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Military service, deployments, and exposures in relation to amyotrophic lateral sclerosis etiology

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ABSTRACT

Background: Factors underlying a possible excess of amyotrophic lateral sclerosis (ALS) among military veterans remain unidentified. Limitations of previous studies on this topic include reliance on ALS mortality as a surrogate for ALS incidence, low statistical power, and sparse information on military-related factors.
Objectives: We evaluated associations between military-related factors and ALS using data from a case-control study of U.S. military veterans.
Methods: From 2005 to 2010, we identified medical record-confirmed ALS cases via the National Registry of Veterans with ALS and controls via the Veterans Benefits Administration's Beneficiary Identification and Records Locator System database. In total, we enrolled 621 cases and 958 frequency-matched controls in the Genes and Environmental Exposures in Veterans with Amyotrophic Lateral Sclerosis study. We collected information on military service and deployments and 39 related exposures. We used unconditional logistic regression models to estimate odds ratios (ORs) and 95% confidence intervals (CIs). We used inverse probability weighting to adjust for potential bias from confounding, missing covariate data, and selection arising from a case group that disproportionately included long-term survivors and a control group that may or may not differ from U.S. military veterans at large.
Results: The odds of ALS did not differ for veterans of the Air Force, Army, Marines, and Navy. We found higher odds of ALS for veterans whose longest deployment was World War II or the Korean War and a positive trend with total years of all deployments (OR = 1.27; 95% CI: 1.06, 1.52). ALS was positively associated with exposure to herbicides for military purposes, nasopharyngeal radium, personal pesticides, exhaust from heaters or generators, high-intensity radar waves, contaminated food, explosions within one mile, herbicides in the field, mixing and application of burning agents, burning agents in the field, and Agent Orange in the field, with ORs between 1.50 and 7.75.
Conclusions: Although our results need confirmation, they are potentially important given the large number of U.S. military veterans, and they provide clues to potential factors underlying the apparent increase of ALS in veteran populations.

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Abbreviations: ALS, amyotrophic lateral sclerosis; ALSFRS-R, ALS Functional Rating Scale-Revised; BIRLS, Beneficiary Identification and Records Locator System; CARC, Chemical Agent Resistant Compound; CI, confidence interval; DU, depleted uranium; four wars, World War II and the Korean, Vietnam, and 1990–1991 Persian Gulf War; GENEVA, Genes and Environmental Exposures in Veterans with Amyotrophic Lateral Sclerosis study; GIS, geographic information system; Gulf War, 1990–1991 Persian Gulf War; IP, inverse probability; IQR, interquartile range; MSAS, minimally sufficient adjustment set; NIEHS, National Institute of Environmental Health Sciences; NP, nasopharyngeal; OR, odds ratio; PLS, primary lateral sclerosis; Registry, U.S. National Registry of Veterans with ALS; VA, U.S. Department of Veterans Affairs; weight, inverse probability weight; WWII, World War II.

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1. Introduction

Amyotrophic lateral sclerosis (ALS) is a debilitating neurodegenerative disease involving motor neuron loss in the central nervous system (Mitchell and Borasio, 2007). A possible association between military-related factors and ALS was first suggested in connection with the 1990–1991 Persian Gulf War (hereafter "Gulf War"). Five of seven previously published studies reported an increased rate of ALS incidence, hospitalization, or mortality among veterans deployed to the Gulf War compared to veterans deployed elsewhere (Barth et al., 2009; Coffman et al., 2005; Haley, 2003; Horner et al., 2003, 2008; Kang and Bullman, 2001; Smith et al., 2000). Another study found a higher ALS mortality rate among men who reported military service than men who did not (Weisskopf et al., 2005). This result was recently confirmed by studies in the U.S. (Weisskopf et al., 2015), Denmark (Seals et al., 2016), and Scotland (Bergman et al., 2015). Most of these studies, and 22 others on this topic that we recently reviewed (Beard and Kamel, 2015), were limited by reliance on ALS mortality as a surrogate for ALS incidence, low statistical power, and sparse information on military-related factors. In addition, two-thirds of these studies did not include information on specific military exposures. Thus, the factors underlying the possibly increased rate of ALS among veterans remain unidentified.

The Genes and Environmental Exposures in Veterans with Amyotrophic Lateral Sclerosis study (GENEVA), conducted from 2005 to 2010, is a case-control study of veterans with ALS from the U.S. National Registry of Veterans with ALS (hereafter "Registry") (Allen et al., 2008) and frequency-matched veteran controls identified via U.S. Department of Veterans Affairs (VA) databases (Schmidt et al., 2008). To enroll in GENEVA, participants had to confirm that they had been members of the U.S. Army, Air Force, Navy, Marine Corps, Coast Guard, activated Reserves or National Guard at some point in time (Beard, 2015). They did not have to have been deployed to war. We evaluated associations between ALS and several aspects of military service and deployments as well as 39 related exposures among veterans in GENEVA.

2. Materials and methods

2.1. Study population and case definition

Enrollment of cases first in the Registry, then in GENEVA, was described previously (Allen et al., 2008; Schmidt et al., 2008). Briefly, the Registry was started because of the possible connection between ALS and deployment to the Gulf War (Allen et al., 2008; Kasarskis et al., 2004; Schmidt et al., 2008). Potential cases were recruited for the Registry from 2003 to 2007 (i.e., from the year Haley (2003) and Horner et al. (2003) were published to when funding expired). Recruitment strategies included publicizing the Registry and searches of national VA databases for patients with *International Classification of Diseases, 9th Revision* (World Health Organization, 1977), codes of the form 335.2X (motor neuron diseases) (Allen et al., 2008). In total, 7116 potential cases were identified, 4626 completed a telephone screening (Beard, 2015), and 2600 reported a past diagnosis (Allen et al., 2008). Of these, 2400 consented to join, 2265 provided medical records for review by ALS specialist neurologists, and 2122 had a diagnosis of ALS or a related motor neuron disease confirmed according to the Revised El Escorial Criteria (Allen et al., 2008; Brooks et al., 2000). These 2122 veteran cases were followed via standardized semi-annual telephone interviews until 2009.

Ascertainment of GENEVA cases from those enrolled in the Registry is shown in Fig. 1. Of 1856 ALS cases, 1837 gave permission to be recontacted for further studies, 1356 consented to join the Registry DNA bank, and 847 were able to be contacted regarding GENEVA enrollment. Of these, 726 consented to join and 630 were interviewed of which 621 were included in this analysis because they were not missing covariate data. These cases include those with clinically definite, probable, possible, or suspected ALS.

Enrollment of GENEVA controls was described previously (Schmidt et al., 2008). Fig. 2 shows ascertainment of GENEVA controls from an age-stratified random sample of 10,000 records obtained in June 2005 from the Veterans Benefits Administration's Beneficiary Identification and Records Locator System (BIRLS) database (Schmidt et al., 2008). Of 8966 potential controls with addresses available, 4420 were mailed invitations, 2728 were able to be contacted by telephone, and 1618 were screened for eligibility. Nine individuals not part of the original BIRLS sample contacted GENEVA regarding enrollment and were screened for eligibility. In total, 1536 potential controls were eligible, 1055 consented to join, and 975 controls were interviewed of which 958 were included in this analysis because they were not missing covariate data.

Controls were frequency-matched to cases on diagnosis age (within five years) and on use of the VA health care system before diagnosis date (cases) or interview date (controls) (Schmidt et al., 2008). We matched on age because it is a risk factor for ALS (Mitchell and Borasio, 2007). VA health care use served as a surrogate for socioeconomic status, which may be related to ALS (Sutedja et al., 2007).

GENEVA was approved by Institutional Review Boards of the Durham VA Medical Center, Duke University Medical Center, and the National Institute of Environmental Health Sciences; the Institutional Review Board of the University of North Carolina at Chapel Hill approved this ancillary study. All participants gave written or oral informed consent before enrollment.

2.2. Exposure assessment

For cases, we extracted clinical characteristics from medical records and collected baseline (closest to GENEVA enrollment) ALS Functional Rating Scale-Revised (ALSFRS-R) score (Cedarbaum et al., 1999) via the Registry semi-annual telephone interviews (Beard, 2015). For cases and controls, we used standardized telephone interviews for GENEVA (Beard, 2015) to gather information on military service, deployments, and exposures that occurred before diagnosis date (cases) or interview date (controls), as well as on potential confounders (Beard, 2015; Schmidt et al., 2008). Proxy interviews were necessary for 34 (5%) cases, but no controls. More detail regarding interview procedures is provided elsewhere (Schmidt et al., 2008).

Self-reported information on military service included branch of longest service (i.e., the branch in which the veteran served the longest total time), number of branches, rank, total service time, and end of most recent service (Supplementary data, p. S3). Self-reported information on deployments to World War II (WWII) and the Korean, Vietnam, and Gulf Wars (hereafter "four wars") as well as operations in nine other locations included ever deployment to any war/operation, war/operation of longest deployment (i.e., the war or operation to which the veteran was deployed for the longest total time), total time of all deployments, and end of most recent deployment (Supplementary data, p. S3). We also had self-reported information on ever deployment to any other country; ever receiving imminent danger pay, hardship duty, or combat zone tax exclusion benefits for deployment to 17 foreign countries and/or five sea regions (plus fill-in options); and total time deployed to those countries/sea regions (Supplementary data, p. S4).

We had self-reported information on 39 specific military exposures which we chose by adapting the questionnaires used in the Iowa Gulf War study (Doebbeling et al., 2002) and the Millennium Cohort Study (Ryan et al., 2007; Smith and Millennium Cohort Study Team, 2009) for use in GENEVA (Beard, 2015; Schmidt et al., 2008). In addition, we added a few questions on exposures that were specific to one or more of the four wars (e.g., Agent Orange exposure during the Vietnam War). We queried 32 of 39 exposures only in reference to exposure during deployment to the four wars, which covered 16–231 cases and 30–338 controls depending on the war(s). For the seven non-war-specific exposures, information included ever exposure and, for some, a quantification of exposure (e.g., number of shots). For 31 of 32 war-specific