Published in final edited form as:

Muscle Nerve. 2015 September ; 52(3): 339–343. doi:10.1002/mus.24688.

Pre-morbid Type 2 Diabetes Mellitus is not a prognostic factor in ALS

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Abstract

Objective—To determine whether history of pre-morbid type 2 diabetes mellitus (DM2) is a prognostic factor in amyotrophic lateral sclerosis (ALS).

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Disclosures:

Theodore Hyman reports no disclosures.

Amy Shui reports no disclosures.

Margaret Allred reports no disclosures.

Jingxia Liu reports no disclosures.

David Schoenfeld reports no disclosures.

Hong Yu reports no disclosures.

Merit Cudkowicz has provided consulting for Neuraltus Pharmaceuticals, Cytokinetics and Teva.

Methods—The relationship between DM2 and survival was analyzed in a study population consisting of 1,322 participants from six 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—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.

Keywords

survival; prognosis; ALS; diabetes; BMI

Introduction

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^{1, 2} or more favorable outcomes after diagnosis^{3–8}. These findings are consistent with the general perception that ALS patients might be premorbidly “fitter” than the general population, with a higher prevalence among athletes^{9–11} and people with a beneficial vascular risk profile^{12–14}. The hypothesis that metabolic perturbations may contribute to either the onset or the progression of ALS is strengthened by pre-clinical data suggesting that ALS animal models show abnormal energy metabolism^{15–17} and that their survival can be modulated by dietary changes^{18, 19}. While multiple recent epidemiologic studies have established that factors associated with type 2 diabetes mellitus (DM2) correlate with lower incidence^{1, 2, 12–14} and/or slower progression of ALS^{3–7}, whether DM2 is an independent prognostic factor is not clear. In this study, we examined the prevalence of diabetes in ALS clinical trial participants and its influence on ALS disease progression and survival.

Materials and methods

Clinical trial database

The relationship between DM2 and ALS progression and survival was analyzed in a clinical trial study population consisting of 1,322 participants in six clinical trials^{20–25}. Trial participants were followed in North America at multiple Northeast ALS Consortium (NEALS) and Canadian ALS Consortium (CALS) sites^{20–25} between 1999 and 2012. Subjects could only participate in one trial at a time but we cannot exclude that one subject may have participated in more than one trial at different time points. Four type I diabetic participants were excluded from the original sample of 1,326. All participants met El Escorial World Federation of Neurology criteria for the diagnosis of possible, probable lab-supported, probable, or definite ALS at the time of enrollment. Survival times were

calculated as time to death, tracheostomy, or permanent assistive ventilation, with either event considered a survival endpoint (survival times were calculated starting from trial enrollment). Permanent ventilation was defined as invasive or non-invasive ventilation use for more than 22 hours/day for 14 consecutive days. Height, weight, vital capacity (VC) percent of predicted, and total ALS functional rating scale score (ALSFRS-R) were recorded at baseline and at each follow-up visit. VC was measured as FVC (forced vital capacity) in all the trials included in this study with the exception of the lithium trial where VC was measured as SVC (slow vital capacity). This study was conducted under the approval of the Partners Healthcare Institutional Review Board and the Northeast ALS Consortium (NEALS).

Statistical analysis

All analyses were performed using SAS statistical software version 9.3 (SAS Institute Inc., Cary, NC).

Descriptive statistics and tabulations of baseline clinical and demographic patient characteristics were run overall and by study. The association between BMI at baseline and history of type 2 diabetes mellitus was tested using chi-square and t-tests. Disease progression was measured by analyzing the change in ALSFRS-R over time using random slopes models (N=1,029; the topiramate cohort was excluded from this analysis because study participants were assessed using the original version of the ALSFRS). Survival analysis was performed using log-rank tests and Cox proportional hazard regression models (N=926; the topiramate and creatine cohorts were excluded from this analysis because data about tracheostomy and permanent assistive ventilation were not available). The models included the main covariates of interest, BMI at baseline and history of type 2 diabetes mellitus, and adjusted for the following covariates assessed at the time of enrollment: gender, age, site of onset (bulbar vs. spinal), riluzole use, baseline VC, baseline total ALS functional rating scale score, time since 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. Body mass index (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 WHO (World Health Organization) criteria in analyses of survival: underweight <18.5, normal weight: 18.5–24.99, overweight: 25–29.99, obese: ≥30.

Results

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 type 2 diabetes mellitus at baseline was 5.4%. There was a significant association between history of pre-morbid type 2 diabetes mellitus and BMI at baseline ($P<0.0001$). BMI at baseline was higher in those with history of pre-morbid type 2 diabetes mellitus (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] -0.010–0.348, $p=0.07$) or after controlling for gender, age, site of onset, riluzole use, baseline VC, baseline ALSFRS-R, time since symptom onset to screening, diagnostic delay and history of cardiovascular disease (diff=0.116, 95% CL -0.053–0.286, $p=0.18$). When history of pre-morbid type 2 diabetes mellitus and baseline BMI were analyzed jointly in an adjusted model, disease progression did not differ by diabetes status (diff=0.157, 95% CL -0.018–0.332, $p=0.08$) but did differ by baseline BMI (diff=0.009, 95% CL -0.001–0.016, $p=0.02$).

Diabetes and ALS survival

Survival did not differ by diabetes status (Log-Rank Test, $p=0.98$) (Figure 1), but did differ by baseline BMI (Log-Rank Test, $p=0.008$).

In multivariate analysis, there was no significant association between type 2 diabetes mellitus and survival ($p=0.18$), but there was a dose-dependent association between survival and baseline BMI: 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, $p=0.001$). When diabetes and BMI were analyzed jointly in the adjusted model, survival was not significantly associated with diabetes status ($p=0.34$) but was associated with baseline BMI (treated as a continuous variable, $p=0.003$). Survival was also associated with BMI when BMI was stratified by WHO criteria. Compared to people who had normal BMI, the obese group was at 38% less risk of reaching a survival endpoint (HR 0.62, 95% CI 0.46–0.84, $p=0.001$).

Prevalence of DM2 in ALS

The observed prevalence of DM in the six clinical trial databases was 5.4%. The expected prevalence of diabetes in this cohort was calculated by using the prevalence of diabetes by gender and age in the American population published by the Center for Disease Control (<http://www.cdc.gov/diabetes/statistics/prev/national/fig2004.htm>; accessed on 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 trial databases is that diabetic subjects may have been under enrolled in the trials, although DM2 itself was not a criterion of exclusion. Alternatively, history of DM2 may have not been captured accurately in the databases. In order to determine the prevalence of DM2 in a non-clinical trial based ALS cohort, we calculated the prevalence of diabetes in two independent ALS clinic-based populations (from Massachusetts General Hospital and Johns Hopkins University) (Supplementary Methods). The prevalence of diabetes 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

In this study we found that type 2 diabetes mellitus (DM2) is not an independent prognostic factor for ALS. Prevalence of DM2, however, was lower than expected in both clinical trial and clinic-based ALS cohorts. Our study has several limitations. The influence of diabetes

on ALS progression and survival was analyzed by combining the datasets from six previous 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 datasets, we were able to evaluate the influence of DM2 on ALS outcomes. The prevalence of type 2 diabetes mellitus in the participants in the ALS clinical trials was lower than expected. This may be due to the tendency to recruit “healthier” subjects in controlled clinical trials²⁶. 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 under-reported. The CDC 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 United States population, including information on the prevalence of disease. The NHIS is also based on self-report. However, differences in how medical history was queried may have affected the responses of trial participants and survey responders, respectively. The expected prevalence of DM2 in two independent ALS clinic-based cohorts was also lower than expected. These clinic-based cohorts are located in tertiary academic centers and they too may 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 determine whether DM2 is a modifier of ALS risk. Of note, a recent population-based case-control study from Sweden suggests that pre-morbid diabetes is inversely associated with ALS risk, in line with our findings²⁷.

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 pre-clinical evidence to suggest that some of the mutated proteins that have been associated with ALS, SOD1 and TDP-43, may have a physiologic role in glucose and lipid metabolism. SOD1 mutant mice exhibit lower body mass and reduced fat reserves prior to development of motor symptoms¹⁹. TDP-43 conditional knockout mice show weight loss, fat depletion, and rapid death²⁸. Conversely, over-expression of TDP-43 in transgenic mice results in increased fat deposition and adipocyte hypertrophy¹⁵. 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 utilization^{15, 16, 19} and mitochondrial dysfunction¹⁷ in these mice. Further, high-throughput transcriptome analysis identified Tbc1d1, a key regulator of glucose translocation in skeletal muscle, as a key downstream target of TDP-43²⁸ and TDP-43 overexpression in skeletal muscle resulted in impaired glucose uptake¹⁵. Interestingly, a hypercaloric diet resulted in increased body weight and survival in the SOD1 mutant mouse model of ALS¹⁹. 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 survival²⁹. These results suggest that interventions aimed at altering whole-body energy metabolism may be beneficial in motor neuron disease. The relevance of these pre-clinical 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. Specifically, in our study, 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 of 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, whether a hypercaloric diet is beneficial for people with ALS is unknown. A recently completed phase 2 randomized trial of high-calorie diet showed that hypercaloric nutrition is safe and tolerable in people with ALS receiving percutaneous enteral nutrition³⁰. 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, our study demonstrates that DM2 does not affect survival in patients with ALS, but suggests that DM2 is underrepresented among patients with ALS. It will be important to further examine 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Study funding: Salary support to TMM, R01NS078398, U01NS084970; salary support for statistical analysis U01NS049640

Sabrina Paganoni is funded by an NIH Career Development Award (2K12HD001097-16).

Matthew Harms is funded by NIH, Biogen Idec.

Nicholas Maragakis is funded by NIH, Department of Defense ALSRP, ALS Association, and has provided consulting for Cytokinetics and Shire.

Nazem Atassi is funded by NIH (1K23NS083715) and received fellowship grants from the American Academy of Neurology (AAN), Muscular Dystrophy Association (MDA), and the Anne B. Young, M.D., Ph.D., Fellowship in Therapeutic Development (a joint MGH/Biogen Idec. Training Program that Dr. Atassi completed in September 2014). He has research grants from the Harvard NeuroDiscovery Center and ALS Therapy Alliance (ATA), and provides consulting for Biogen Idec.

Timothy Miller is funded by NIH/NINDS, NIH/NIA, ALS Association, Muscular Dystrophy Association, Tau Consortium, Packard Center for ALS Research, Target ALS, University of Missouri SCIRP, Isis Pharmaceuticals, Biogen Idec.

Abbreviations

ALS	Amyotrophic Lateral Sclerosis
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ALSFRS-R	ALS functional rating scale score
BMI	Body Mass Index
CALS	Canadian ALS Consortium
CI	Confidence Interval
CL	Confidence Limits
DM2	type 2 Diabetes Mellitus
FVC	Forced Vital Capacity
HR	Hazard Ratio
N	Number
NEALS	Northeast ALS Consortium
NHIS	National Health Interview Survey
SD	Standard Deviation
SOD1	Superoxide Dismutase 1
TDP-43	TAR DNA-binding protein 43
WHO	World Health Organization

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Figure 1. Survival by diabetes status

Survival did not differ by diabetes status in ALS clinical trial databases (N=926; Log-Rank Test, $p=0.98$).

Table 1

Baseline clinical and demographic characteristics of the clinical trial study population

	Topiramate Study	Creatine Study	Celecoxib Study	Co-Q10 Study	Lithium Study	Ceftriaxone Study	Overall
Baseline (N)*	293	103	300	31	84	511	1,322
Median follow-up in days	359	182	372	299	168	531	365
Reached survival endpoint (%)	Unavailable	Unavailable	19.3%	9.7%	6.0%	57.1%	38.7%
Male (%)	64.5%	61.2%	64.7%	51.6%	64.3%	60.3%	62.3%
Mean Age (SD)	57.8 (12.4)	58.9 (11.5)	54.7 (12.0)	53.7 (10.9)	56.8 (11.2)	55.4 (10.4)	56.1 (11.5)
Bulbar (%)	19.1%	25.2%	17.7%	16.1%	20.2%	21.9%	20.3%
Riluzole use (%)	Unavailable	52.4%	68.3%	71.0%	98.8%	73.4%	71.8%
History of pre-morbid DM (%)	4.4%	6.8%	4.7%	6.5%	4.8%	6.1%	5.4%
Mean baseline BMI (SD)	26.3 (4.7)	32.6 (5.7)	26.8 (4.3)	26.3 (5.0)	26.4 (4.2)	27.3 (5.2)	26.6 (5.1)
Mean baseline VC (SD)	80.6 (20.8)	78.0 (24.9)	84.4 (17.0)	83.3 (15.5)	87.6 (17.9)	85.1 (16.8)	83.1 (18.7)
Mean baseline ALSFRS-R (SD)**	Unavailable	38.4 (5.1)	39.4 (5.1)	41.8 (5.1)	38.0 (5.2)	36.7 (5.8)	39.0 (5.7)

N= number of subjects. SD=standard deviation. Bulbar= bulbar onset ALS. DM= type 2 diabetes mellitus. BMI= body mass index. VC= vital capacity (percent of predicted). ALSFRS-R= ALS functional rating scale revised [mean baseline total ALSFRS-R total score shown here].

* Four subjects with type I diabetes were excluded from the sample (two from the Ceftriaxone study, one from the Creatine study, and one from the Topiramate study).

** Subjects in the Topiramate study were assessed using the ALSFRS. The ceftriaxone cohort was followed significantly longer than the other studies; therefore a higher percentage of study participants reached a survival endpoint.