because of the fear of potential loss of benefits. Consequently, the rates may be higher among the deployed personnel than reported here.

Conversely, one might speculate that more of the

nondeployed cases had either never learned of the study or had little incentive to be identified. To maximize awareness of the study, we worked with the American Academy of Neurology to publicize the study to almost 11,000 practicing neurologists nationwide to whom nondeployed veterans might seek care. Also, through a national media campaign, we alerted the larger veteran population to the study. Our success in these efforts was evidenced by hundreds of letters, e-mails, and telephone calls regarding the study that were received from neurologists, veterans whose comrades developed the disease, and veterans with ALS or their surviving family members. In many instances, the veterans with ALS had served during either the Vietnam or Korean War and a few had served during the Second World War, adding support for our belief that we reached the larger veteran population.

One may also be concerned that, although nondeployed veterans and active duty military personnel were made aware of the study, they may not have been motivated to participate. However, we received many calls from patients, and their families and friends, with strong interest in the study and hope that it would reveal important information about the cause or treatment of ALS. But it is also notable that 30 potential cases refused to allow screening or record review, and another 17 potential cases who screened eligible for the study failed to respond to contact attempts or provide their records for review. These were evenly distributed among the deployed and nondeployed groups. When we included such indeterminate cases as confirmed cases in our analysis, the association between ALS and deployment persisted.

Perhaps more compelling evidence in support of near-complete ascertainment of cases among the nondeployed is found in their rate of occurrence. When standardized to the 1990 US general population, the average annual rate of ALS among the nondeployed military population was 1.4 per 100,000 persons per year as compared to the generally accepted overall population rate for the United States of 1 to 2 per 100,000. (For comparison, the rate among the deployed military population, when standardized to the 1990 US general population, was 3.6 per 100,000 persons per year.)

Nonetheless, it is unlikely that there will ever be complete certainty that all cases were identified. Consequently, we also conducted a capture-recapture analysis to generate an estimate of the possible magnitude and impact on the relative risk of underascertainment of cases among the deployed and nondeployed military personnel. The overall risk ratio remained significantly elevated; thus, even with correction for potential underascertainment of cases, there is an elevated risk of ALS among those deployed to the Gulf Region during the Gulf War.

Beyond detection of cases, another potential source of bias is the determination of case status. Although the study neurologists who did the medical

record reviews were not explicitly blinded to the deployment status of the cases, we believe that any bias is minimal and likely to yield conservative results. Case status was determined by two independent reviews of the medical record (when available) using externally established, objective criteria; only 10% of the diagnoses were determined from the death certificate alone. Moreover, the outcome of the review process indicated a more stringent review of the deployed case series. Ten of the 15 subjects determined not to have ALS were from the set of deployed potential cases whereas a greater number of suspected ALS cases was included among the nondeployed case series.

Most cases of sporadic ALS are of unknown etiology; only about 10% of case series have a family history of ALS. This appears to be the experience for this case series as well. A preliminary analysis of data from the in-home interviews suggests that six cases, of which two were deployed to the Gulf Region during the Gulf War, have a family history of ALS. Potential etiologies must be viewed to include genetic predisposition and a range of possible environmental exposures.¹⁷⁻²³ Although we found significant elevated risks for two service branches—Air Force and Army—this may not enable researchers to narrow the array of possible risk factors. Elevated risks were also found for deployed Navy and Marine Corps personnel and deployed Reserves/National Guard, but these lacked significance, most likely owing to the low statistical power, as discussed previously. Clues to possible risk factors may be gleaned from the analysis of data from the in-home interviews of these veterans or their representatives. Clues may also come from cross-comparison of the self-reported data with the array of environmental risk factors associated with the specific periods of the veteran's deployment and location in the Gulf Region during the Gulf War.⁵

Acknowledgment

The authors thank the numerous organizations and individuals who assisted in the case-finding activities, including the national ALS Association and especially Mary Lyon, ALS CARE group, ALS Interest Group and ALS Digest, ALS Network, Great Lakes ALS Group, Western ALS Study Group, International Alliance of ALS/MND Association, NC ALS Chapter, Muscular Dystrophy Association, the American Academy of Neurology, Society for Neuroscience, World Federation of Neurology, Paralyzed Veterans of America, Veterans of Foreign Wars, American Gulf War Association, American Legion, Disabled American Veterans, National Gulf War Resource Center, VA Persian Gulf War Veterans Illnesses organization, and numerous military and nonmilitary news organizations. Drs. Horner and Kamins were with the VA Epidemiologic Research and Information, Durham VA Medical Center, and Dr. Feussner with the Office of Research and Development, Department of Veterans Affairs, when this study was conducted. Dr. Richard Tim is now with Raleigh Neurologic Associates, Raleigh, NC. D. Howard is now with the University of North Carolina at Chapel Hill. The authors also thank Dr. Drue Barrett of the Centers for Disease Control and Prevention for helpful comments on study design, Michael Dove and the team at the Defense Manpower Data Center in Monterey, CA, for providing data on deployment status and other characteristics of the military population, and Valerie Palmer and Linda Dempsey-Hall for assistance in data collection. The authors especially thank the brave men and women of the

military who protect American freedoms, serving their country with distinction and heroism.

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