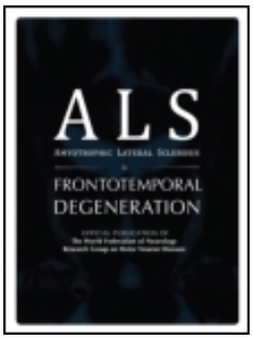

Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration

ISSN: 2167-8421 (Print) 2167-9223 (Online) Journal homepage: informahealthcare.com/journals/iafd20

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To cite this article: Pam Factor-Litvak, Ammar Al-Chalabi, Alberto Ascherio, Walter Bradley, Adriano Chío, Ralph Garruto, Orla Hardiman, Freya Kamel, Edward Kasarskis, Ann McKee, Imaharu Nakano, Lorene M. Nelson & Andrew Eisen (2013) Current pathways for epidemiological research in amyotrophic lateral sclerosis, Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 14:sup1, 33-43, DOI: 10.3109/21678421.2013.778565

To link to this article: https://doi.org/10.3109/21678421.2013.778565

Published online: 16 May 2013.

Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2013; 14(Suppl. 1): 33–43

informa
healthcare

ORIGINAL ARTICLE

Current pathways for epidemiological research in amyotrophic lateral sclerosis

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Abstract

Amyotrophic lateral sclerosis (ALS) is a rapidly progressive neurodegenerative disease. The current status of the epidemiology, challenges to its study, and novel study design options are discussed in this paper. We focus on recent results from large-scale population based prospective studies, case-control studies and population based registries, risk factors, and neuropathologic findings in chronic traumatic encephalomyelopathy. We identify areas of interest for future research, including time-trends in the incidence and prevalence of ALS; the meaning of lifetime risk; the phenotypic description of ALS; the definition of familial versus sporadic ALS, syndromic aspects of ALS; specific risk factors such as military service, life style factors such as smoking, the use of statins, and the presence of β-N-methylamino-L-alanine (BMAA), an excitotoxic amino acid derivative possibly produced by cyanobacteria found in almost every terrestrial and aquatic habitat; the emergence and disappearance of an endemic ALS in areas of the Pacific; and gene-environment interactions in the etiology of ALS. To move the epidemiology forward, we suggest using well-characterized cohorts of newly diagnosed ALS patients to identify risk and prognostic factors; storing biological material for future studies; building on the National ALS Registry as a resource of future studies; working in multidisciplinary consortia; and addressing the possible early life etiology of ALS.

Key words: *ALS, population based study, case-control study, center based, multicenter study, Guamanian ALS*

Introduction

Numerous approaches have been used to elucidate the etiology of amyotrophic lateral sclerosis, a devastating neurodegenerative disease, which leads to death, on average, within three years of diagnosis. Among the approaches used are basic laboratory studies, studies in animal models such as *SOD1* transgenic mice, cell based models, autopsy studies and molecular genetic studies. Data from human based studies are needed to inform these investigations, and results from these investigations likewise are required to inform the topics of human investigations. Thus, epidemiologic

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ISSN 2167-8421 print/ISSN 2167-9223 online
DOI: 10.3109/21678421.2013.778565

studies play a crucial role in studying a relatively rare disease such as ALS.

A recent PubMed search identified over 1000 papers with the key words ALS and epidemiology. These studies have provided information regarding sociodemographic characteristics, disease phenotype and geographic variation of ALS cases. Case-control studies have examined risk factors such as lead exposure, smoking, and pesticide exposure. Several prospective cohort studies have also identified risk and protective factors.

Despite the increase in research base, as Armon points out (1), there are inherent limitations to the epidemiologic investigations of rare and, on average, rapidly fatal diseases such as ALS. First, case ascertainment and follow-up poses specific problems, leading to selection bias. For example, it is likely that case-control studies ascertain cases with longer survival times; these do not reflect the larger pool of ALS cases. A second example, also leading to selection bias, is refusal to participate in non-treatment studies, as ALS patients perceive no direct benefit. In cohort studies, loss to follow-up of subjects leads to bias if the proportion lost is differential to development of disease.

A second limitation in epidemiologic studies of ALS is poor definition of the phenotype. While studies undertaken in large research consortia widely use the El Escorial ALS criteria (2) to characterize their patient populations, older and smaller studies do not. The lack of precise diagnosis and measures of disease severity are likely to have introduced measurement error into the studies. The third limitation is one common to many epidemiologic studies and concerns data collection methods. Many epidemiologic studies rely, at least in part, on questionnaires administered to subjects. In case-control studies, recall may differ between cases and controls, as cases may search their memories in order to explain the cause of their disease. This is less of a problem in cohort designs. More recent studies have used biomarkers of exposure to circumvent such bias. If biospecimens are available before disease onset in cohort studies, then their analysis provides unequivocal evidence of exposure preceding disease onset. Analysis of biospecimens in case-control studies requires more caution in the interpretation, as disease processes may change the accumulation of exposures or metabolism of exposures. Furthermore, using generally accepted data collection instruments, including questionnaires, allows for comparisons across studies and additionally for data to be combined across studies.

The purpose of this paper is to review selected recent epidemiologic findings in ALS and to discuss potential areas of new epidemiological research as well as ways to move the field forward. There are many excellent reviews of ALS epidemiology (e.g. (3,4)) and, rather than replicating these, the aim is to highlight important new findings. This paper is divided into two sections: first, a description of recent studies and an update of new analyses of ongoing studies; and, secondly, a discussion of chronic traumatic encephalomyelopathy and its pathological relationship to ALS. The paper concludes with ideas to move the field forward.

New and ongoing epidemiologic studies of ALS

The studies discussed are described in Table I, along with recent findings. Most of these studies are population based or are based on large international consortia. Population based studies reduce the impact of selective case ascertainment. Complete or near-complete ascertainment makes phenotypic descriptions more accurate. National and international consortium studies both reduce the impact of selective case ascertainment and ensure sufficient numbers of cases for meaningful analyses. Two population based registries of ALS cases in the Republic of Ireland (RoI) and Northern Ireland (NI), which have been in place since 1995 (5–8), provide data on incidence rates and phenotypic variations in Ireland. Overall, the crude incidence rate has remained at 2.6/100,000 person-years over the course of the study, the same as the overall prevalence rate. Clinical and epidemiologic features of ALS cases are similar in RoI and NI, and no difference in survival over time has been noted. However, the RoI cohort has a survival advantage (hazard ratio (HR) 0.72, 95% confidence interval (CI) 0.60–0.87), possibly due to the availability of a multidisciplinary specialty clinic and earlier intervention with nutritional support and gastronomy in RoI. The population based rate of frontotemporal dementia among cases was found to be 14% (9), and the population based rate in incident cases of executive function impairment was 40%; cases with executive function impairment had a survival disadvantage (10).

In Cuba, a pilot study of mortality from ALS in Havana Cuba was estimated at 0.83/100,000 (11), a rate consistent with that in U.S. Hispanics, estimated from a systematic review to be 0.9/100,000 (95% confidence interval (CI) 0.8–1.1/100,000) (12). In this study, case ascertainment is likely to be unbiased due to equal access to health care with the caveat that ALS may be underdiagnosed, especially in rural areas, due to fewer neurological services available. Furthermore, mortality from ALS appears to increase with age, contrary to the observation in European based population registries (13). ALS in Cuba is more common in those self-identified as having Spanish origin (i.e. Spanish grandparents) compared to those with some African background, and age at onset is lower in populations with darker skin than in those with lighter skin.

There are two ongoing population based consortium studies in Europe. The European Resisters for ALS (EURALS) consortium was established in

Table I. Summary of Recent Epidemiological Studies and Major Findings (mainly presented at the conference).

Study population /specific risk factor (References)	Special features	Major findings
Population based registry in Ireland and Northern Ireland 1996 to present (5–10)		Population based rate of frontotemporal dementia = 14% Population based rate of executive impairments = 40%, with a survival disadvantage Patients in southern Ireland have a survival advantage
Cuba (11, 12)	Ad mixed population	Mortality lower in Cuba than in previously reported populations – similar to reported mortality in U.S. Hispanics Mortality continues to increase in older age groups, contrary to that reported in European based population registries ALS more common in those with self-identified Spanish origin (Spanish grandparents) compared to those with darker skin (Mulattos, i.e. with some African background) Clinic based data from Havana suggest that age of onset is lower in population with darker skin than in those self-identifying as Spanish origin
Pan European: EURALS (14–17)	Consortium established in 2003 Originally 6 population based registries in Europe: 3 from Italy and Ireland, Scotland and northern England Added registries from France, the Netherlands, southern England and Germany	Descriptive epidemiology Effect of chronicity on results from therapeutic trials Case-control studies for physical activity, trauma, sports, coffee and smoking Meta-analysis shows that epidemiologic features are quite similar across the registries with one exception: site of onset in the phenotype. In particular appears to be increased bulbar onset in patients in Northern Europe compared to Southern Europe: unclear why this is so (perhaps genetics?)
EuroMOTOR	Consortium based on population based case registries	Currently performing population based case-control studies focusing on environment Unbiased since population based and from the total population of 32 million will have 1600 population based cases and controls Will include biorepository focusing on exposomics
UK studies: National Epidemiology	3 centers: north England (Sheffield); Midlands (Birmingham); London	Questionnaire based compatible with ACES US study, EURALS study in Europe and EuroMOTOR study 200 cases and 200 controls with DNA for genotype/phenotype analyses
UK studies: Population registries (14, 17, 20–22)	3 registries: Scotland, Preston, south-east England	Key findings from south-east England which includes a population of 4 million (1) Lifetime risk of ALS is 1/300 (2) Ethnicity: population includes 20% of Afro-Caribbean ancestry (3) Genotype/phenotype analyses to determine whether ALS is syndrome (4) Risk to relatives: over a 16-year period about 1% of sporadic cases may be misclassified as they will have an affected family member. Thus, risk to someone who has an affected sibling is 8 times the background risk. To translate this, assume background risk of not getting ALS is 99.7% so if you have a sib it drops to 97.6% (still more likely to die from other causes)
Japan (23–25)	Death certificate based studies: 1995–2004	Age specific mortality rates rapidly rise up to age 70 and sharply decline thereafter Between 1995 and 2004 mortality in males at or above age 70 increase; slight decline in men below age 70. Similar patterns for females Two new clusters of ALS in Japan: north-east and central (in addition to the Kii Peninsula)
Western Pacific: Chamorro of Guam and Rota in Southern Mariana Islands, Alu and Jokai speaking people of south-west Guinea and Japanese from Kii Peninsula (26–30)		High incidence and subsequent disappearance within 3 decades of the discovery, suggesting a strong environmental etiology

(*Continued*)

Table I. (*Continued*)

Study population /specific risk factor (References)	Special features	Major findings
Guam (32–37)		ALS first appears in historical record in mid-1860s. By early 1950s incidence between 70 and 150 per 100,000 (work of Len Kurland and Don Mulder). Additionally, ALS (and PD) developed in long-term Filipino migrants to Guam who lived traditional lifestyle, and Chamorro migrants who left Guam at an early age and never returned Disappearance in 1980s. Supports environmental etiology: toxic metals and cyad BMAA cyanobacteria
Military service	1st Gulf War 1990–1991 (42)	3–4 increase in risk in Air Force and Army deployed compared to non-deployed personnel of the same era. Average age at deployment: 27. Total number deployed = 750-800,000. Peak mortality rate from ALS following deployment was in 1995
	American Cancer Society cohort (43)	Military service vs. no military service. Reviewed by Institute of Medicine and concluded that although evidence sparse, studies are generally supportive of the association
Kaiser Permanente Study in Northern California (45–46)	3 million participants	Overall incidence = 1.7 per 100,000 Male:Female = 1.6 Highest rates in non-Hispanic Caucasians (3.4 per 100,000); intermediate rates in black and Hispanic groups (2.2-2.5 per 100,000) and lowest among Asians (0.8 per 100,000) Both blood and bone lead increased among cases compared to controls. Now looking at gene-environment interactions
Cancer prevention Study from 1982 and follow up (43, 47–50) Subset recruited in 1992 and followed prospectively with repeated questionnaires	1 million people Biological samples available	Approximately 805 incident cases Addressing risk factors such as vitamin E, and smoking Smokers have increased risk, about 40% higher, with no dose response. Puzzling given that there are dose response relationships with other outcomes Vitamin E: long duration of supplements associated with reduced risk. Results vary by analysis Military service in WWII: 60% increase, but puzzling since no duration effect. Also this was for WWII only and not for Vietnam or Gulf War I Kamel: in this (small) case-control study there was no association with military service
Florida, New Hampshire, Two Rivers (40, 41, 76)		Data suggesting associations with "clusters" of cases near bodies of water with frequent blooms of cyanobacteria leading to increased concentrations of BMAA. BMAA exposure may be associated with protein misfolding leading to protein aggregation and neuronal death
Center based case-control study of ALS in New England (52–55)	Environmental risk factors Clinic based cases, community controls	Specific occupational exposures: pesticides, metals, solvents, EMF Smoking, caffeine, alcohol Medical conditions: head trauma, lipid metabolism and medications, especially statins Findings: associations with occupational lead exposure (questionnaire data), biomarkers: blood and bone lead ; also possibly with hexane, glycols, head injury, smoking Military service (mainly WWII vets): no association, but relatively small study. Speculates that perhaps all the military associations really are due to exposure to lead, firing ranges, etc.
Geneva: Genes and Environment in Veterans with ALS. (56)	Veteran's Affairs registry of 670 cases and 1000 matched controls.	Confirmed blood lead association

Chronic traumatic encephalopathy and motor neuron disease variant (57, 59, 60)	Brain bank ($n = 57$)	Early symptoms include emotional/behavioral changes, mood changes, impulsivity, and disinhibition. Some may include rage behavior with aggression/violence Then, memory, executive dysfunction and later overt dementia Subset develop motor symptoms (about 10%) and they die at earlier stage of CTE CTE associated with changes in brain volume, shrinkage of brain, enlarged ventricles, distinct microscopic pathology, accumulation of protein hyperphosphorylated tau, TDP-43 Question of whether CTE is on the ALS spectrum
Italian football: trauma and ALS (58)		Previous studies suffer from few patients, inadequate power, inadequate controls, poor definition of trauma and time between trauma and ALS onset is not precise

2003 and consists of population based registries from Italy, Ireland, Scotland, northern England, France, the Netherlands, southern England (14) and Germany (15–17). The incidence of ALS in Europe, evaluated via a meta-analysis, was found to be 2–2.5/100,000 population/year. A population based case-control study has been initiated to examine associations between trauma, physical activity, smoking and coffee consumption and ALS. The second consortium is EuroMOTOR, which is currently performing population based case-control studies in Ireland, Italy and the Netherlands of environmental factors and which includes a biorepository of DNA, serum, lymphocytes, CSF and other tissues to perform proteomics, transcriptomics, genomics and metabolomics.

Two initiatives are currently underway in the United Kingdom. The National Epidemiology Study is based in three centers (Sheffield, Birmingham and London) and is performing case-control studies with questionnaires compatible with those used in the ACES U.S. study, the EURALS study and the EuroMOTOR study. These studies will include data relating genotype to phenotype. The second initiative is a set of population based registry studies in Scotland (17), Preston and south-east England (SEALS) (14). The latter registry includes a population that is approximately 20% Afro-Caribbean ancestry. Based on the SEALS data, the estimated lifetime risk of ALS is 1/300–similar to that estimated by others (e.g. (18)), including the Piedmont registry in Italy (19). Furthermore, using this registry, the risk to relatives may be higher than previously reported. The SEALS registry estimates that over a 16-year period, 1% of sporadic ALS cases may have an affected family member, and the risk may be eight times higher for a person with an affected sibling (20–22).

Geographical and time-trend studies, which rely on death certificate data, are options for ALS studies, as long as ALS is noted as the primary cause of death. If ALS is not so noted, then there is potential for underascertainment of cases. Initiatives in Japan include study of temporal trends (23) and geographic clusters of ALS cases. Based on death certificate data, the total age-specific ALS mortality rates for the period between 1995 and 2004 rapidly rose up to age 70 years and sharply declined thereafter. However, between 1995 and 2004, mortality rates in males at or above age 70 years increased, and there was a slight decline in younger males. Similar patterns were found in females (24,25). Two new ALS regions of high incidence (in addition to the Kii Peninsula) have also been identified in Japan; one in the north-east and one in the central portion of the country (22).

The high incidence and subsequent disappearance, all within three decades, suggests a strong environmental etiology for ALS in the Western Pacific among the Chamorro in Guam and Rota in the

Southern Mariana Islands, the Alu and Jokai speaking people of south-west Guinea and the Japanese in the Kii Peninsula (26–28). Additional evidence includes the high incidence of ALS in Filipino migrants to Guam, who lived a traditional life style for more than a decade, and the high incidence of ALS (for several decades) in the Chamorro migrants, who left Guam at an early age and developed disease decades later. Despite the decline in the incidence of ALS in Guam, the Southern Mariana Islands and south-west Guinea, several recent reports indicate an increase in the Kii Peninsula region, possibly due to changes in drinking water sources (29,30).

Among the environmental agents suspected to be related to these clusters are two candidate neurotoxins: metals and β-N-methylamino-L-alanine (BMAA), an amino acid that is not one of the 20 amino acid constituents of normal animal proteins produced by cyanobacteria. Experimental evidence for these neurotoxins relates to the deposition and colocalization of calcium and aluminum in the brain and spinal cord neurofibrillary tangle bearing neurons and in the development of animal models of motor neuron disease (31). Current studies are focused on susceptibility alleles and gene-environment interactions in ALS patients and the general Chamorro population (32–34). However, a recent genetic analysis in a large extended family in the Kii Peninsula suggests no linkage to the TRPM7 locus, a site that has been linked to ALS in Guam (35), suggesting that there may be differences between ALS in Guam and in the Kii Peninsula.

Further evidence for the associations between cyanobacteria production of BMAA and ALS derives from the observation that the diet of the Chamorro contains high proportions of cycad flour and flesh from animals eating cycad seeds (fruit bats, deer and pigs); cycad seeds contain high concentrations of BMAA (36). Necropsy studies found BMAA in brains of Chamorros dying from ALS (37) and in the brains of ALS patients in Florida (38), where there is evidence of bioaccumulation of BMAA in the food chain (39). Further evidence derives from studies finding an increased incidence of ALS in regions bordering lakes with frequent cyanobacterial blooms (40,41).

Several investigators reported on risk factors for ALS suggested by large case-control or cohort studies. Among these was military service. In the 1st Gulf War cohort (1990–1991) reported by Horner et al. (42), there was an estimated 3–4-fold risk of ALS in Air Force and Army personnel deployed compared to non-deployed personnel during the same time-frame. Furthermore, the peak mortality from ALS was in 1995, very shortly after the end of the deployment period. In the American Cancer Society cohort (43), military service during World War II was associated with an estimated 1.6 times increase in deaths due to ALS; no associations were found for service in either the Vietnam War or in Gulf War I. Review of the data by the Institute of Medicine (44) concluded that there is limited but suggestive evidence of an association between military service and later development of ALS, and that further research should explore the exact exposures that may account for this association, i.e. chemical or metal exposure, involvement in traumatic events, or intensive physical activity.

The community based case-control studies of ALS in the Kaiser Permanente Northern California population have considered a number of risk factors. This research is based on a population of over three million participants in the Kaiser Health Plans in Northern California (45). Major findings include that the estimated incidence of ALS is 1.7 per 100,000; the male to female ratio is 1.6 and with the highest rates of ALS occurring in non-Hispanic Caucasians (3.4 per 100,000), intermediate rates in black and Hispanic groups (2.2–2.5 per 100,000) and the lowest rates in Asian groups (0.8 per 100,000). Regarding major risk factors, both blood and bone lead is increased in cases compared to controls, and there are now ongoing analyses considering the possible gene-environment interactions related to this finding (46).

The American Cancer Society Cancer Prevention Study II (CPS-11), beginning in 1982, is a prospective cohort followed with periodic questionnaires and has been used to examine the incidence of and risk factors for ALS. This study is based on approximately 1 million people. Major results from this study include an increased risk for ALS associated with smoking in females but not in males (47), an increased risk with military service (43), and a decreased risk for ALS associated with long duration use of vitamin E supplements (48). A subset of participants in the CPS-II and participants in four additional cohorts – the Nurses Health Study, the Health Professionals Follow-up Study, the Multiethnic Cohort, and the National Institutes of Health-AARP Diet and Health Study – have been combined in a larger longitudinal study for risk factors for ALS. In this population, long-term use of vitamin E supplements was associated with a 36% lower risk of ALS (49), and smoking was associated with an increased risk in both males and females (50). Interestingly, the estimated association with smoking does not exhibit a dose-response relationship, suggesting more than a simple increase in risk. Conflicting results on the association between smoking and ALS have been reported by two cohort studies in Europe (51).

Two case-control studies of ALS focus on environmental risk factors. The first was conducted in New England between 1993 and 1997 and included 110 cases and 256 matched controls. ALS was associated with lead exposure (reported, blood lead concentrations and bone lead concentrations) (52), smoking (53), head injury (54) and several other occupational exposures (55). The second study derives from the Department of Veterans Affairs ALS

Registry, which has 670 cases and approximately 1000 controls. Analyses thus far find that exposure to lead is related to ALS (56).

In summary, the newer studies of ALS have largely been population or consortium based, minimizing selection biases. Many have also added evaluation of biomarkers as mentioned above; to the extent that they are either collected prior to disease onset or are thought not to be influenced by disease presence, they will provide valuable information regarding exposure-outcome relationships.

Chronic traumatic encephalomyelopathy

Chronic traumatic encephalomyelopathy (CTE) was proposed as a variant of chronic traumatic encephalopathy, which is associated motor neuron disease. Subjects with CTE present with early symptoms of mood changes, impulsivity and disinhibition (57). These may progress to aggressive and violent behaviors along with deficits in memory, executive dysfunction and, later on, overt dementia. The evidence that contact sports may be associated with CTE-like symptoms and neuropathology is especially intriguing in light of a possible increase in ALS incidence among professional Italian football players. However, interpretation of these data is limited because studies often have inadequate statistical power, inadequate control groups, poor definitions of trauma, and the estimate of time between the traumatic event(s) and ALS onset is not precise (1). Thus, larger studies are proposed to evaluate this association. Nevertheless, a 2009 publication (58) found an increased number of ALS cases among soccer players (standardized morbidity ratio (SMR) 6.45; 95% confidence interval 2.78–12.70). Notably, the SMR was elevated only among soccer players and not among professional basketball players or elite cyclists (zero cases in each). Among soccer players, the risk was highest in those who played midfield and in those with careers lasting greater than five years, suggesting a dose-response relationship. Furthermore, the authors posit that midfielders may have different physiologic characteristics compared to players in other positions, specifically higher maximal oxygen uptake relative to body mass, perhaps either due to selection or training. Alternatively, because soccer is played on grass fields, the increase in ALS may be in part due to exposure to pesticides, fertilizers or BMAA, all of which have been suggested to be linked to ALS. It is also possible, although highly unlikely, that there is a shared genetic predisposition to ALS and soccer success.

Approximately 10% of CTE patients develop motor symptoms (59,60) and die at an earlier stage of CTE, compared to those who do not develop motor symptoms. CTE is associated with changes in brain volume, especially shrinkage, with enlarged ventricles and with distinct microscopic pathology, including accumulation of protein hyperphosphorylated tau and TDP-43.

Discussion

In the past 20 years, much attention has been paid to the identification of risk factors for ALS. For a number of reasons, including the low incidence, variable course and complex etiology, ALS is difficult to study. Newer studies are addressing key methodological issues; however, several important questions remain to be addressed in future epidemiologic research.

First, questions remain regarding the definitional aspects of ALS for clinical and observational studies; the controversy regarding whether the incidence, prevalence and lifetime risk of ALS are constant; and the question of ALS incidence in population subgroups. These are crucial for determining participation in clinical trials of potential treatments and for the proper comparison of future epidemiologic studies. A related issue is determining the lifetime risk of ALS. Lifetime risk likely varies based on the age cut-off point, and the choice of such cut-off point can suggest an increase or decrease in age-specific ALS prevalence. For example, there are data which suggest that the lifetime risk up to age 70 years is 1/800; if there is an increase in age to 85 years, then the lifetime risk is close to 1/300 to 1/400 (12,20,61). With respect to the incidence of ALS in population subgroups, it appears that the incidence is lower in non-European populations (11,12), but these reports may not be reliable since they are based on small numbers. It is also not clear whether the phenotype(s) of ALS vary by population subgroup.

Secondly, questions regarding the definition of familial ALS and on the clustering of neurodegenerative disease in kindreds are unanswered. Many studies describe familial ALS in different ways, and there is no standard definition regarding the number and relationships of affected kinship members that are required to define the disease as 'familial' (62,63). Inconsistent classification of familial ALS could hinder gene discovery (62).

Moreover, competing risks also make the definition complex, as a family member who would have developed ALS may die from other causes prior to the development of ALS, resulting in a lower estimate of the proportion of familial cases (64). A related issue is whether neurodegenerative disease aggregates in ALS kindreds. There are some preliminary data suggesting such clustering; however, the only published study (65–67) suggests that the degree of clustering is lower than previously thought. Recent findings of the associations between the *C9ORF72* repeat expansion and ALS suggest a new definition of familial cases, and the number of repeats may reflect the phenotypic variability in ALS presentation (reviewed in (67)). This genetic variant is estimated to account for 34.2% of familial ALS cases. Combined with the identification of other genetic variants known to be associated with ALS (e.g. *SOD1*), it may be possible to identify a genetic

variant associated with over half of familial cases. If this is the case then epidemiologic investigations of both familial and sporadic ALS will benefit as a more distinct separation of these two types of ALS will be possible.

The third issue relates to definitional aspects of ALS. Some have argued that ALS is a complex degenerative disorder that may present a spectrum of phenotypes, including other neuromuscular diseases as well as other neurodegenerative diseases. At present, no data are available to evaluate this conjecture, and this was identified as a fruitful avenue for future study.

Related to the spectrum hypothesis are questions regarding cognitive impairment in ALS. Recent studies have included evaluations of frontal temporal dementia, as present or absent, but cognitive impairment may be on a continuum. The recent finding that the *C9ORF72* repeat is found in both ALS and FTD lends support to the continuum hypothesis (68). Further, more research also needs to be carried out to determine if cognitive decline in ALS occurs more frequently in those with a family history of neurodegenerative disorders (67).

Fourthly, it is crucial for treatment and prevention that research to identify environmental risk factors be pursued with vigor. For example, although cigarette smoking has been identified as a risk factor, the dose-response relationships are not straightforward. Caffeine consumption and alcohol consumption are suggestive as protective factors, but these conclusions are based on few data and need confirmation (69). Serum urate may represent a new and under-studied protective risk factor, as it is a natural antioxidant (70,71). The definition of military service as a risk factor was noted as an area for further research, as military service per se does not capture individual measures of purported risk factors. For example, does military service serve as a proxy variable for exercise, potential toxic exposures (e.g. lead, cyanobacteria producing BMAA) or physical trauma? Furthermore, military exposures may continue in civilian life, e.g. those who were pilots in the military may be more likely to become pilots as civilians and therefore be subject to similar exposures. There is also the possibility of genetic susceptibility to these individual risk factors, as well as the possibility that risk factors (alone or in combination) may affect gene expression and DNA/RNA trafficking.

The use of statins has received attention as clinicians are confused as to how to advise ALS patients taking these medications. The evidence regarding use of statins and survival time is conflicting. Some data suggest that there is no difference in survival for patients taking statins and those not taking statins (72); however, these data are not from a randomized controlled clinical trial. Other data suggest that statins may be associated with faster progression and that this association may be gender specific (73). It was suggested that in studies evaluating statins as a risk factor, data on lipid profiles should also be collected, although some small studies find no relationship between total cholesterol and ALS (74).

Finally, the emergence of the new ALS cluster and the reemergence of clusters in the Kii Peninsula draw attention to the interesting possible associations with exposure to a neurotoxin produced by cyanobacteria (75,76), and furthermore, some of these endemic ALS cases may be associated with *C9ORF72* (77). BMAA may be more ubiquitous than thought, and the ALS clusters, e.g. in the Two Rivers area (78) and in New Hampshire (40,41), occur in areas with water bodies with frequent cyanobacterial blooms. Evidence supporting the BMAA theory derives from the accumulation of BMAA in brains of patients with ALS and Alzheimer's disease (38) and from the identification of geographic clusters of ALS patients adjacent to water bodies subject to frequent cyanobacterial blooms. Direct exposure to such water bodies via residence, domestic water supply or recreation, consumption of food sources derived from such water bodies and that aerosolization of BMAA from wave action and absorption via the respiratory track, may all be potential routes of exposure. Although one group was unable to find BMAA in ALS brains, this could be due to measurement of soluble BMAA and not BMAA bound to proteins. Because BMAA causes proteins to misfold and aggregate, specific affected proteins may lead to different disorders (38).

Moving the field forward

We suggest several areas of future research to move the field forward. These include collaborative multicenter studies and meta-analyses that focus not on single exposures but on unifying hypotheses underlying already studied single exposures, as well as incorporating new methods of exome sequencing, deep genomic sequencing and epigenetic markers. The examination of the early origins of ALS by the use of questionnaires examining exposures in utero (i.e. maternal smoking, fetal growth) or in early childhood is also proposed. Finally, ALS can also be viewed as a spectrum disorder, with the spectrum being defined by survival time, site of onset, type and pattern of progression and presence of cognitive impairment.

Based on the above discussion, we suggest three means by which the field can move forward. First, we suggest using well-characterized population based groups of newly diagnosed ALS cases and appropriately selected controls to identify both risk and preventative factors. Such studies require collection and appropriate storage of biological samples to examine new hypotheses when they become available. They also require appropriate epidemiologic data collection using well validated and comparable measures. Secondly, we suggest using National ALS registries as a surveillance resource to develop testable research

questions and then carry out population based studies. This is akin to the Surveillance, Epidemiology and End Results (SEER) network of the National Cancer Institute. Finally, we stress that these studies require interdisciplinary collaboration to address complex issues relating to complex disorders such as gene-environment, gene-gene, and environment-environment interactions.

Declaration of interest: The International ALS Conference was in part funded by Biogen Idec, Sanofi-Aventis, Knopp Biosciences, and Pfizer, which also in part supported the publication of this supplement. All authors received reimbursement for attending the meeting.

The authors report no other conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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