Original Research
Medical Journal of the Islamic Republic of Iran. Vol. 22, No.1, May 2008. pp. 47-51

Occurrence of amyotrophic lateral sclerosis among Iran-Iraq war veterans

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Abstract

Background: Amyotrophic lateral sclerosis (ALS) is a progressive neurological disorder with high mortality and morbidity. Some risk factors have been implicated for ALS such as exposure to high magnetic fields, and trace elements like selenium, cadmium and lead. A few studies have been carried out throughout the world to evaluate the prevalence of ALS among veterans. This study was aimed to evaluate ALS frequency among Iran – Iraq war veterans.

Methods: Medical records of 52580 veterans were studied and those with suspected neuromuscular disorders were referred to a blind neurologist. ALS was verified according to World Federation of Neurology criteria. Student t-test and chi-square test were used for analysis and a P value less than 0.01 was considered significant.

Results: Eleven definite ALS and two possible ALS cases were identified among the subjects. The mean age of onset of the disease was 43.7±9.7 years. All subjects had a record of at least three months involvement in action and symptoms began to show up after 16.5±3.6 years. The mean interval between exhibition of symptoms and the definitive diagnosis of the disease was 16.5 months.

Conclusion: The prevalence of ALS in our population was significantly greater than that of international surveys (P<0.01). The onset of the disease occurred at a significantly lower age than typical ALS (P<0.01). Military service might therefore be a risk factor for ALS.

Keywords: amyotrophic lateral sclerosis, military service.

Introduction

Amyotrophic lateral sclerosis (ALS) is a neuro-degenerative disorder of undetermined etiology that primarily affects the motor neurons. It is a rapidly progressive condition and most patients eventually succumb to respiratory failure in a few years. Although no specific environmental factors have been linked with certainty to an increased risk of ALS, epidemiological research suggests an increased risk of ALS among electrical utility workers, high dietary intakers of glutamate, smokers and those exposed to trace elements such as selenium, iron, manganese, copper, zinc, cadmium and lead [1].

There are some reports suggesting that military service may be a risk factor for developing ALS [2,3]. These studies covered a large population of US veterans with appropriate methods for case identification and were based on rich

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and precise medical records of US soldiers. However, there might have been limitations in the mentioned studies including the peculiar conditions of the war, the limited war time and zone, and the fairly short follow up interval for subject recruitment. During this war which lasted for 17 months, the US troops were mainly stationed in the Persian Gulf zone. The short period of the war together with the particular climate and environmental conditions of the Persian Gulf and the fact that considerable damage was done to the wildlife due to unprecedented oil spill formed a set of circumstances that require a more comprehensive analysis.

In contrast with this war, the Iran-Iraq war lasted for almost eight years, and started September 22, 1980. In this war a wide range of weapons and artilleries were deployed. Iran was even attacked by mass destruction weapons and chemical bombs (UN document S/16433 Mar. 26, 1984). The longer period of war as well as the variety of the used weapons enables us to conduct a comprehensive study on the effects of long-term exposure to various weapons among our veterans and since the war came to an end in 1988, we are now able to study the long term consequences of military service in terms of developing war associated disorders such as ALS. Therefore we decided to evaluate the prevalence of ALS among veterans who participated in the Iran–Iraq war from Khorasan Province which is located in the northeastern part of Iran, farthest from the Iraq borders and the Persian Gulf.

Methods

This study was approved by the ethics committee of Mashhad University of Medical Sciences and the Veteran Foundation of Khorasan Provinces. Subjects entered the study voluntarily and willingly.

In this cross–sectional study, 52580 veterans with documented medical files in the Iranian Veterans Office (IVO) were studied. All of these veterans had served for at least 3 months at some point during the war period, September 1980 through June 1988. Medical records of all of these veterans were evaluated precisely by four trained health providers of IVO and those who had suspected neuromuscular complaints or unexpected swallowing or respiratory problems were referred to a neurologist. We also evaluated all medical records of the neurology wards of Mashhad University, Ghaem Hospital, which is a referral center of Neurology in Khorasan Provinces.

Inclusion criterion was a history compatible with ALS in a veteran coming from Khorasan provinces. Exclusion criteria included any of the following: 1) Exposure to chemical substances considered as a risk factor for ALS except in action, 2) Positive family history for ALS in first relatives, 3) Significant co-morbid general medical disorders, 4) History of exposure to electromagnetic fields, 5) Previous significant central nervous system trauma, 6) Residence in the Persian Gulf zone or near Iraqi borders after 1988, and 7) High serum levels for heavy metals (especially lead).

Specific data collection sheets were designed and data including age, sex, age of disease onset, presenting symptoms, ALS type (bulbar onset and non-bulbar onset), length of service at war, and history of injury were collected for each patient.

In case the subject was still alive, a comprehensive physical examination was carried out. For deceased subjects, medical records and the death certification were evaluated. ALS was verified by medical records review according to the most recent World Federation of Neurology (WFN) EL-escorial criteria for ALS [4,5] (Fig. 1). All possible differential diagnoses (e.g. cervical spondylosis, multiple sclerosis, cervical myelopathies, brain stem lesions, lead toxicity, hyperthyroidism, hyperparathyroidism, etc.) were ruled out before definite diagnosis.

Data was analyzed by SPSS (version 13.0, SPSS Inc. Chicago, IL) software. Qualitative variables were expressed using percentages and

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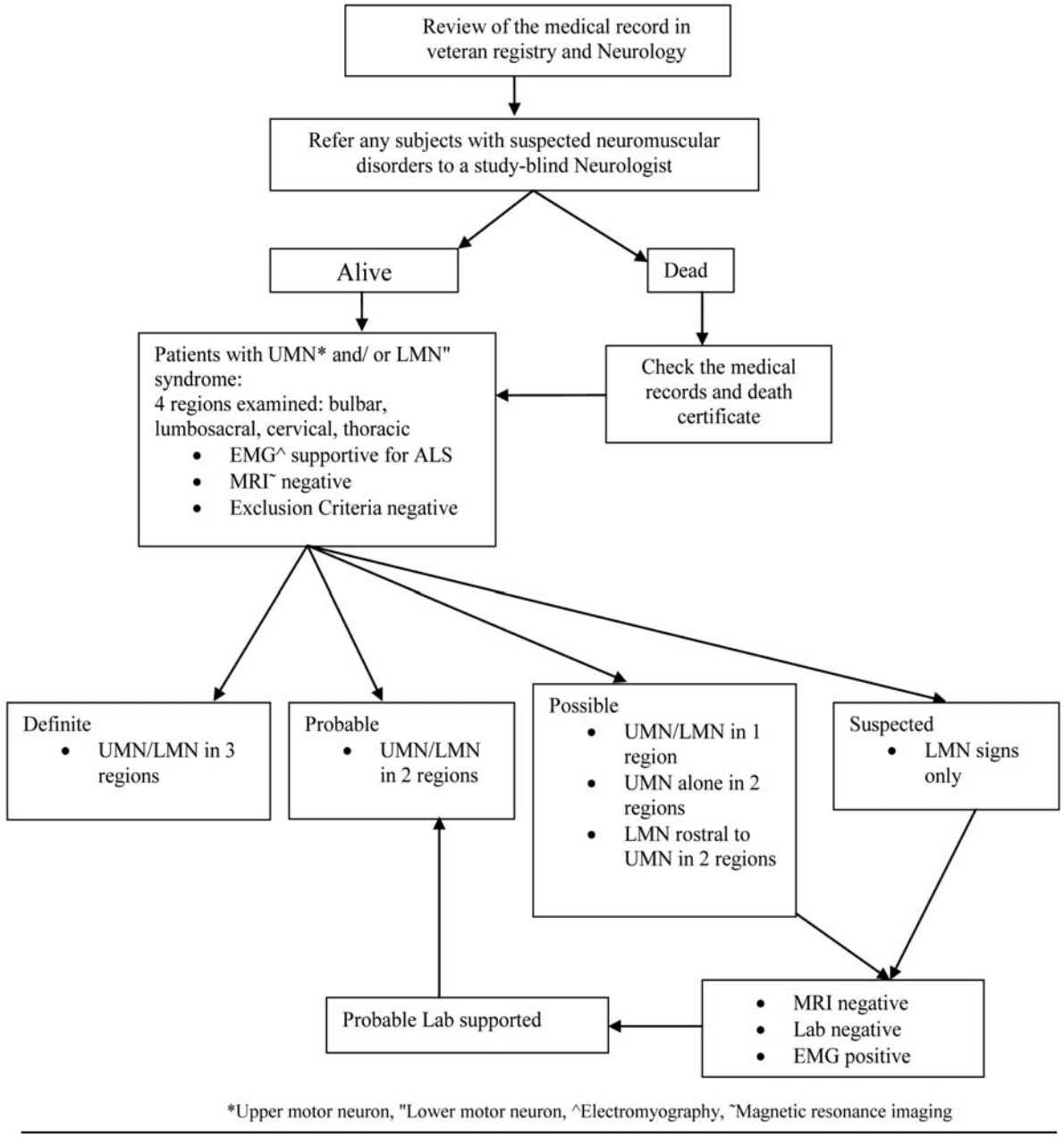


Fig. 1. Algorithm for diagnosis of ALS in this study.

quantitative data were explained with mean, standard deviation, and/or confidence interval. Student t-test and chi-square test were used for comparing the results with the mean normal values of community. A P value less than 0.01 was considered statistically significant.

Results

In this study eleven men with definite and two with possible ALS were identified. Three of these subjects had succumbed because of complications of their disease and another one had become bedridden and was mechanically ventilated.

The patients were mostly young people (Basiji) who volunteered to participate in the war. This resulted in an average age as low as 43.7±9.7. The minimum and maximum ages

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Case	Age at disease onset (year)	Interval between symptom onset and diagnosis (month)	Location of first presentation	Interval between being in the front line and symptom onset (year)	Duration of being in the front line (month)
1	40	18	Right lower limb	10	15
2	38	36	Right lower limb	17	6
3	45	6	Bulbar	19	4
4	49	24	Right upper limb	15	5.5
5	40	3	Left per limb	19	4
6	34	24	Right lower limb	15	24
7	43	6	Right upper limb	20	26
8	39	11	Left upper limb	10	3
9	42	4	Right upper limb	20	16
10	53	12	Left upper limb	15	3
11	34	11	Right upper limb	14	11
12	41	36	Right lower limb	20	30
13	71	24	Bulbar	20	6

Table 1. Demographic data of the patients.

were 34 and 71 respectively and there were only two patients over 50.

The mean interval between onset of symptoms and disease diagnosis was 16.5 months. The average period between involvement in the front lines and symptoms presentation was 16.5 years.

Two of our patients presented with bulbar symptoms, whereas the rest were classified as limb-onset ALS. In the latter group, symptoms commenced in the right upper limb in four cases, the left upper limb in three and the right lower limb in the four remaining patients. None of our subjects showed atypical symptoms such as sphincter disorders, sensory problems, extraocular muscle palsies and/or extrapyramidal signs. There was only one case with pure upper and one with pure lower motor neuron involvement and both were classified as possible ALS (Table 1).

Electrodiagnostic studies showed fasciculation potentials and high amplitude, and long duration motor unit action potentials, indicating long term denervation, in all patients. Brain and cervical MRI proved normal in all cases as well as laboratory studies including CBC, ESR, blood biochemistry, serum protein electrophoresis, serum B_{12} level, serum lead level and thyroid function tests.

Discussion

The incidence and prevalence rate for ALS is surprisingly uniform throughout the world and varies from 6 to 8 in 100000 [1]. A few studies have been done throughout the world to evaluate the prevalence of ALS among veterans. In the two studies among US veterans the prevalence of ALS was estimated 2 folds greater than the general population [2,3]. In our study the prevalence of ALS was 24.59 in 100000 which is significantly greater than world reports as well as US veterans studies ($P<0.01$). The discrepancies which exist between our findings and those of US might be due to several facts including the peculiarities of the Iran-Iraq war, the duration of war and the longer follow up intervals in our study. Therefore it is possible that the US veterans' studies will show more ALS cases if they follow the same pattern.

Although our sample population was too small to make firm claims regarding the ALS presentation and the existence of differences between our findings and the results of the parallel studies, it is clear that the onset age was lower in the current study, suggesting that military service might lead to ALS or at least accelerate the occurrence of ALS. Most patients with ALS are more than 50 years old at the onset of

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symptoms and this incidence increases with each decade of life [6-8]. The mean age of disease onset in our subjects was significantly lower than the general population (43.7 years, $P<0.01$).

In an epidemiology study [9] it has been shown that chemical nerve agents might contribute to ALS development. Among our subjects, 5 had served in regions previously exposed to chemical weapons (mustard gas and nerve agents). It is possible that the greater frequency of ALS in young veterans is due to either exposure to nerve agents [9], alpha particle-emitting heavy metals (e.g., depleted uranium) in dust from exploded munitions [10] or vigorous exercises and possibly traumatic injuries [11]. We believe that considerable damage to wildlife in the Persian Gulf due to the oil spill might have a role in war-associated disorders for inhabitants in this area as well as soldiers from other countries. However, our ALS veterans have been living far away from the Persian Gulf and have never visited this area since 1988.

There were some limitations in our studies. We did not have medical records of our soldiers prior to the war. As mentioned before, they participated in action voluntarily and most of them were not trained soldiers. Furthermore some subjects had refused to refer to the veteran registry to leave traceable records for personal reasons. Also there might have been unregistered deaths due to ALS which we failed to identify because of the long gap after the end of the war.

In conclusion, military service might be a risk factor for ALS. We suggest a multicentric study with an appropriate sample size to be designed to confirm the relationship between military service and ALS and to discover specific agents which are responsible for the increased frequency of ALS in veterans.

Acknowledgment

The authors would like to thank Dr. Hanayee and Mr. Rezazadeh, who assisted in identifying war veterans with ALS; and Dr. Khajedaluyee, who reviewed the statistical procedures and made helpful suggestions.

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