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Timothy M. Miller, MD, PhD
PRE-MORBID TYPE 2 DIABETES MELLITUS IS NOT A PROGNOSTIC FACTOR IN AMYOTROPHIC LATERAL SCLEROSIS

SABRINA PAGANONI, MD, PhD,1,2,3 TEOHEDORE HYMAN, BS,4 AMY SHU, MA,5 PEGGY ALLRED, PT, DPT,4 MATTHEW HARMS, MD,4 JINGXIA LIU, PhD,4 NICHOLAS MARAGAKIS, MD,6 DAVID SCHOFENFELD, PhD,5 HONG YU, MS,1 NAZEM ATASSI, MD, MMSc,1 MERIT CUDKOWICZ, MD, MSc,1 and TIMOTHY M. MILLER, MD, PhD4

1Neurological Clinical Research Institute, Harvard Medical School, Massachusetts General Hospital, Boston, Massachusetts, USA
2Department of Physical Medicine and Rehabilitation, Harvard Medical School, Spaulding Rehabilitation Hospital, Boston, Massachusetts, USA
3VA Healthcare System, Boston, Massachusetts, USA
4Department of Neurology, Washington University School of Medicine, 115 Biotech Building, Box 8111, 660 South Euclid, Street, St. Louis, Missouri 63110, USA
5Massachusetts General Hospital Biostatistics Center, Boston, Massachusetts, USA
6Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

ABSTRACT: Introduction: The aim of this study was to determine whether a history of pre-morbid type 2 diabetes mellitus (DM2) is a prognostic factor in amyotrophic lateral sclerosis (ALS). Methods: The relationship between DM2 and survival was analyzed in a study population consisting of 1,322 participants from 6 clinical trials. Results: Survival did not differ by diabetes status (log-rank test, \( P = 0.98 \)), but did differ by body mass index (BMI) (log-rank test, \( P = 0.008 \)). In multivariate analysis, there was no significant association between diabetes and survival (\( P = 0.18 \)), but the risk of reaching a survival endpoint decreased by 4% for each unit increase in baseline BMI (HR 0.96, 95% CI 0.94–0.99, \( P = 0.001 \)). DM2 was less prevalent among ALS clinical trial participants than predicted. Conclusions: A history of pre-morbid DM2 is not an independent prognostic factor in ALS clinical trial databases. The low DM2 prevalence rate should be examined in a large, prospective study to determine whether DM2 affects ALS risk.


Understanding the risk and prognostic factors for amyotrophic lateral sclerosis (ALS) may unveil novel pathogenic pathways and guide development of effective treatments. Emerging evidence suggests that features of the “metabolic syndrome,” such as pre-morbid obesity and dyslipidemia, are associated with either a reduced risk of developing ALS or more favorable outcomes after diagnosis. These findings are consistent with the general perception that ALS patients may be pre-morbidly “fitter” than the general population, with a higher prevalence among athletes and people with a beneficial vascular risk profile. The hypothesis that metabolic perturbations may contribute to either the onset or the progression of ALS is strengthened by preclinical data suggesting that ALS animal models have abnormal energy metabolism and that their survival can be modulated by dietary changes. Although multiple recent epidemiologic studies have established that factors associated with type 2 diabetes mellitus (DM2) correlate with lower incidence and/or slower progression of ALS, it is not clear that DM2 is an independent prognostic factor. In this study, we examined the prevalence of diabetes in ALS clinical trial participants and its influence on the disease progression and survival.

METHODS

Clinical Trial Database. The relationship between DM2 and ALS progression and survival was analyzed in a clinical trial study population of 1,322 participants in 6 clinical trials. Trial participants were followed in North America at multiple Northeast ALS Consortium (NEALS) and Canadian ALS Consortium (CALS) sites between 1999 and 2012. Subjects could only participate in 1 trial at a time, but they may have participated in more than 1 trial at different time-points. Four type 1 diabetic participants were excluded from the original sample of 1,326. All participants met El Escorial World Federation of Neurology criteria...
Diabetes and ALS Progression. Baseline clinical and demographic data of the clinical trial study population are summarized in Table 1. The overall prevalence of pre-morbid DM2 at baseline was 5.4%. There was a significant association between history of pre-morbid DM2 and BMI at baseline ($P<0.0001$). BMI at baseline was higher in those with a history of pre-morbid DM2 (mean 30.4) than in those without (mean 27.1) ($P<0.001$).

Disease progression did not differ by diabetes status either in unadjusted analysis [diff = 0.168, 95% CL (confidence limits) −0.010 to 0.348, $P=0.07$] or after controlling for gender, age, site of onset, riluzole use, baseline VC, baseline total ALSFRS score; time from symptom onset to screening; diagnostic delay (defined as time between symptom onset and diagnosis); and history of cardiovascular disease. History of cardiovascular disease was self-reported by study subjects. BMI was calculated as: weight (kg) / height (m)$^2$. BMI was treated as a continuous variable in all analyses.

BMI was also analyzed after stratification according to World Health Organization (WHO) criteria in analyses of survival: underweight (<18.5); normal weight 18.5–24.99; overweight 25–29.99; and obese $\geq$30.

Descriptive statistics and tabulations of baseline clinical and demographic patient characteristics were run overall and by study. The association between body mass index (BMI) at baseline and history of DM2 was tested using chi-square and $t$-tests. Disease progression was measured by analyzing the change in ALSFRS-R score; time from symptom onset to screening; diagnostic delay (defined as time between symptom onset and diagnosis); and history of cardiovascular disease. History of cardiovascular disease was self-reported by study subjects. BMI was calculated as: weight (kg) / height (m)$^2$. BMI was treated as a continuous variable in all analyses.

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In this study we found that DM2 is not an independent prognostic factor for ALS. The prevalence of DM2, however, was lower than expected in both clinical trial and clinic-based ALS cohorts. This study has several limitations. The influence of diabetes on ALS progression and survival was analyzed by combining the data sets from 6 clinical trials. Because ALS is a rare disease, clinical trials have typically been relatively small, thus requiring aggregation of studies to gain sufficient power to investigate prognostic factors. By pooling multiple clinical trial data sets, we were able to evaluate the influence of DM2 on ALS outcomes. The prevalence of DM2 in the participants in the ALS clinical trials was lower than expected. This may have been due to the tendency to recruit “healthier” subjects in the controlled clinical trials. 26 Most trials excluded subjects with clinically significant laboratory abnormalities, such as elevated creatinine that may be present in some diabetics, and also excluded subjects with unstable medical conditions. Trial exclusion criteria may therefore have resulted in selection bias and underrepresentation of diabetics in our study population. In addition, differences in ascertainment methods between the study population and the reference population may have affected our results. Trial participants were defined as diabetic based on self-report when asked about past medical history at trial entry, and it is possible that DM2 may have been underreported. The U.S. Centers for Disease Control data used to calculate expected DM2 prevalence are based on the National Health Interview Survey (NHIS), a survey that provides information on the health of the U.S. population, including information on the prevalence of diabetes. The NHIS is also based on self-report. However, differences in how medical history was queried may have affected trial databases is that diabetic subjects may have been under-enrolled in the trials, although DM2 itself was not an exclusion criterion. Alternatively, a history of DM2 may not have been captured accurately in the databases. To determine the prevalence of DM2 in a non-clinical trial-based ALS cohort, we calculated the prevalence of diabetes in 2 independent ALS clinic-based populations (from Massachusetts General Hospital and Johns Hopkins University; refer to Methods in Supplementary Material, available online). The prevalence of DM2 in these clinic-based cohorts was significantly lower than expected (Massachusetts General Hospital ALS Clinic: observed prevalence 7.8% vs. expected prevalence 12.9%; Johns Hopkins University ALS Clinic: observed prevalence 6.9% vs. expected prevalence 12.8%).

**DISCUSSION**

- **Prevalence of DM2 in ALS.** The observed prevalence of DM2 in the 6 clinical trial databases was 5.4%. The expected prevalence of DM2 in this cohort was calculated by using the prevalence of DM2 by gender and age in the American population, according to the U.S. Centers for Diseases Control (http://www.cdc.gov/diabetes/statistics/pb/national/fig2004.htm; accessed April 24, 2014). The expected prevalence of DM2 in this cohort was 11.3%. One potential explanation for the observed low prevalence of DM2 in the clinical
the responses of trial participants and survey respon-
sers, respectively. The expected prevalence of DM2 in 2 independent ALS clinic–based cohorts was also lower than expected. These clinic-based cohorts are located in tertiary academic centers, and they may also fail to reflect the true prevalence of DM2 in the general ALS population. Alternatively, ALS patients who have a history of DM2 may actually have a worse disease course and therefore be unable to participate in clinical trials or travel to ALS clinics. Further studies are needed to determine the prevalence of DM2 at the population level to conclude whether DM2 is a modifier of ALS risk. Of note, a recent population-based case–control study from Sweden suggested that pre-morbid diabetes is associated inversely with ALS risk, which is in line with our findings.27

The complex interplay between the molecular pathways of energy production, substrate utilization, glucose/lipid metabolism, and ALS pathophysiology are only beginning to be investigated. There is preclinical evidence to suggest that some of the mutated proteins that have been associated with ALS, superoxide dismutase 1 (SOD1) and transactive-response DNA-binding protein-43 (TDP-43), may have a physiological role in glucose and lipid metabolism. SOD1 mutant mice exhibit lower body mass and reduced fat reserves before development of motor symptoms.15 TDP-43 conditional knockout mice showed weight loss, fat depletion, and rapid death.28 Conversely, overexpression of TDP-43 in transgenic mice results in increased fat deposition and adipocyte hypertrophy.15 Interestingly, the weight loss and fat depletion detected in both TDP-43 knockouts and SOD1 mutant mice appeared to be secondary to increased lipolysis and fat oxidation, suggesting altered substrate utilization15,16,19 and mitochondrial dysfunction.17 Further, high-throughput transcriptome analysis identified Tbc1d1, a key regulator of glucose translocation in skeletal muscle, as a key downstream target of TDP-43,28 and TDP-43 overexpression in skeletal muscle resulted in impaired glucose uptake.15 Interestingly, a hypercaloric diet resulted in increased body weight and survival in the SOD1 mutant mouse model of ALS.19 More recently, SOD1 mutant mice that were placed in a leptin-deficient background were shown to have increased body weight and fat mass as well as improved survival.29 These results suggest that interventions aimed at altering whole-body energy metabolism may be beneficial in motor neuron disease. The relevance of these preclinical findings to human disease is unclear. Our study confirmed BMI as a prognostic factor in ALS with a dose-dependent reduction in risk of reaching a survival endpoint for each unit increase in BMI. Specifi-
cally, obesity was associated with longer survival, confirming observations that were previously made by us and others on the prognostic value of BMI in ALS.3,6,7 One possible explanation for these findings is that BMI is simply a marker of disease severity. However, in our cohort, BMI was an independent prognostic factor, even after adjusting for measures of disease severity. Nevertheless, it is unknown whether a hypercaloric diet is beneficial for people with ALS. A recently completed phase 2 randomized trial of high-calorie diet showed that hypercaloric nutrition is safe and tolerable in those with ALS who receive percutaneous enteral nutri-
tion.30 Future studies of nutritional interventions, possibly at earlier stages of the disease, may help clarify whether a hypercaloric diet is associated with improved outcomes in ALS.

In conclusion, we have demonstrated that DM2 does not affect survival in patients with ALS, but the findings suggest that it is underrepresented among patients with ALS. It will be important to examine further the relationship between ALS and DM2 or other metabolic disorders in future studies, which may provide new insights for disease pathogenesis or guide future therapies.

Statistical analysis was conducted by Amy Shui, MA, and David Schoenfeld, PhD, Massachusetts General Hospital Biostatistics Center, Harvard Medical School, Boston, Massachusetts.

REFERENCES