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The Association of Antecedent Conditions on Disease Duration and Diagnosis Age of Amyotrophic Lateral Sclerosis Patients

Sabrina Hollinger

ABSTRACT

Background: Amyotrophic Lateral Sclerosis (ALS) is a fatal neurodegenerative disease. Previous research has shown that antecedent conditions are less prevalent in ALS patients than the general population. Current research has suggested some conditions are protective against ALS. The purpose of this study is to examine the relationship between antecedent conditions and ALS, using age of diagnosis and disease duration.

Methods: Patient data was obtained through the Emory ALS Clinic in Atlanta, Georgia. Patients' histories were analyzed to see if they had any antecedent conditions (high blood pressure, high cholesterol, diabetes, obesity, asthma, arthritis, COPD, kidney disease, liver disease, non-ALS neurological disease, and thyroid disease) at their time of diagnosis. Patients with antecedent conditions compared with the control population (ALS patients without any antecedent diseases) are analyzed through chi square test to see the distributions on age of diagnosis and disease duration. Ordinal logistical regression modelling was completed to see the magnitude of effect antecedent conditions has on disease duration and age of diagnosis.

Results: All antecedent conditions had an older age at ALS diagnosis than the control population except obesity, kidney disease, and liver disease ($p<0.05$). Disease duration was found to be significantly shorter compared to the control population when looking at high blood pressure, diabetes, obesity, arthritis, and kidney disease ($p<0.05$). When looking at the antecedent conditions as a whole, those with cardiovascular diseases, or between 1 and 3 diseases, had a very significant older age of diagnosis ($p<0.0001$), and a significant shorter disease duration ($p<0.05$).

Conclusions: Antecedent conditions high blood pressure, high cholesterol, and COPD can be seen as protective against ALS due to their delayed age of diagnosis. A possible explanation is that these antecedent diseases could be biochemically neuroprotective against ALS in a currently unknown pathway. Antecedent disease association, with reduced disease duration, is likely due to the advanced age of the patient.

KEYWORDS

amyotrophic lateral sclerosis, antecedent condition, disease duration, diagnosis age, prognosis, high blood pressure, hypertension, high cholesterol, hyperlipidemia, dyslipidemia, obesity, diabetes, asthma, arthritis, COPD, chronic obstructive pulmonary disease, thyroid, kidney, liver

THE ASSOCIATION OF ANTECEDENT CONDITIONS ON DISEASE DURATION AND DIAGNOSIS AGE OF AMYOTRPOHIC LATERAL SCLEROSIS (ALS) PATIENTS

By

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APPROVAL PAGE

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Chapter I

Introduction

Amyotrophic Lateral Sclerosis (ALS) is a debilitating neuromuscular disease that affects almost 4 in 100,000 people in the United States (Mehta et al., 2014). Those afflicted with the disease face losing control over major muscle groups such as arms, legs, and core muscles including their diaphragm. Only 5 to 10% of ALS is attributed to a familial gene; the majority is considered idiopathic (Andersen, 2000).

Previous research on ALS shows a link connection those without common conditions having ALS (Korner et al., 2013; Mitchell et al., 2015). These common conditions, such as elevated blood pressure, high cholesterol, obesity, and diabetes were found to be less prevalent in the ALS population than a control population (Dorst et al., 2011; Dupuis et al., 2008; Korner et al., 2013; Mitchell et al., 2015).

Current literature suggests the association of certain factors, like age at diagnosis and gender of the patient, may lead to shorter disease duration in patients diagnosed with ALS. Emerging research now links several common conditions to either having no effect or lengthening disease duration. However, literature has not yet been able to fully explore the effects of these factors and common conditions on the patients' age at diagnosis. This is an important factor as the younger an individual is at time of ALS diagnosis, the longer the disease duration will be (Wei et al., 2015; Wolf et al., 2014).

Chapter II

LITERATURE REVIEW

Overview

Amyotrophic lateral sclerosis (ALS) is a debilitating neurological disease that attacks the motor neurons. As of 2011, it affects nearly 4 per 100,000 people in the United States as of 2011 (Mehta et al., 2014). The cause of ALS is largely attributed to being idiopathic, with less than 10 percent being related to a familial gene. (Andersen, 2000).

Prior to an ALS diagnosis, many patients consider themselves to be healthier than the general population (Turner, 2013). Some research has shown lifelong athletes having a higher risk of developing ALS than non-athletes (Chio et al., 2009). ALS does not directly relate to having an active lifestyle, but factors that are associated with an active lifestyle also lead to an increase in ALS susceptibility (Beghi, 2013; Huisman et al., 2013; Valenti et al., 2005).

Current research is seeking to improve longevity after a patient receives a diagnosis of ALS. The only FDA-approved treatment, Riluzole, has been shown to improve longevity, but only when taken within the first 6 months of therapy (Cetin et al., 2015). Common factors related t0 disease duration are age at onset, gender, and race (Jawaid, Murthy, et al., 2010; Korner et al., 2013; Watanabe et al., 2014; Wolf et al., 2014).

This study will attempt to analyze the relationship between many antecedent conditions and the disease duration and diagnosis age of ALS. More specifically, these conditions include cardiovascular (including hypertension, hyperlipidemia, obesity, and

diabetes), autoimmune (asthma, chronic obstructive pulmonary disease [COPD], thyroid disease, and arthritis), non-ALS neurological disease, kidney disease, and liver diseases. These diseases are of interest when they manifest in the patient prior to ALS diagnosis.

Epidemiology of Amyotrophic Lateral Sclerosis

Disease Duration

The average life expectancy of ALS patients is currently less than two years after diagnosis (Cetin et al., 2015). Researchers are looking at many variables in order to help give patients a more accurate prognosis. Currently known and accepted factors for survival include age at diagnosis, gender, body weight at diagnosis, and interval between onset and diagnosis (Gil et al., 2007; Wei et al., 2015; Wolf et al., 2014).

One line of current research is how concurrent illness in ALS patients affects disease duration (Korner et al., 2013; Moreau et al., 2012; Paganoni, Deng, Jaffa, Cudkowicz, & Wills, 2011). While some studies have found that common conditions; such as hyperlipidemia and diabetes did not affect the length of survival (Dedic et al., 2012; Korner et al., 2013; Sutedja et al., 2011), other studies found that the common conditions did have a positive of negative effect (Moreau et al., 2012; Paganoni et al., 2011). Lung ability, (e.g. full vital capacity and maximal inspiratory capacity), was found to be an accurate predictor for disease duration (Schmidt et al., 2006). Uric acid and tauroursodeoxycholic (TUDCA) acid, a hydrophilic bile, have also been linked with a prolonged survival in ALS patients (Elia et al., 2015; Paganoni et al., 2012). There are currently no studies that have successfully demonstrated a link between ALS disease duration and other non-ALS neurological diseases.

Age of Diagnosis Models

An accepted variable to predict disease duration in ALS patients is age at diagnosis; however, the age at which an individual will be diagnosed cannot be predicted. Within the general population, ALS increases in prevalence with increasing age, reaching a peak at the 60-69 age range (Mehta et al., 2014). Research supports the stance that

ethnicity has a role in the age of diagnosis, as those with Asian race are found to be diagnosed at an earlier age than Caucasians (Wei et al., 2015).

Comparing age of diagnosis with antecedent conditions, diabetes mellitus type 2 is found to be correlated with a later onset of 4 years compared to those without diabetes, adjusting for gender, ethnicity, and site of onset (Jawaid, Salamone, et al., 2010). Body mass index (BMI) at time of diagnosis was not found to have an association with age of onset (Jawaid, Murthy, et al., 2010).

Antecedent Conditions of Interest

Cardiovascular Conditions

For this study, cardiovascular conditions of interest include hyperlipidemia (high cholesterol), hypertension (high blood pressure), obesity (BMI greater than or equal to 30.0), and diabetes mellitus (both type 1 and type 2). Many studies have examined these cardiovascular diseases within the same population but the effects of combinations of these diseases are relatively unstudied (Korner et al., 2013; Mitchell et al., 2015).

- Hyperlipidemia – Hyperlipidemia is a commonly studied antecedent condition among ALS patients. Some studies have found that the presence of hyperlipidemia can extend the length of survival after diagnosis (Dedic et al., 2012; Dorst et al., 2011; Dupuis et al., 2008; Sutedja et al., 2011). Other studies have found hyperlipidemia to not be related to disease duration (Korner et al., 2013; Paganoni et al., 2011; J. W. Yang et al., 2013).
- Hypertension – In research, hypertension has shown a mixed association with the disease duration in ALS patients. Relating to effect on disease duration, hypertension has been shown to be beneficial (Sutedja et al., 2011), neutral (Korner et al., 2013), and detrimental (Moreau et al., 2012).
- Diabetes – In ALS patients, diabetes is less prevalent than the general population (Mariosa, Kamel, Bellocco, Ye, & Fang, 2015; Mitchell et al., 2015). Research has also shown patients with diabetes to have a 4 year later onset of ALS

compared to ALS patients without diabetes (Jawaid, Salamone, et al., 2010). However, it also has been shown to not have any effect on survival length (Korner et al., 2013).

- Obesity – Obesity is primarily studied in regards to the BMI calculation itself, not the categories affected by BMI. Studies have shown that those with a lower BMI, between 18.5 and 24.9 or the 'healthy' range, are found to be at a higher risk of ALS than individuals with a higher BMI (Mitchell et al., 2015; O'Reilly et al., 2013). Survival models have shown that a slower rate of change in BMI after diagnosis is related to longer disease duration (Jawaid, Murthy, et al., 2010; Paganoni et al., 2011; Sutedja et al., 2011).

Autoimmune Conditions

Autoimmune conditions of interest include asthma, COPD, arthritis, and thyroid disease. Some studies have found that these conditions are found at a higher prevalence in the ALS population compared to the general population (Turner, Goldacre, Ramagopalan, Talbot, & Goldacre, 2013). However, other studies have found these conditions are at a lower prevalence (Mitchell et al., 2015). These conditions can be related to pulmonary function, which is found to be a direct predictor of disease duration in ALS patients (Schmidt et al., 2006). Autoimmune therapies have been shown to help slow the progression of ALS, as there are similar pathways that lead to the development of autoimmune diseases and ALS (Alexianu, 1995; Schulte-Herbruggen, Braun, Rochlitzer, Jockers-Scherubl, & Hellweg, 2007; E. J. Yang et al., 2010)

Other Conditions

Kidney and liver diseases have not been extensively studied in ALS populations, but have been found to be less prevalent when compared to the general population (Mitchell et al., 2015). Uric Acid, which can be an indicator of kidney function, was found to be associated with longer disease duration in male ALS patients (Johnson et al.,

2013; Paganoni et al., 2012). TUDCA (a hydrophilic bile in the liver) has been shown in a pilot study to improve the ALSFRS-R (ALS functional ratings scale) scores (Elia et al., 2015).

Neurological diseases, such as dementia and Parkinson's, have conflicting associations with ALS. These range from being more common in ALS patients compared to general population, or not being related to the ALS diagnosis, to being less prevalent (Korner et al., 2013; Mitchell et al., 2015; van Doormaal et al., 2013). Multiple Sclerosis is one neurologic disease with research indicating such a correlation (Etemadifar, Abtahi, Akbari, & Maghzi, 2012) and there being no correlation (van Doormaal et al., 2013) within ALS patients.

Previous Research

The ALS patients included in this study have previously been examined for the prevalence of common conditions relative to the general population (Mitchell et al., 2015). The population of 1288 patients were examined for multiple pre-existing conditions, then matched with a control population based age, gender, and geographic region. The pre-existing conditions studied include hypertension, hyperlipidemia, diabetes, obesity, asthma, arthritis, COPD, thyroid disease, liver disease, non-ALS neurological disease, and kidney disease.

Results showed that the ALS patients had lower prevalence of all diseases of interest when age, gender, and spatially matched to the general population. The ALS 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) were lower than the odds of those in the general population. See Table A for the 95% confidence intervals.

There are two pathways to explain the lower prevalence. One method is "Other condition as ALS protection", where the presence of antecedent conditions is protective against ALS. This could through a currently unknown biochemically neuroprotective pathway. Another explanation is "ALS as other condition protection" where the ALS disease interferes with the underlying causes of the antecedent conditions.

Table A. 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, (95% Confidence Interval)**
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)

Purpose of Research

There are several different factors that have been examined individually for their effect on the prognosis in those with ALS, with some examining a larger array of conditions. This study will analyze the relationships between individual conditions and ALS patients. The conditions will also be analyzed together on ALS disease duration and

age of diagnosis to see if there is any interaction within the antecedent conditions. Logistic regression will be done to shed light on possible factors for age of diagnosis, along with clarifying the impact the antecedent conditions have. This will help clarify avenues for future research to understand underlying causes of ALS along with possible areas to focus when creating new treatments.

Chapter III

Abstract

Background: Amyotrophic Lateral Sclerosis (ALS) is a fatal neurodegenerative disease. Previous research has shown that antecedent conditions are less prevalent in ALS patients than the general population. Current research has suggested some conditions are protective against ALS. The purpose of this study is to examine the relationship between antecedent conditions and ALS, using age of diagnosis and disease duration.
Methods: Patient data was obtained through the Emory ALS Clinic in Atlanta, Georgia. Patients' histories were analyzed to see if they had any antecedent conditions (high blood pressure, high cholesterol, diabetes, obesity, asthma, arthritis, COPD, kidney disease, liver disease, non-ALS neurological disease, and thyroid disease) at their time of diagnosis. Patients with antecedent conditions compared with the control population (ALS patients without any antecedent diseases) are analyzed through chi square test to see the distributions on age of diagnosis and disease duration. Ordinal logistical regression modelling was completed to see the magnitude of effect antecedent conditions has on disease duration and age of diagnosis.
Results: All antecedent conditions had an older age at ALS diagnosis than the control population except obesity, kidney disease, and liver disease ($p<0.05$). Disease duration was found to be significantly shorter compared to the control population when looking at high blood pressure, diabetes, obesity, arthritis, and kidney disease ($p<0.05$). When looking at the antecedent conditions as a whole, those with cardiovascular diseases, or between 1 and 3 diseases, had a very significant older age of diagnosis ($p<0.0001$), and a significant shorter disease duration ($p<0.05$).

Conclusions: Antecedent conditions high blood pressure, high cholesterol, and COPD can be seen as protective against ALS due to their delayed age of diagnosis. A possible explanation is that these antecedent diseases could be biochemically neuroprotective against ALS in a currently unknown pathway. Antecedent disease association, with reduced disease duration, is likely due to the advanced age of the patient.

Introduction

Amyotrophic lateral sclerosis (ALS) is a debilitating neurodegenerative disease with a relatively unknown etiology. Many times, those diagnosed with ALS have previously led healthy and active lifestyles (Huisman et al., 2013; Turner, 2013). Researchers have looked at multiple antecedent conditions to see if there is any link between these conditions and ALS, yet there have been no conclusive results (Dedic et al., 2012; Etemadifar et al., 2012; Jawaid, Salamone, et al., 2010; Korner et al., 2013; Paganoni et al., 2012). Only 5 to 10 percent of the ALS population can be attributed to genetic factors (Andersen, 2000) while the rest are idiopathic.

Existing research has found several factors that impact disease duration and age of onset of ALS in patients. Onset age has been found to occur earlier in those of Asian race, or male gender (Watanabe et al., 2014; Wei et al., 2015). Shorter disease duration is related to patients that have a more advanced age at onset of ALS symptoms (Gil et al., 2007; Jawaid, Murthy, et al., 2010; Watanabe et al., 2014).

When looking at antecedent conditions, it has been shown that the ALS patients have lower rates than that of the general public (Korner et al., 2013; Mitchell et al., 2015). These lower rates have led to speculation that the conditions could act as protection against ALS, possibly due to the hyper-metabolic state found in ALS patients (Jawaid, Salamone, et al., 2010).

The effect of these conditions have been shown to have a positive (Dorst et al., 2011; Moreau et al., 2012; Paganoni et al., 2012), neutral (Dedic et al., 2012; Korner et al., 2013), or negative (Jawaid, Murthy, et al., 2010) effect on duration of ALS in

patients. The effect on age at diagnosis is more consistent when studied, and shows a delayed age of diagnosis (Jawaid, Salamone, et al., 2010; Korner et al., 2013).

This study will focus on how multiple types of antecedent conditions (high blood pressure, high cholesterol, diabetes, obesity, asthma, arthritis, COPD [Chronic Obstructive Pulmonary Disease], thyroid disease, kidney disease, liver disease, and non-ALS neurological disease) effect ALS through diagnosis age and disease duration.

Methods

A case control study of antecedent conditions on diagnosis age and disease duration of an ALS population was performed. The ALS population consisted of 1439 patients from the Emory ALS Clinic, in Atlanta Georgia confirmed to have ALS at their first clinic visit. The Internal Review Boards of Emory University, Georgia Institute of Technology, and Georgia State University approved all protocols of this study.

Antecedent Conditions

The prevalence of high blood pressure, high cholesterol, diabetes, obesity, arthritis, asthma, COPD, thyroid disease, neurological disease (excluding ALS), kidney disease and liver disease were assessed at the first visit by medical personnel and a self-completed patient entry survey. Additional information for gathering the data can be seen in a previously published paper (Mitchell et al., 2015).

Study Populations

Two study populations were identified from the ALS clinic population. Control population was determined by the confirmed ALS patients having no antecedent conditions of interest at their first visit. The antecedent conditions population was determined by the ALS patients having at least one of the following: high blood pressure, high cholesterol, diabetes, obesity, arthritis, asthma, COPD, thyroid disease, neurological disease, kidney disease, or liver disease, at their first visit.

These study populations were then analyzed to see if they met the qualifications of the two groups of interest. All patients were included in Group 1(n=1349). Group 1 included patients with a confirmed diagnosis age. Those with a date of death in their medical records were also placed in Group 2 (n=787). Group 2 was used to analyze disease duration with ALS patients.

Statistical Analysis

All statistical tests were completed using SAS 9.3. Chi square analysis was done to compare the distributions of the control population and antecedent disease population for both outcomes of interest. For age of diagnosis, the chi square compared the distribution above and below the mean age of diagnosis of the entire population. For the length of survival, the chi square compared the distribution above and below the mean length of survival of the subset of the total population. The distributions were compared between the control group and the antecedent disease group for both the age of diagnosis and survival length.

Ordinal logistic regression was completed for both age of diagnosis and length of survival to assess for confounders and compare the antecedent diseases with known risk factors. This was done to examine what extent each of the antecedent diseases and other factors related to the age of diagnosis and survival length.

For both models, male gender and Caucasian race were set as the reference group. Race was assessed as Caucasian, African American, and Other. The ordinal logistic regression for age of diagnosis included all antecedent diseases, race, and gender. The ordinal logistic regression for length of survival included all antecedent diseases, race, gender, and age of diagnosis.

Results

Demographics

Group 1, consisting of those who had a confirmed ALS diagnosis, is 60% male and 40% female, with 57% of the population having at least one antecedent condition. Group 2, those who had a confirmed ALS diagnosis and date of death, is 57.7% male and 42.3% female, along with 54% having at least one antecedent condition. Gender falls on a more equal distribution in group 2 than group 1($p<0.05$). All of the antecedent conditions except high cholesterol, diabetes, and obesity occur within the same distribution between both population groups. (See **Table 1** for additional demographic information)

Group 1, those with a confirmed ALS diagnosis, has a diagnosis age mean of 60.1 years with a standard deviation of 12.5 years. The mean diagnosis age among the control population was 56.6 years; males at 54.5 and females at 59.1 years of age. Those with antecedent disease had an average of 63.1 years; males at 62.4 years and females at 64.1 years of age. A substantially greater proportion of individuals with antecedent conditions are older when compared to those without antecedent conditions of interest ($p<0.0001$).

Group 2 has average disease duration of 2.1 years with a standard deviation of 2.1 years. Those without antecedent conditions of interest have an average of 2.4 years; with males at 2.5 and females at 2.4 years of survival. Those with antecedent conditions have disease duration of 1.9 years; with males at 2.0 and females at 1.7 years of survival. The antecedent condition group had a substantially shorter disease duration when compared with those without antecedent conditions ($p<0.0001$).

Chi Square Analysis

Chi Square test was used to compare age of diagnosis and disease duration between antecedent conditions and those without any antecedent conditions. Antecedent condition populations include: Sole condition (only having one antecedent condition of interest), Multiple condition (having multiple antecedent conditions including the

condition of interest), Cardiovascular (having any number of the following: High blood pressure, High cholesterol, Diabetes, or Obesity), Autoimmune (having any of the following: Asthma, Arthritis, COPD, Thyroid disease), and finally Amount (the number of any antecedent conditions present). For example, a patient with the conditions of diabetes and asthma would be located in the Multiple condition group for asthma and for diabetes, the cardiovascular group, the autoimmune group, and the Amount group of 2.

Sole and Multiple condition populations are found in **Table 2**. Cardiovascular, Autoimmune, and Amount populations are found in **Table 3**. Mean age of diagnosis and disease duration of the antecedent condition populations are reported along with the number of patients analyzed for that comparison within the tables.

Age of Diagnosis

High blood pressure and high cholesterol are found to have a substantially significant older distribution than the control ALS population as Sole antecedent condition, or Multiple antecedent condition ($p<0.0001$). A significant later age of diagnosis distribution is also found for diabetes, asthma, arthritis, COPD, thyroid diseases, and non-ALS neurological diseases, in Multiple antecedent condition groups ($p<0.05$).

In the cardiovascular group, substantial significance for a later age of diagnosis distribution is found for all categories except the four cardiovascular conditions group ($p<0.001$). Autoimmune conditions only show substantial significance when other antecedent diseases are involved for having a later age of diagnosis distribution than the control ($p<0.0001$).

Up to three antecedent condition groups have a substantially significantly older distribution ($p<0.0001$). Those with four antecedent conditions have a significant older distribution at diagnosis ($p<0.05$). There is no significance found for those with five or six antecedent conditions.

Disease Duration

High blood pressure, high cholesterol, diabetes, obesity, arthritis and kidney disease all have a different distribution than the control for Multiple antecedent conditions ($p<0.05$). The significance found shows that those antecedent condition populations have a shorter disease duration that the control population.

Cardiovascular conditions show significance for disease duration for one, two, and three conditions or having any cardiovascular condition at all ($p<0.005$). Those categories are correlated to a shorter disease duration when compared to the control population.

Amount antecedent conditions of one, two, and three results in a substantially shorter disease duration than the control ($p<0.0005$). Significance is not found in those with four, five, or six antecedent conditions due to a limiting sample size.

Ordinal Logistical Regression

Ordinal logistical regression modelling is used for age of diagnosis and disease duration. High blood pressure, high cholesterol, COPD, 'Other' race, and gender were found to be significant variables with an association to a delayed the age of diagnosis past the mean (60.1 years). 'African American' race and obesity are found to have a significant association to an earlier age of diagnosis. When looking at disease duration, age of diagnosis and 'Other' race are significant variables associated with shortening disease duration under the mean (2.1 years). 'African American' race has a significant association with lengthening disease duration beyond the mean. See **Table 4** for the odds ratios for all variables tested.

Other Results

The population was gender stratified to look for additional patterns. Significance results mirror that of the overall population for both genders. Antecedent conditions were also analyzed with permutations of two antecedent conditions. Significance is only found in the more prevalent condition permutations, such as high blood pressure and high cholesterol, where a large sample size is present. Any significance is reflected in the grouping of diseases.

Discussion

Results of the chi square analysis indicates an overall pattern that those with antecedent conditions have a later age of diagnosis, and shorter disease duration, than those without antecedent conditions within the ALS population. When controlled for confounders, only high blood pressure, high cholesterol, obesity, and COPD are found to be significant factors in diagnosis age.

Antecedent Conditions on Age of Diagnosis

When looking at individual antecedent conditions, every condition of interest is found to have a later age of diagnosis excluding obesity (see *What about Obesity?*). High blood pressure, high cholesterol, and COPD are found to be significant factors in delaying the age of diagnosis. These conditions have also been found to be less prevalent in the ALS population (Korner et al., 2013; Mitchell et al., 2015; Sutedja et al., 2011).

With the prevalence lower in the ALS population, there may be a mechanism in which these antecedent conditions are protective against ALS in an unknown pathway. Diabetes and high cholesterol have been previously suggested to be biochemically neuroprotective against ALS (Dupuis et al., 2008; Jawaid, Salamone, et al., 2010).

ALS could possibly develop due to hypervigilance of the body's systems, which can be seen with hyper-metabolism in patients, which could also explain the delayed

onset (Desport, Torny, Lacoste, Preux, & Couratier, 2005; Jawaid, Salamone, et al., 2010; J. W. Yang et al., 2013). If the body has a lower level of hypervigilance, it would allow these antecedent conditions to form (Mitchell et al., 2015). The less severe hypervigilance would, as a separate function, cause ALS to develop at a later age. Those with a higher level of hypervigilance would not develop antecedent conditions, but would develop ALS at an earlier age.

Antecedent Conditions on Disease Duration

No antecedent conditions are found to be significant factors in predicting the disease duration in patients. Some researchers have found that cardiovascular conditions are beneficial to ALS patients as ALS progresses (Dorst et al., 2011; Dupuis et al., 2008), but further research supports that the conditions do not have a significant impact on ALS disease duration (Dedic et al., 2012; Korner et al., 2013; Paganoni et al., 2011).

The shorter disease duration found in the antecedent condition groups can be attributed to the fact that those groups have a later age of diagnosis. Advanced age is known to be a predictor of shorter disease duration (Gil et al., 2007; Watanabe et al., 2014). Antecedent conditions are found more in older patients whether due to the condition protecting against ALS, or the prevalence of the conditions increasing with age.

What about Obesity?

Obesity is the only antecedent condition found to be a significant predictor of a younger age of diagnosis. Many studies show that obesity can be beneficial to ALS patients in terms of survival (Jawaid, Murthy, et al., 2010; Shimizu et al., 2012). Other research has found obesity to be less prevalent in ALS patients than the general population (Mitchell et al., 2015; O'Reilly et al., 2013; Paganoni et al., 2011). While these results (shorter disease duration) appear to be conflicting, further understanding of how the variables were defined is needed.

When obesity is found to be beneficial to survival, the variable measured is the rate of change in BMI (Jawaid, Murthy, et al., 2010; Shimizu et al., 2012). Other studies have focused on unhealthy weight, taking any BMI above 24.9 to be considered of interest, with the effects varying as BMI changes (O'Reilly et al., 2013; Paganoni et al., 2011).

Our measure of obesity is a BMI greater than or equal to 30.0 at the time of diagnosis and change in BMI is not reflected in our study. Obesity likely has multifaceted implications on the disease duration and diagnosis of ALS that cannot be interpreted with this broad and static definition used.

Limitations

One limitation is lack of complete demographic information. Many patients did not have a race in their records, or declined to give their race. This resulted grouping a large portion of the patients into the 'Other' race category. Sample size is also a limitation throughout the study. Despite the large overall population used, less than 25 individuals are found to have thyroid disease, kidney disease, liver disease, or non-ALS neurological disease. A larger population of ALS patients with these antecedent conditions would allow for more accurate results.

Conclusion

Antecedent conditions, found less prevalent in ALS patients than the general population, are also found to have an effect of the age of diagnosis. High blood pressure, high cholesterol, and COPD are found to be significant factors associated in delaying the age of diagnosis. Obesity was found to be a significant factor associated in an earlier age of diagnosis, most likely due to an improper classification and its complex effects in ALS patients. The delay of age of diagnosis among those with antecedent conditions could be due to the hyper-metabolic or hyper-vigilant state present in ALS patients.

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Appendix A

Table 1. Demographics of Emory Clinic ALS population by Diagnosis Age and Disease Duration

Population Characteristics	Diagnosis Age Population			Disease Duration Population		
	Overall	*Control*	*Disease*	*Overall*	*Control*	*Disease*
N	1439	619	820	787	364	423
Age[#ł]						
mean (SD)	60.1 (12.5)	56.6(13.3)	63.1 (8.0)	61.2(12.4)	57.4 (13.2)	64.5 (10.6)
Survival Length (years)						
mean (SD)[ł]	-	-	-	2.1 (2.1)	2.4 (2.3)	1.9 (1.8)
Gender* %(N)						
Male[ł]	60.0 (864)	62.7 (388)	58.0 (476)	57.7 (454)	61.5 (224)	54.4 (230)
Female[ł]	40.0 (575)	37.3 (231)	42.0 (344)	42.3 (333)	38.5 (140)	45.6 (193)
Race %(N)						
Caucasian	57.4 (826)	56.4 (349)	58.4 (479)	59.1 (465)	57.1 (208)	60.8 (257)
African American	12.3 (177)	12.4 (77)	12.2 (100)	10.7 (84)	11.0 (40)	10.4 (44)
Other	30.2 (434)	31.1 (193)	29.4 (241)	30.2 (238)	32.7 (119)	28.1 (119)
Antecedent Conditions %(N)						
High Blood Pressure	40.0 (532)	-	64.9 (532)	36.0 (283)	-	66.9 (283)
*High Cholesterol**	26.3 (378)	-	46.1 (378)	24.0 (189)	-	44.7 (189)
*Diabetes**	7.7 (111)	-	13.5 (111)	6.4 (50)	-	11.8 (50)
*Obesity**	9.0 (129)	-	15.7 (129)	7.1 (56)	-	13.2 (56)
Arthritis	5.1 (74)	-	9.0 (74)	5.0 (39)	-	9.2 (39)
Asthma	4.9 (71)	-	8.7 (71)	4.8 (38)	-	9.0 (38)
COPD	3.1 (45)	-	5.5 (45)	2.8 (22)	-	5.2(22)
Thyroid	1.5 (22)	-	2.7 (22)	1.8 (14)	-	3.3 (14)
Neurological disease	0.8 (11)	-	1.3 (11)	1.0 (8)	-	1.9 (8)
Kidney Disease	0.8 (12)	-	1.5 (12)	1.3 (10)	-	2.4 (10)
Liver Disease	0.8 (12)	-	1.5 (12)	0.9 (7)	-	1.7 (7)

[#]Age at first visit to clinic

*Age of Diagnosis population significantly different than Disease Duration Population ($p<0.05$)

ł Control population significantly different than antecedent condition population ($p<0.05$)

Table 2. Antecedent Condition Effect of Age of Diagnosis and Disease Duration of ALS Population, Chi Square Analysis

	Age of Diagnosis			**Disease Duration**		
Population	Mean (s.d)	N†	P-value	Mean (s.d)	N†	P-value
Control*	56.2 (13.3)	1439	**<.0001**	2.4 (2.3)	787	**<.0001**
Antecedent Condition						
Blood pressure						
Sole	63.4 (10.5)	819	**<.0001**	1.9 (2.0)	481	**0.0079**
Multiple	64.3 (10.5)	1151	**<.0001**	1.8 (1.7)	647	**<.0001**
Cholesterol						
Sole	63.3 (10.4)	718	**<.0001**	1.9 (1.5)	404	0.0612
Multiple	65.3 (10.2)	997	**<.0001**	1.7 (1.5)	553	**<.0001**
Diabetes						
Sole**	50.6 (12.8)	631	0.1410	3.2 (3.3)	371	0.7035
Multiple	63.6 (10.1)	730	**<.0001**	1.8 (1.8)	414	**0.002**
Obesity						
Sole	52.9 (9.6)	654	**0.0185**	1.6 (0.9)	379	0.4646
Multiple	57.3 (11.1)	750	0.3847	1.7 (1.2)	421	**0.0347**
Asthma						
Sole	56.0 (11.9)	641	0.4821	3.0 (2.0)	377	0.1819
Multiple	61.1 (12.1)	690	**0.0367**	2.3 (1.7)	402	0.6881
Arthritis						
Sole ‡	60.3 (9.0)	638	0.2404	2.3 (2.3)	373	0.7382
Multiple	65.6 (8.4)	693	**<.0001**	1.8 (1.9)	403	**0.0379**
COPD						
Sole ‡	60.4 (16.1)	634	0.2707	2.7 (3.7)	370	1
Multiple	64.3 (11.8)	664	**<.0001**	1.9 (2.5)	386	0.5496
Thyroid						
Multiple	67.4 (7.4)	641	**0.0004**	2.5 (2.1)	378	0.2899
Neurological						
Multiple**	68.7 (7.1)	630	**0.0007**	1.8 (2.1)	372	0.1457
Kidney						
Multiple**	69.4 (13.5)	631	0.0732	0.9 (0.6)	374	**0.0063**
Liver						
Multiple**	56.0 (10.9)	631	0.3839	3.5 (3.5)	371	1

Chi Square Analysis with population distribution above or below the mean of the total population (60.1 for Age of Diagnosis, 2.12 for Disease Duration). Mean (s.d) is in years, represents Age of Diagnosis or Disease Duration

* Control population compared to any antecedent condition population

† N represents size of population with antecedent condition of interest and control population (no antecedent conditions)

** Fisher's exact test used due to small sample size for Age of Diagnosis and Disease Duration

‡ Fisher's exact test used due to small sample size for Disease Duration

Table 3. Categories of Antecedent Condition on Age of Diagnosis and Disease Duration, Chi Square Analysis

	Age of Diagnosis			**Disease Duration**		
Antecedent Condition	Mean (s.d)	N	P-value	mean (s.d.)	N	P-value
Cardiovascular						
1	62.8 (11.0)	762	**<.0001**	1.8 (1.8)	584	**0.0002**
2	64.8 (11.0)	641	**<.0001**	1.7 (1.4)	486	**0.0011**
3	63.3 (9.1)	508	**<.0001**	1.7 (1.7)	393	**0.0196**
4*	63.5 (10.7)	461	0.1242	1.7 (1.2)	371	0.2462
any	63.5 (10.8)	1357	**<.0001**	1.8 (1.7)	742	**<.0001**
Autoimmune						
Sole Type	59.2 (12.5)	686	0.3806	2.7 (2.4)	396	0.1702
Multiple Types	63.9 (10.7)	812	**<.0001**	2.1 (2.0)	466	0.6600
Amount of Conditions						
1	61.3 (11.3)	747	**<.0001**	2.1 (2.0)	582	**0.01**
2	65.0 (10.7)	663	**<.0001**	1.6 (1.4)	502	**0.0002**
3	65.7 (10.0)	530	**<.0001**	1.4 (1.4)	412	**0.0005**
4	62.7 (9.4)	478	**0.0149**	2.4 (1.9)	380	0.6715
5*	64.8 (5.5)	456	0.0614	2.5 (2.4)	367	1
6‡	65.0†	454	0.3935	-	-	-

Chi Square Analysis with population distribution above or below the mean of the total population (60.1 for Age of Diagnosis, 2.12 for Disease Duration). Mean (s.d.) is in years, represents Age of Diagnosis or Disease Duration

† Sample size of one

* Fisher's exact test used due to small sample size for Age of Diagnosis and Disease Duration

‡ Fisher's exact test used due to small sample size for Age of Diagnosis

Table 4. Ordinal Logistic Regression Modeling of Age of Diagnosis and Disease Duration			
Model	**Variable**	**Odds Ratio**	**95% Confidence Interval**
Age of Diagnosis			
	Blood Pressure	**0.461**	**0.334**	**0.636**
	Cholesterol	**0.385**	**0.285**	**0.521**
	Diabetes	0.711	0.458	1.104
	Obesity	**2.268**	**1.494**	**3.443**
	Asthma	1.001	0.588	1.705
	Arthritis	0.608	0.358	1.034
	COPD	**0.419**	**0.212**	**0.826**
	Neurological	0.303	0.072	1.279
	Kidney	0.375	0.106	1.322
	Liver	3.522	0.706	17.571
	Thyroid	0.896	0.615	1.306
	Race (Black)	**1.577**	**1.2456**	**1.99767**
	Race (Other)	**0.676**	**0.563**	**0.81**
	Gender (Female)	**0.776**	**0.69235**	**0.87046**
Disease Duration			
	Blood Pressure	1.06	0.705	1.595
	Cholesterol	1.048	0.723	1.518
	Diabetes	1.044	0.586	1.862
	Obesity	1.085	0.629	1.871
	Asthma	0.629	0.329	1.201
	Arthritis	0.919	0.48	1.759
	COPD	1.366	0.568	3.283
	Neurological	0.973	0.252	3.757
	Kidney	2.3	0.59	8.968
	Liver	0.347	0.081	1.485
	Thyroid	0.846	0.536	1.334
	Race (Black)	**0.624**	**0.464**	**0.837**
	Race (Other)	**1.807**	**1.438**	**2.271**
	Gender (Female)	1.080	0.938	1.241
	Age	**1.049**	**1.036**	**1.062**

Race reference group is Caucasian. Gender reference group is Male. For age of diagnosis model, estimates above 1 lower the age of diagnosis. For disease duration, estimates above 1 shorten the duration.