HHS Public Access
Author manuscript
Neurodegener Dis. Author manuscript; available in PMC 2018 January 26.

Published in final edited form as:
Neurodegener Dis. 2017 ; 17(2-3): 110–116. doi:10.1159/000453359.

Environmental and occupational exposures and amyotrophic lateral sclerosis (ALS) in New England

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Abstract

Background—Recent data provide support for the concept that potentially modifiable exposures are responsible for sporadic amyotrophic lateral sclerosis (ALS).

Objective—To evaluate environmental and occupational exposures as risk factors for sporadic ALS.

Methods—We performed a case-control study of ALS among residents of New England. The analysis compared questionnaire responses from 295 patients with a confirmed ALS diagnosis to those of 225 controls without neurodegenerative illness.

Results—Self-reported job or hobby-related exposure to one or more chemicals, such as pesticides, solvents, or heavy metals, increased the risk of ALS (adjusted odds ratio (OR) 2.51 95%CI 1.64–3.89). Industries with higher toxicant exposure potential (construction, manufacturing, mechanical, military, or painting) were associated with elevated occupational risk (adjusted OR 3.95 95%CI 2.04–8.30). We also identified increases in the risk of ALS associated with frequent participation in water sports, particularly water-skiing (adjusted OR 3.89 95%CI 1.97–8.44). Occupation and water-skiing both retained independent statistical significance in a composite model containing age, gender, and smoking status.

Conclusions—Our study contributes to a growing body of literature implicating occupational- and hobby-related toxicant exposures in ALS etiology. These epidemiologic study results also provide motivation for future evaluation of water-body related risk factors.

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Competing financial interests: The authors declare they have no actual or potential competing financial interests.

Keywords

environmental; exposure; occupation; toxicant; water

Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive, fatal neurodegenerative condition for which no cures exist and treatments are limited. In industrialized nations within Europe and North America, the incidence of ALS is approximately 1.5 to 2.5 per 100, 000 population and is higher in men than women [1]. Despite the growing knowledge about the genetics of ALS, the majority of cases occur sporadically, without clear family history. Current theories postulate that similar to cancer, ALS is a multistep process, and that disease develops when genetic susceptibilities and exposures to various risk factors occur together [2].

Many environmental and occupational risk factors have been evaluated, including certain occupations [3, 4], military service [5, 6], tobacco use [7, 8], electric shock [9], head injury [10], as well as exposure to toxicants including organic solvents [7, 11], heavy metals such as lead [12] and mercury [13], pesticides [12, 14], as well as the cyanobacteria-derived neurotoxin Beta-N-methylamino-L-alanine (BMAA) [15].

A recent umbrella review of existing meta-analyses and systematic reviews of non-genetic factors in the epidemiologic literature identified the toxic metal lead as the single risk factor that “presented convincing evidence for association with ALS” (n=1228 cases, $P=2.13 \times 10^{-6}$) [12]. Among the additional factors studied by meta-analysis, farming exposure, other heavy metals, and head injury were supported by “suggestive evidence”, while electromagnetic fields and pesticides have “weak evidence”, and smoking was not significantly associated [12]. These summarized data provide support for the concept that potentially modifiable exposures are responsible for sporadic ALS. Our objective was to evaluate the association between environmental / occupational exposures and ALS using a unique New England based case-control study.

Methods

Participants were enrolled through the Department of Neurology at Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire and the Department of Neurological Sciences at the University of Vermont Medical Center, Burlington, Vermont. The eligible ALS patients were newly diagnosed cases with either probable or definite ALS according to the Awaji-modified El Escorial criteria [16]. Eligible diagnoses included primary muscular atrophy (PMA), but not primary lateral sclerosis (PLS). To decrease the influence of recall bias, we selected a control group consisting of neurology clinic patients with other idiopathic diseases that would prompt them to undertake a similar search for factors in their prior life that might have caused their disease. Diagnoses include multiple sclerosis, brain and spinal cord tumors, adult-onset epilepsy, and non-familial neuromuscular diseases, such as idiopathic peripheral neuropathies. Patients with neurodegenerative diseases, such as Alzheimer’s and Parkinson’s diseases were excluded from participation as controls. Participants were approached by study staff in the clinic, and were required to be at least 21 years of age and residents of New England or the bordering New York region at the time of enrollment (ALS cases June 2009 – December 2015, controls August 2010 – December 2015). Of the potential participants approached about the study, the questionnaire completion rate was 90% for ALS cases and 52% for controls. Reasons for non-participation among cases were effort required (33%), and reluctance to share personal information (67%), while controls cited time involved (33%), social perception of sickness (32%), reluctance to share personal information (18%), and lack of monetary benefit (17%). For the current analysis, we had eligible participant questionnaire data on n=295 ALS cases and n=224 controls. All study procedures were approved by the Committee for Protection of Human Subjects at Dartmouth College and the Committee on Human Research in the Medical Sciences, University of Vermont.

We evaluated environmental risk factors using a questionnaire based on the ALS Consortium of Epidemiologic Studies (ACES) modules. Questions analyzed included family history of ALS, smoking status, concussion history, and occupational titles. “Did your job(s) or hobbies involve exposure to potentially harmful chemicals…” was used to ascertain exposure to toxic metals or pesticides. We also collected data on waterbody proximity and use. We asked “have you ever lived in a home located on or near (within a 2 mile distance) a lake, river, pond, estuary, ocean, or body of water?” “Have there ever been blue-green algae “blooms” or green surface scum on the water body’s surface?” Patients were asked to report if they participated in the following activities at least twice a month for a year or longer: swimming in lakes or rivers; boating, sailing, or kayaking; water-skiing, or wind-surfing. Analyses are presented in relation to ALS risk in Tables 1 – 5.

Coding of occupational titles was performed manually using standardized occupation classification (SOC) codes to assign job titles to an industry. We assessed the ALS risk associated with occupations that are likely to involve industrial chemical exposure, specifically participants with job titles involved in construction, manufacturing, mechanics, military, or painting (Supplemental Table S2). The title of the primary occupation was available for the majority (86%) of participants. The complete list of occupations held for >6 months was available on a subset (26%) of participants. Coded occupational titles for ALS patients were analyzed in relation to the clinic-based control group (Table 4). For comparison purposes, the code for primary occupation of the ALS patients was also analyzed in relation to the primary occupation of a different control group from a population-based study [17]. The population-control participants were shared from a prior study, which identified residents of New Hampshire or Vermont using a commercial database from Experian for the period 2005–2006 [17]. The analysis was restricted to males (n=94). Since the population-controls ages were 30 through 74 years old, we restricted this supplementary analysis to the 169 male ALS patients within this age-range (Supplemental Table S1). This analysis allowed us to see if the results were consistent using a population-based control group with the results obtained using the clinic-based control group.

The risk of ALS associated with each specific exposure or lifestyle factor recorded in the questionnaire was modeled using case-control status as the outcome in a logistic regression analysis with adjustment for age, and gender. Composite models were constructed to evaluate independence of effects combining factors in a multivariate model. The logistic regression analyses were performed using R: A Language and Environment for Statistical Computing, version 3.2.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Characteristics of the study population show that a higher proportion (64%) of ALS patients were male, compared to 53% of the controls (Table 1). Controls and cases were similar in age (median ages 61 and 62). Family history of ALS in a blood relative was more common in ALS patients (9%) than in controls (4%). ALS patients were slightly more likely to have smoked within the year of enrollment than controls (9% of ALS patients, 5% of controls) (P=0.082) (Table 1).

The questionnaire requested information on job or hobby-related use of the following chemicals: lead, mercury, solvents, cooling / cutting / lubricating oils, or pesticides. Self-reported exposure to chemicals was significantly associated with ALS risk (OR 2.51 95%CI 1.64 – 3.89, P=0.00003) (Table 2). The specific chemical exposures most strongly associated with this increased ALS risk in models adjusted for age and gender were solvents (P=0.0069), lead (P=0.011), and pesticides (P=0.028) (Table 2).

Compared with other occupations, increased risk of ALS was associated with both having a primary occupation that likely involves industrial chemicals (coded as construction, manufacturing, mechanics, military, or painting) (OR 3.95 95%CI 2.04 – 8.30), or a history of ever holding such an occupation for 6 months or longer (OR 4.24 95%CI 1.59–12.45), adjusted for age and gender (Table 3). Similar risk elevation was observed in an analysis of primary occupation restricted to males (Table 3).

Patients reported ever living full-time within two miles of a waterbody more frequently than did controls (ALS patients 77% vs. controls 67%) (OR 1.59 95%CI 1.05 – 2.42) (Table 4). A large proportion of participants reported boating, sailing or kayaking (42% of ALS patients, 32% of controls) (OR 1.51 95%CI 1.01–1.42). Frequent participation in water-skiing was associated with a 3-fold higher risk (OR 3.89 95%CI 1.97 – 8.44).

In a composite model including multiple risk factors, with adjustment for age, gender, and smoking status, we observed statistically significant increased ALS risks independently associated with frequent water-skiing (P=0.00066) and primary occupation using industrial chemicals (P=0.00081) (Table 5). These P-values remain statistically significant with consideration for multiple comparisons (P<0.006).

Validation analysis of coded primary occupational titles for male ALS patients in relation to males from a population-based control group showed consistent, positive association with exposure to industrial chemicals (age-adjusted OR 2.97 95%CI 1.47–6.39) (Supplemental Table S1).

Discussion

ALS is a multi-step progressive lethal disease characterized by muscle weakness due to loss of motor neurons [2]. Our epidemiologic study of ALS risk factors in Northern New

England strongly supports a major role for environmental chemicals and occupational exposures in the disease etiology. The study also introduces new human evidence of a possible waterbody-related exposure factor.

Consistent with the 2016 umbrella review of meta-analyses that established convincing evidence of an association between ALS and lead exposure, we found that the risk of ALS was increased 2.7-fold among our patients reporting jobs or hobbies that cause lead exposure [12]. Blood levels of lead have been reported to be elevated in ALS patients [18, 19].

The umbrella review also found a statistically significant 1.44 fold increased risk for pesticide exposure in >1000 cases [12]. We found a 3.4-fold risk associated with self-reported pesticide exposure, consistent with several other population studies [4, 20–22]. Excess ALS mortality was reported among workers exposed to a component of the herbicide Agent Orange 2,4-diphenoxyacetic acid (2,4, D) (RR 3.45 95%CI 1.10 – 11.11) compared to others who were not so exposed but worked for the same employer [23]. A recent paper related blood levels of several organochlorine pesticides (pentachlorobenzene P=0.04, and cis-chlordane (P=0.005) to increased odds of ALS [22].

In addition to lead and pesticides, the 1.8-fold risk we observed with exposure to solvents is consistent with the increased ALS risk identified from exposure to cleaning solvents or degreasers in Washington state both via self-report (OR 1.8 95%CI 1.2 – 2.8) and with inferred from exposure based on occupation (OR 1.9 95%CI 1.1 – 3.3) [24]. A matched case control study (n=51) also identified an elevated ALS risk associated with residential exposure to aromatic solvents (OR 5.03 95%CI 1.29–19.53) [11].

Results of our occupational analysis are consistent with some prior studies, but not others. Another case-control study conducted in New England 1993 – 1996 found a similar increased risk of ALS for workers ever employed as construction workers (OR 2.9 95% CI, 1.2–7.2) or production workers (OR 2.2 95%CI 1.1 – 4.4), particularly precision metal workers (OR = 3.5; 95% CI, 1.2–10.5) [25]. Important classes of chemicals inferred from the occupational data in this study showing elevated ALS risk included aliphatic chlorinated hydrocarbons, ethylene/propylene glycols, glycol ethers, heptane, and hexane [25]. On the other hand, a U.S. nationwide prospective cohort of one-million participants followed 1982–2002 did not observe statistically significant associations between the longest held occupation and ALS mortality [26].

Our composite model indicated a 3-fold association between water-skiing and ALS risk that is independent of age, gender, smoking, exposure to chemicals, or occupation. Exposure to cyanobacteria and the cyanotoxin BMAA is one possible explanation for the association of increased risk of ALS from exposure to water bodies. Exposure routes for cyanotoxins that have been proposed include inhalation of aerosolized particles, (which could occur during activities such as waterskiing) [27], ingestion, and direct contact through water sports [28]. A recent animal model study demonstrated that vervet monkeys chronically fed BMAA developed tauopathies similar to those seen in neurodegenerative diseases like Alzheimer's disease and ALS [29]. It is unclear to what degree the water-body associations we observed might have been due to BMAA vs. other causes. Our results motivate further investigation of water-body related environmental risk factors.

Limitations of our study include relatively small sample sizes that impair statistical power within certain subgroups. Detailed information on the dates of participation or exposure were not collected, thus we could not calculate latency. Our primary analyses of risk factors for ALS were based on comparisons of ALS patients with controls recruited from among patients with idiopathic neurological diseases that, as in ALS, often cause patients to search their memories for possible lifetime exposures that might have caused their disease. Although some of the diagnoses of the clinic-based controls could have risk-factors in common with ALS, such relationships would be expected to bias the results towards the null. We hoped thereby to correct for differential recall of events (recall bias). We found that exposure to only certain environmental factors and not all were statistically significantly associated with ALS, which adds weight to the conclusion that these associations are real and not due to recall bias. For example, exposure to lead was associated with increased ALS risk, but not exposure to mercury. A potential drawback of the use of clinic-based controls is that recall bias would increase the frequency of reported exposures in both groups, thereby reducing the likelihood of detecting important environmental exposure risks. However, when we compared the responses of the clinic control patients to those of our population-based controls, we found that clinic controls reported less frequent exposure to occupations with likely exposure to chemicals than the population-based controls (7% v 14%), though the difference was not statistically significant. Therefore, we believe that recall bias did not significantly influence the results of our study and that the observed positive associations for ALS risk factors are likely robust. In addition, the CDC's Behavioral Risk Factor Surveillance Survey results show that 47% of 55–64 year olds in New Hampshire are never smokers, indicating that the smoking history of our clinic-based controls our is similar to that of the general population in the region [30].

Our results provide evidence of environmental and occupational exposures that likely play a role in the etiology of sporadic ALS. Future investigations using biosample-based exposure assessment will be useful for elucidating the more detailed dose- and specific chemical class relationships. Our findings also suggest that further investigation of water-body related factors in additional populations is warranted. ALS may have a multi-stage etiology involving "hits" from several different genetic and environmental factors [31]. Identifying the preventable exposures that increase risk of ALS is a critical step in reducing the incidence of this devastating disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We would like to thank the study participants and our sources of funding: ALS Association grants SC5181 and 15-IIP-213; Centers for Disease Control (CDC) / Agency for Toxic Substances and Disease Registry (ATSDR) contract 200-2014-59046. The Dartmouth Clinical and Translational Science Institute, under award number KL2TR001088 from the National Center for Advancing Translational Sciences (NCATS) of the National Institutes of Health (NIH).

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Table 1

Population characteristics by ALS status.

Characteristic		Controls N=224 (%)	Cases N=295 (%)	P-value*
Gender	Female	106 (47)	105 (36)	
	Male	118 (53)	190 (64)	0.010 [a]
Age	median	61	62	0.54
Family History ALS	No	198 (96)	269(91)	
	Yes	9 (4)	25(9)	0.07 [ab]
Smoking status	Never	110 (52)	131 (46)	
	Former	91 (43)	131 (46)	0.50 [ab]
	Current	10 (5)	25 (9)	0.082 [ab]
Pack-years	none	91 (57)	140 (55)	
	1 to 20	41 (26)	59 (23)	0.83 [ab]
	20+	27(17)	55(22)	0.38 [ab]
Concussion	No	140(68)	198(72)	
	Yes	67(32)	78(28)	0.22 [ab]
Electric shock	No	189(94)	258(93)	
	Yes	12(6)	19(7)	0.61 [ab]

*P-value adjusted for age[a] and gender[b]. Missing age n=148 (n=95 controls, n=45 cases), family history n=18, smoking n =21, pack-years n=106, concussion n=36, electric shock n=41.

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Table 2

Toxicant exposures and sources related to ALS status.

		Controls	Cases	Overall	Male
Toxicant		N (%)	N (%)	OR(95%CI) [ab]	OR(95%CI) [a]
Use of chemicals in job or hobby	No	153 (78)	155 (58)	Reference	Reference
	Yes	44 (22)	113 (42)	2.51(1.64,3.89)	1.88(1.12,3.19)
Solvents	No	169 (87)	198 (75)	Reference	Reference
	Yes	26 (13)	64 (25)	2.03(1.23,3.44)	1.51(0.84,2.79)
Lead	No	184 (95)	229 (87)	Reference	Reference
	Yes	9 (5)	33 (13)	2.74(1.31,6.32)	2.58(1.13,6.71)
Mercury	No	188(96)	250(95)	Reference	Reference
	Yes	7(4)	13(5)	1.35(0.53,3.77)	1.5(0.48,5.62)
Cooling/cutting lubricants	No	188 (96)	254 (97)	Reference	Reference
	Yes	7 (4)	8 (3)	0.76(0.26,2.27)	0.57(0.19,1.75)
Pesticides	No	187 (96)	228 (87)	Reference	Reference
	Yes	8 (4)	34 (13)	3.44(1.6,8.29)	3.28(1.36,9.19)

*Odds ratios (OR) adjusted for age[a] and gender[b]. Missing chemical n=54, solvents n=62, lead n=64, mercury n=61, lubricants n=62, pesticides n=62.

Table 3

Occupations related to ALS status.

		Controls	Cases	Overall	Male
		N (%)	N (%)	OR(95%CI) [ab]	OR(95%CI) [a]
Military service	Never	166 (80)	205 (72)	Reference	Reference
	Ever	42 (20)	79 (28)	1.09(0.67,1.78)	1.49(0.88,2.54)
Deployed	Never	179 (87)	237 (86)	Reference	Reference
	Ever	27 (13)	39 (14)	0.73(0.41,1.31)	0.96(0.53,1.76)
Primary occupation involves industrial chemicals	No	169 (94)	210 (79)	Reference	Reference
	Yes:	11 (6)	55 (21)	3.95(2.04,8.3)	8.74(3.37,29.9)
	Construction	2(1)	17(6)		
	Manufacturing	5(3)	25(9)		
	Mechanic	0 (0)	6 (2)		
	Military	0 (0)	6 (2)		
	Painting	4 (2)	1 (0)		
Ever held occupation >6 months involving industrial chemicals	No	69 (76)	22 (51)	Reference	Reference
	Yes	22 (24)	21 (49)	4.24(1.59,12.45)	4.86(1.65,16.21)

*Odds ratios (OR) adjusted for age[a] and gender[b]. Missing military n=27, deployed n=37, primary occupation n=74, history n=384.

Table 4

Waterbody proximity and use in relation to ALS status.

Exposure		Controls N (%)	Cases N (%)	OR(95%CI) [ab]
Reside full-time within 2mi of waterbody	No	65 (33)	64 (23)	Reference
	Yes	132 (67)	214 (77)	1.59(1.05,2.42)
- If yes, ever algae blooms in this waterbody	No	90(73)	143(74)	Reference
	Yes	33(27)	50(26)	1.06(0.62,1.84)
Water-Ski	No	178 (95)	207 (81)	Reference
≥2x per month, for 1 year or more	Yes	10 (5)	47 (19)	3.89(1.97,8.44)
Boat, sail, or kayak	No	126 (68)	153 (58)	Reference
≥2x per month, for 1 year or more	Yes	59 (32)	111 (42)	1.51(1.01,2.28)
Wind-surfing	No	177 (94)	240 (96)	Reference
≥2x per month, for 1 year or more	Yes	12 (6)	11 (4)	0.6(0.25,1.42)
Swim	No	106(55)	122(46)	Reference
≥2x per month, for 1 year or more	Yes	87(45)	143(54)	1.43(0.97,2.1)

*Odds ratios (OR) adjusted for age[a] and gender[b]. Missing reside n=44, blooms n=30, water ski n=77, boat n=70, windsurf n=79, swim n=61.

Table 5

Composite models of ALS risk factors.

		Controls	Cases	Overall	Male
		N (%)	N (%)	OR(95%CI) [ab]	OR(95%CI) [a]
Smoking status	Never	110 (52)	131(46)	Reference	Reference
	Former	91 (43)	131(46)	1.12(0.72,1.75)	1.3(0.7,2.43)
	Current	10 (5)	25(9)	2.48(0.96,7.27)	2.72(0.83,10.82)
Primary occupation involves industrial chemicals	No	169 (94)	210(79)	Reference	Reference
	Yes	11 (6)	55 (21)	4.1(1.91,9.87)	2.45(1.21,5.2)
Water-Ski	No	178 (95)	207 (81)	Reference	Reference
≥2x per month, for 1 year or more	Yes	10 (5)	47 (19)	3.71(1.8,8.47)	2.91(1.18,8.3)

*Odds ratios (OR) adjusted for age[a] and gender[b]. Missing smoking n =21, primary occupation n=74, water-ski n=77.