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Antecedent disease is less prevalent in Amyotrophic Lateral Sclerosis

Cassie S. Mitchell, Ph.D.,
Department of Biomedical Engineering, Georgia Institute of Technology and Emory University

Sabrina K. Hollinger, B.S.,
Department of Biomedical Engineering, Georgia Institute of Technology and Emory University

Shivani D. Goswami, B.S.,
Department of Biomedical Engineering, Georgia Institute of Technology and Emory University

Meraida A. Polak, R.N.,
Department of Neurology, School of Medicine, Emory University

Robert H. Lee, Ph.D., and
Department of Biomedical Engineering, Georgia Institute of Technology and Emory University

Jonathan D. Glass, M.D.
Department of Neurology, School of Medicine, Emory University

Abstract

Background/Aims—Recent studies suggest antecedent disease could impact the pathophysiology of the motoneuron disease Amyotrophic Lateral Sclerosis (ALS). We perform a case-control study to examine the prevalence of 11 antecedent diseases in ALS.

Methods—Prevalence of antecedent disease in a 1288 patient ALS population (Emory University ALS Clinic, Atlanta, GA, USA) is compared to an age, gender, and geography-matched 7561 subject control population using a statistical odds-ratio (OR) with 95% confidence interval.

Results—Association of ALS with odds of arthritis (OR = 0.14); non-ALS neurological disease (OR = 0.14); liver disease (OR= 0.19); chronic obstructive pulmonary disorder or COPD (OR = 0.23); kidney disease (OR = 0.32); adult asthma (OR = 0.39); diabetes (OR = 0.47); hypertension (OR = 0.56); obesity (OR = 0.6); hyperlipidemia or hypercholesterolemia (OR = 0.62); and thyroid disease (OR = 0.78).

Corresponding Author Cassie S. Mitchell, Ph.D., cassie.mitchell@bme.gatech.edu, 1-404-276-8475, Georgia Institute of Technology, 313 Ferst Drive, Atlanta, GA 30332. shollinger3@gatech.edu. gt849s@gatech.edu. mpolak@emory.edu. rlee2@emory.edu. jglas03@emory.edu.

Conclusions—The prevalence of antecedent disease was overall less in the ALS population. We present two potential lines of inquiry to explain these results: 1) "Other disease as ALS protection" — antecedent diseases infer biochemical neuroprotection to ALS; 2) "ALS as other disease protection"— the underpinnings of ALS could infer protection to other diseases, possibly via the mechanism hypervigilant regulation or "too-high" regulatory feedback gains.

Keywords

Amyotrophic Lateral Sclerosis (ALS); Lou Gehrig's disease; antecedent condition

Introduction

For years, researchers have searched for a demographic, environmental, pathological or other commonality among ALS patients that could explain the disease's seemingly complex etiology. This has led to an array of studies suggesting a potential role for individual antecedent conditions, including cardiovascular [1, 2], metabolic [3], neurological [4], and autoimmune factors[5]. Previous studies, typically much smaller in size, have examined a few antecedent conditions [e.g.1, 2, 6-8].

In particular, given the apparent hyper-metabolic state that accompanies ALS progression, the role of metabolism and metabolic disease has been of most interest. Overall, results have shown a statistically lower prevalence of cardiovascular disease [2], hypertension [1, 2, 6], and obesity [1, 9]. Thyroid disease [10, 11] and diabetes [2, 6] have been studied to a lesser degree, with limited examination qualitatively showing lower prevalence in ALS. The most studied antecedent condition is high blood cholesterol, also known as hyperlipidemia or hypercholesterolemia, which also remains the most controversial, with some studies finding a higher [12] others a lower prevalence [6] in ALS patients.

However, numerous other antecedent conditions have yet to be examined at all, such as the possible role of lung, liver, and kidney disease. Here we present the analysis of the prevalence of a wide variety of antecedent conditions, including liver disease, kidney disease, asthma, chronic obstructive pulmonary disease (COPD), arthritis, non-ALS neurological disease, hypertension, hyperlipidemia, diabetes, obesity, and thyroid disease, in a large ALS clinic population (n = 1288 patients).

Methods

We perform a case control study of antecedent disease in age, gender and geography-matched ALS and control populations. The ALS study population consisted of 1288 patients from the Emory ALS Clinic (Emory University Hospital, Atlanta, Georgia, which is located in southern USA). The control study population consisted of 7561 participants residing in the same geographical area. The Internal Review Boards of Emory University and Georgia Institute of Technology approved all protocols of this study.

Antecedent condition assessment

The prevalence of hyperlipidemia, diabetes, hypertension, thyroid disease, asthma, chronic obstructive pulmonary disease (COPD), liver disease, kidney disease, arthritis, and non-ALS

neurological disease were assessed using a standardized medical history survey administered by specially trained personnel. Briefly, the survey asked if a physician had ever diagnosed or treated the participant with said condition and if it had been subsequently affirmed in the last year. Medical and prescription records were used to verify survey responses. Obesity was assessed using recorded height and body weight to calculate body mass index (BMI). A BMI greater than 30 was considered obese.

Study populations and criteria

Surveyed participants included ALS patients and control subjects who were age 20+ years and resided in the southern United States, as defined by the Center for Disease Control [13]. All ALS participants were patients of the Emory University ALS Clinic. Note that in the geographical region assessed in this study, 45-70% of the ALS population are seen at one of approximately thirteen ALS specialty clinics [14] of which about one-third are seen at the Emory ALS Clinic. All ALS patients had a confirmed diagnosis of ALS, which included the presence of exclusionary diagnostic tests (MRI, CSF, etc.) and multi-visit Emory ALS Clinic assessment by a neurologist. Control subjects with measured body weights that were considered extreme outliers (males less than 126 pounds or greater than 299 pounds and females less than 100 pounds or greater than 274 pounds) were excluded [13].

Statistical Analysis

The control population was ratio-matched by age and gender to the ALS population to insure equivalent study population distributions (see Table 1). A standard odds-ratio (OR) statistical test with a 95% confidence interval (CI) was used to assess the prevalence of each condition in the ALS population compared to the prevalence of the control population.

Assessment of other confounds

Socio-economic (i.e. income and education) and health care maintenance information (i.e. regular follow-up with a physician) was not available for all subjects. Therefore, in addition to our data, we also examined other published data sets, which had assessed the impact of these confounds on condition prevalence [e.g. 15, 16, 17]. For each data set, we calculated standardized factors of change to determine the maximum possible bias on condition prevalence. The overall calculated maximum bias (a factor of 2) was converted to an odds-ratio limit (i.e. an OR <0.5) from which the findings of this study could be directly compared (see Discussion).

Results

Of the 1396 ALS patients who completed the survey, 1288 ALS patients met the stated diagnostic criteria. The percentage of ALS patients with at least one known family member with ALS was 5.05%, which is consistent with previously published estimates [18]. The average and standard deviation of ALS onset age was 60.0 ± 12.2 years for females and 56.9 ± 12.4 years for males. Thus, we conclude that ALS population in this study is representative of a typical ALS population [19]. Of the 15167 control subject surveys meeting inclusion criteria, 7561 were used to ratio-match the control population distribution

to the age and gender distribution as the ALS population. The age and gender distributions of the ALS and control population are shown in Table 1.

Table 2 compares the prevalence of each condition in the ALS population to the age and gender ratio-matched control population using a statistically calculated odds-ratio (OR) with a 95% confidence interval (CI) given in parentheses. Note that an OR = 1 represents an equal prevalence in both the ALS and control populations; an OR < 1 is represents lower prevalence in the ALS population; and an OR > 1 is represents a greater prevalence in the ALS population. The overall average prevalence of each of the assessed conditions is as follows: arthritis (ALS = 5.36%, control = 29.5%, OR = 0.14); non-ALS neurological disease (ALS = 0.7%, control = 4.68%, OR = 0.14); liver disease (ALS = 0.85%, control = 4.34%, OR = 0.19); COPD (ALS = 2.87% control = 11.53%, OR = 0.23); kidney disease (ALS = 0.93%, control = 2.86%, OR = 0.32); adult asthma (ALS = 4.89%, control = 11.53%, OR = 0.39); diabetes, including type I and II (ALS = 7.38%, control = 14.47%, OR = 0.47); hypertension (ALS = 36.34%, control = 50.43%, OR = 0.56); obesity (ALS = 20.57%, control = 30.17%, OR = 0.6); hyperlipidemia or hypercholesterolemia/dyslipidemia (ALS = 30.67%, control = 41.69%, OR = 0.62); and thyroid disease, including hyper- and hypothyroidism (ALS = 6.91%, control = 8.70%, OR = 0.78).

Discussion

This is the first study to identify lower prevalence across multiple diseases in the same very large ALS patient population. However, these results generally support the findings of previous smaller studies examining individual diseases in ALS patients [e.g.1, 2, 6, 20].

Other confounding factors potentially affecting antecedent disease prevalence include socio-economics (income and education) and regular healthcare maintenance with a physician. Unfortunately, such data was not available for all subjects in this study. However, many additional studies have also examined the possible influence of these factors on condition prevalence in non-ALS populations [e.g. 15, 16, 17]. The maximum confounds' bias (see Methods) on condition prevalence ranges from a factor of 1.2 to 2.0 (equivalent to an OR of 0.83 to 0.5 in this study), with an average factor of change equal to 1.5 (equivalent to an OR of 0.66). Thus, the calculated maximum possible predicted impact of confounds on the results of this ALS population is a factor of 2 (an OR = 0.5). Therefore, any condition with an OR < 0.5 would still be significantly less in this ALS population irrespective of the unlikely presence of maximum possible confound bias.

Notably, 7 of the 11 assessed conditions have an OR < 0.5, including arthritis, neurological disease, liver disease, COPD, kidney disease, asthma and diabetes. This suggests that even in the extreme case of maximum possible bias, such potential confounds would not affect our conclusions about these conditions. Additionally, it is worth noting that 2 of the 4 conditions with OR > 0.5 (hypertension at 0.56 and obesity at 0.60) have been previously shown in multiple studies to have a lower prevalence in ALS patients [e.g. 1, 2, 6, 9]. The prevalence of hyperlipidemia in ALS patients (OR = 0.62) remains controversial in the literature [e.g. 6, 12], which could be potentially attributed to different studies' confounds or methods. Finally, other small studies [e.g. 10, 11] also found that thyroid disease (OR =

0.78) tends to be less prevalent in ALS but is not necessarily statistically less. In summary, we conclude that unexamined factors or confound biases are not responsible for our overall results as they are more likely no larger than a factor of 1.25 (OR of 0.8) in the population.

The magnitude of the odds-ratios, with conditions like arthritis, non-ALS neurological disease, and liver disease being a factor of 4 to 7 times less prevalent in the ALS population, suggest possible protective mechanisms. "Other disease as ALS protection" has been previously suggested. Conversely, another possibility is "ALS as other disease protection", which has not been previously suggested. We discuss these two possibilities below.

Several have pointed to the possibility that other conditions, such as diabetes [9] or hyperlipidemia [21] could be biochemically neuroprotective to motoneurons. However, others have shown that having these conditions results in no change in ALS onset age or disease duration [6, 22]. Thus, the validity of the "disease as ALS protection" hypothesis remains unresolved.

Another possibility is that the underlying physiological pre-cursors of ALS could actually be protecting against other conditions prior to the onset of ALS symptoms, analogous to how one *S* gene infers resistance to malaria without pathological consequence while 2 copies results in the pathological sickle cell anemia phenotype [23]. We hypothesize that one possible "ALS as disease protection" mechanism could be that, in some individuals, the underlying regulatory processes aggressively over-react to correct imbalances from homeostasis, making them "hypervigilant" to perturbation (in control theory, referred to as a too-high feedback gain). Hypervigilant regulation would initially be overall protective, perhaps against an array of many different perturbing conditions, as long as stable control was maintained. However, motoneurons are already susceptible to changes in regulatory process delay due to their physical length (i.e. axons can be up to 1-meter in length) and large span of regulatory time constants (e.g. axonal transport regulation is on the order of days to weeks whereas calcium regulation is on the order of milliseconds). Regulatory delays, combined with the too-high feedback gain(s) of hypervigilant regulation, could ultimately result in system instabilities, such as those identified in ALS transgenic mice [24], that could directly correspond to a symptomatic ALS phenotype.

This large-scale study of 1288 ALS patients, combined with the results of similar smaller-scale studies, provide overwhelming evidence that antecedent disease prevalence is less in ALS. However, which condition(s) are protecting whom from what? That question remains unanswered. Clearly more research is needed to assess antecedent health in ALS and corresponding possible protective mechanisms.

Acknowledgments

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Table 1

ALS and control population by age and gender. Note that the control population shown was ratio-matched by age and gender to the ALS population to insure equivalent distributions (see Methods).

Condition	ALS	Control
20-44 yr. male	117	688
45-64 yr. male	404	2375
65+ yr. male	254	1493
All male	775	4556
20-44 female	45	259
45-64 female	258	1511
65+ female	210	1235
All female	513	3005
Total	1288	7561

Table 2

Associations of ALS with odds of antecedent conditions. Parameters are odds-ratio (OR) and 95% confidence interval (CI). The prevalence of each condition is less in ALS compared to the age and gender ratio-matched control condition.

Condition	Odds Ratio, (CI)
Arthritis	0.14, (0.11, 0.18)
Neurological Disease	0.14, (0.07, 0.27)
Liver Disease	0.19, (0.10, 0.35)
COPD	0.23, (0.16, 0.32)
Kidney Disease	0.32, (0.18, 0.57)
Asthma	0.39, (0.30, 0.51)
Diabetes	0.47, (0.38, 0.58)
Hypertension	0.56, (0.49, 0.64)
Obesity	0.60, (0.49, 0.74)
Hyperlipidemia	0.62, (0.54, 0.71)
Thyroid Disease	0.78, (0.60, 1.02)