Motor Neurone Disease and Military Service: Evidence from the Scottish Veterans Health Study

Short running title: Motor neurone disease in veterans

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ABSTRACT

Objectives

In 2003, it was reported that motor neurone disease was linked to military service in the 1990-91 Gulf War. A large study in the US confirmed an association with military service but found no association with specific conflicts or length of service. Non-veteran studies have suggested an association with physical activity, smoking and other risk factors. We used data from the Scottish Veterans Health Study to investigate the association between motor neurone disease and military service in UK veterans.

Methods

Retrospective cohort study of 57,000 veterans born 1945-1985, and 173,000 demographically matched civilians, using Cox proportional hazard models to compare the risk of motor neurone disease overall, and by sex, birth cohort, length of service and year of recruitment. We had no data on smoking prevalence.

Results

Veterans had an increased risk of motor neurone disease compared with non-veterans (adjusted hazard ratio 1.49, 95% CI 1.01-2.21, p=0.046). The increase was independent of birth cohort, length or period of service, or year of recruitment. Risk was associated with a history of trauma or road traffic accident in both veterans and non-veterans.

Conclusions

We confirmed an increased risk of motor neurone disease in military veterans, although the absolute risk is extremely low. We found no evidence that the increased risk was associated

with any specific conflict. We could not rule out that smoking (and perhaps other lifestyle factors) may be responsible for our findings. Trauma may play a role in the increased risk but further studies are needed.

ABBREVIATIONS

ALS – amyotrophic lateral sclerosis

AMI - acute myocardial infarction

CI – confidence intervals

HR – hazard ratio

MND – motor neurone disease

NHS – National Health Service

OR - odds ratio

RR – relative risk

RTA – road traffic accident

SD – Standard deviation

SES - socioeconomic status

What this paper adds

- US studies have shown that military service is associated with an increased risk of motor neurone disease, although no association with specific conflicts or length of service has been found.
- This study demonstrates that UK veterans born 1945-1985 were more likely than non-veterans to develop motor neurone disease, although the absolute risk was extremely low.
- There was no evidence of an association with specific conflicts, or with length of service.
- There was an association between trauma or road traffic accident and motor neurone disease in both veterans and non-veterans, but the magnitude of association was greater in veterans.
- Higher rates of in-service smoking, reported in earlier studies, may explain the difference between veterans and non-veterans.

INTRODUCTION

Motor neurone disease (MND), also known as amyotrophic lateral sclerosis (ALS) in the United States, is a rare but serious progressive degenerative neurological condition. In Scotland, the crude incidence is 2.25 cases per 100,000 population per year, the median survival time from diagnosis is 2.5 years and the 5-year survival rate is 28%. It is more common in men than women.[1] The mean age at onset varies between studies but is generally between 55 and 75 years; there is some evidence that the onset occurs at an earlier age in military personnel.[2]

In 2003, the first report was published of an association between service in the US Armed Forces in the first Gulf War (1991).[3] Case-finding by Horner et al. confirmed an increased risk among all deployed personnel (RR 1.92, 95% CI 1.29-2.84) and a non-significant increase among Reserves and the National Guard.[4] The US Veterans Administration accepted ALS as a presumptive Gulf War-related illness (later extended to all active military service),[5] but Rose cautioned against over-interpretation of the findings of the studies,[6] whilst Armon noted under-ascertainment of cases in Horner et al.'s non-deployed cohort.[7]

In 2005, an analysis of data from the American Cancer Society Cancer Prevention Study II (CPS II) with 3.6 million person-years of follow-up found an increased risk of ALS for any military service (RR 1.58, 95% CI 1.12-2.09). The risk was elevated in every birth cohort examined (1915 to 1939) and was irrespective of length or period of service, which encompassed World Wars 1 and 2, and the Korean and Vietnam Wars.[8] The Scottish Veterans Health Study provided an opportunity to examine the risk of MND in a large population-based cohort of UK veterans spanning a broad range of military experience covering 1960-2012, followed up for up to 30 years, in comparison with civilians having no record of military service.

METHODS

The Scottish Veterans Health Study is a retrospective cohort study that comprises all 56,570 military veterans born between 1945 and 1985 who were registered with National Health Service (NHS) Scotland both prior to military service and following discharge, and a comparison group of 172,753 individuals with no record of military service individually matched (3:1) by year of birth, sex and postcode sector of residence (mean population 5,000). The study cohort and methods have been described in detail elsewhere.[9] All participants were identified via their electronic NHS registration records, which provided demographic information, as well as the dates of entering and leaving military service for the veterans. The records were linked, at the individual level, to acute and psychiatric hospital admissions data (Scottish Morbidity Record SMR01 and SMR 04) and death certificates to provide information on first episode of hospitalisation due to MND, death from MND and all-cause deaths. MND was defined as ICD-9 code 335.2 or ICD-10 code G12.2, at any position in the record. 'Date of diagnosis' was defined as the date of first hospitalisation for MND. The veterans served between 1960 and 2012, and information was available for follow-up events that occurred between 1 January 1981 and 31 December 2012 inclusive. Socio-economic status (SES) was derived from the Scottish Index of Multiple Deprivation (SIMD) (http://www.scotland.gov.uk/Topics/Statistics/SIMD). No data were available on smoking or alcohol use. The data extract was pseudo-anonymised, and approval for the study was granted by the Privacy Advisory Committee of the Information Services Division of NHS Scotland. As a secondary data analysis, individual consent was not required.

Cox proportional hazard models were used to examine the association between veteran status and cumulative risk of MND, using age as the time dependent variable, age at first record of MND as the failure time and death (if no record of MND) as the censor time. Hazard ratios and p values were calculated and the *a priori* rejection level was set at 0.05. Proportionality was tested using methodology based on Schoenfeld residuals.[10] The models were run univariately and then repeated adjusting for the potential confounding effect of SES quintile. The analyses were repeated stratifying by grouped year of birth to examine birth cohort effects. Odds ratios for an association with a history of trauma (defined as prior hospitalisation with ICD-10 S00-S99 or T00-T32, or ICD-9 E880-E888, E890-

E929 or 800-957 in any position) or road traffic accident (RTA) (prior hospitalisation with ICD-10 V00-V99 or ICD-9 E810-E899 in any position), were calculated. It was not possible to identify head or neck trauma as the individual V codes and E codes were not available to us. Mean age at MND diagnosis was calculated and case-fatality at one year and five years following diagnosis were compared for veterans and non-veterans. All analyses were performed using Stata v12.1 (©1985-2011 StataCorp).

RESULTS

After data cleansing, 56,205 (99.3%) veterans and 172,741 (99.9%) non-veterans were included in the analysis. There were 50,970 (90.7%) male veterans and 5,235 (9.3%) female, reflecting the gender balance of the Armed Forces. The mean period of follow-up was 29.3 years, with 6.7 million person years of follow-up among veterans and non-veterans combined. By the end of follow-up, 3,529 (6.3%) veterans and 14,476 (6.3%) non-veterans had died. During follow-up, 38 (0.07%) veterans had a record of MND compared with 78 (0.04%) non-veterans (unadjusted HR 1.56, 95% CI 1.06-2.30, p=0.025; adjusted for SES HR 1.49, 95% CI 1.01-2.21, p=0.046). On sub-group analysis, the difference was only significant among men. There was no significant difference among women, but they contributed only 4.3% of MND cases (Table 1).

Table 1. Cox proportional hazard model of the association between veteran status and risk of motor neurone disease

		Univariate			Multivariate		
		HR	**95% CI**	**P value**	**HR**	**95% CI**	**P value**
Overall		1.56	1.06-2.30	0.025	1.49	1.01-2.21	0.046
Men		1.57	1.05-2.33	0.027	1.49	1.00-2.22	0.050
Women		1.01	0.11-9.06	0.991	1.03	0.11-9.22	0.979
Birth cohort	1945-1954	1.35	0.82-2.23	0.241	1.28	0.77-2.13	0.343
	1955-1964	2.06	1.03-4.17	0.042	1.99	0.99-4.01	0.054
	1965-1974	2.29	0.55-9.67	0.256	2.31	0.50-9.74	0.251

Case fatality	1 year	0.80	0.42-1.53	0.500	0.83	0.44-1.59	0.577

HR hazard ratio; CI confidence interval

There was no statistically significant association with any birth cohort (Table 1), period or length of service.

The mean age at diagnosis in veterans was 49.7 years, SD 9.03, and was similar for non-veterans, mean 49.7 years, SD 10.56. Nine veterans (23.7%) and 25 non-veterans (32.1%) with MND were still alive at the end of the study. The mean survival from diagnosis to death or the end of the study was 4.4 years (SD 6.4) for veterans and 3.6 years (SD 6.4) for non-veterans; among those who had died, the mean survival was 1.0 year (SD 1.1) for veterans and 2.0 years (SD 2.4) for non-veterans. Veterans had a non-significantly lower case-fatality at 1 year (unadjusted HR 0.80, 95% CI 0.42-1.53, p=0.500). Adjustment for SES did not change the results.

A history of trauma or road traffic accident was associated with MND in the overall cohort (unadjusted OR 1.51, 95% CI 1.26-1.81, p=<0.001). Sub-group analysis showed the association to be statistically significant among both veterans (OR 1.71, 95% CI 1.29-2.28, p=0.002) and non-veterans (OR 1.43, 95% CI 1.14-1.80, p=0.006). The odds ratio for developing MND, in veterans with a history of trauma or road traffic accident compared with non-veterans with a similar history, demonstrated that the association was stronger in veterans, OR 1.79, 95% CI 1.05-3.05, p=0.029.

DISCUSSION

Data from the Scottish Veterans Health Study demonstrated a statistically significant association between military service and MND. The increased risk in veterans compared with non-veterans was seen among all birth cohorts although small numbers precluded statistical significance at subgroup level. The increase only reached statistical significance among men, and was unrelated to period or length of service. There was a statistically significant association between MND and a history of trauma or road traffic accident among both veterans and non-veterans. There was no evidence that veterans were younger at disease onset than non-veterans.

The magnitude of association in our study (unadjusted HR 1.56) is comparable to that reported by Weisskopf et al. for ALS in the CPS II study (unadjusted RR 1.58).[8] The two studies combined cover nearly 100 years of military service, encompassing a wide range of military experience and exposures. The Scottish Veterans Health Study has therefore corroborated existing evidence that military service increases the risk of ALS/MND, and has demonstrated that the increased risk is independent of exposure to conflict, length of service or period of service. The Institute of Medicine of the National Academies review of the literature on ALS [11] suggested a number of putative risk factors; intense physical activity, smoking, alcohol, trauma, transmissible agents, lead, pesticides and environmental toxicants. We have demonstrated an increased risk of MND in association with a history of trauma in our study, in both veterans and non-veterans although the association was stronger in the veterans. Serving military personnel are known from other studies to have a higher prevalence of smoking than civilians [12], but are also generally more physically active, which may *inter alia* increase the risk of trauma; both of these factors may also help to explain the increased overall risk of MND observed in veterans, but would require further studies.

Limitations of our study include the rarity of the condition, and the lack of data on personal lifestyle or occupational risk factors, or on head and neck trauma. We were able to infer the likelihood of exposure to conflict from UK military history; the spread of cases throughout the 50-year span of service experienced by our cohort shows no relation to periods of operational activity.

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