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Urate Levels Predict Survival in ALS: Analysis of the Expanded PRO-ACT Database

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Abstract

Introduction—Urate has been identified as a predictor of ALS survival in some, but not all studies. Here we leverage the recent expansion of the PRO-ACT database to study the association between urate levels and ALS survival.

Methods—Pooled data of 1,736 ALS participants from the PRO-ACT database were analyzed. Cox proportional hazards regression models were used to evaluate associations between urate levels at trial entry and survival.

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Drs. Paganoni and Atassi had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Individual authors' contributions:
Sabrina Paganoni: study concept/design; analysis/interpretation of data; drafting/revising the manuscript.
Katharine Nicholson: study concept/design; analysis/interpretation of data; drafting/revising the manuscript.
James Chan: analysis/interpretation of data; drafting/revising the manuscript.
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Nazem Atassi: study concept/design; analysis/interpretation of data; drafting/revising the manuscript.

Disclosure of Interests:
James Chan reports no conflicts of interest.
Amy Shui reports no conflicts of interest.
David Schoenfeld reports no conflicts of interest.

Results—After adjustment for potential confounders (i.e., creatinine and body mass index), there was an 11% reduction in risk of reaching a survival endpoint during the study with each 1 mg/dl increase in uric acid levels (adjusted HR: 0.89, 95% CI 0.82–0.97, $p < 0.01$).

Discussion—Our pooled analysis provides further support to urate as a prognostic factor for survival in ALS and confirms the utility of the PRO-ACT database as a powerful resource for ALS epidemiological research.

Keywords

Uric acid; survival; PRO-ACT; predictor; prognostic factor; outcomes

Introduction

The pathogenesis of amyotrophic lateral sclerosis (ALS) is not well understood and remains a challenge to ALS therapy development. Proposed mechanisms of disease in ALS include motor neuron degeneration and astrocyte dysfunction secondary to damage from oxidative stress, as supported by both autopsy and laboratory studies[1]. A number of potential antioxidant therapies were tested in ALS clinical trials (e.g. acetylcysteine[2], selegiline[3], vitamin E[4], and coenzyme Q10[5]), but no clinically meaningful benefit was seen. More recently, urate has been proposed as an endogenous antioxidant[6, 7] and neuroprotectant[8–13].

Urate is present intracellularly and in bodily fluids as the anionic form of uric acid (2,6,8-trioxy-purine)[14]. The concentration of urate in the blood is dependent on dietary intake (e.g. purines), urate biosynthesis (i.e. oxidation via the enzyme xanthine oxidoreductase), and urate excretion[14]. In rodents, urate is converted to allantoin by urate oxidase (*Uox*). However, during primate evolution multiple independent mutations in the *Uox* gene arose, leading to the absence of functional urate oxidase. Thus, urate is the main end product of human purine metabolism and circulates in blood at high concentrations near the limits of its solubility (accounting for our susceptibility to gout) [14]. The physiologic range of urate levels in blood is 3.6–8.5 mg/dL, with typically higher levels in men than women[14]. Peripherally-generated urate may not readily cross the blood-brain barrier (BBB), as suggested by the 10-fold gradient from the blood to cerebrospinal fluid (CSF), with CSF concentrations ranging from 0.3–0.5 mg/dL[15]. It has been speculated that mutations in the *Uox* gene during evolution, with resulting higher urate blood and CNS levels, conferred a selective advantage to primates related to urate's antioxidant properties central to cancer and aging[8, 14].

If urate were protective against neurodegeneration, one might expect high urate levels to correlate with either disease risk and/or prognosis in several neurodegenerative diseases. While genetically-determined hypouricemia is not associated with neurologic disease[16–20], urate levels were found to be lower in people with ALS than healthy controls and disease mimics[21, 22], while higher urate levels were found to be associated with lower risk of developing Parkinson's disease (PD)[23–25] and Alzheimer's disease[26]. Further, urate levels correlated with prognosis in PD[27–29] and urate elevation was neuroprotective in pre-clinical models of PD[8, 30]. Based on these data, clinical trials of urate elevation are being pursued in PD[16] (NCT02642393). Urate levels have been more recently suggested to represent a

prognostic factor for ALS survival[31]. However, previous studies in ALS cohorts ranging in size from 86 to 942 participants have reported conflicting results[32–39].

The recent development of the Pooled Resource Open-Access ALS Clinical Trials (PRO-ACT) database has allowed the analysis of aggregate data from multiple independent ALS clinical trials[40]. Initial analyses suggested that urate, creatinine, and body mass index (BMI) are all strong predictors of ALS prognosis[41]. However, whether these three variables are independent or reflect shared pathophysiologic mechanisms is unclear. Here we leveraged the recent expansion of the PRO-ACT database to further evaluate the association between urate levels, creatinine, BMI and survival in the largest available cohort of ALS trial participants.

Methods

Database

Data used in the preparation of this article were obtained from the Pooled Resource Open-Access ALS Clinical Trials (PRO-ACT) Database. In 2011, Prize4Life, in collaboration with the Northeast ALS Consortium, and with funding from the ALS Therapy Alliance, formed the Pooled Resource Open-Access ALS Clinical Trials (PRO-ACT) Consortium. The data available in the PRO-ACT Database has been volunteered by PRO-ACT Consortium members. The vision of the PRO-ACT project was to accelerate and enhance translational ALS research by designing and building a data set that would contain the merged data from as many completed ALS clinical trials as possible. Datasets from industry and academic clinical trials were collected, de-identified, cleaned, harmonized and organized according to a comprehensive common data structure, and imported according to the mappings. The initial release of PRO-ACT database has been described and included data from 8,635 people with ALS[41]. In December 2015, six trials were added to PRO-ACT and the database now contains data from 10,723 clinical trial participants. The complete PRO-ACT database is publically available online at www.ALSDatabase.org. It contains demographics data (10,723 records), longitudinal information on ALSFRS(-R) (68,041), vital capacity (55,753), vital signs (340,513), safety labs (2,485,021), concomitant medications (112,101) and adverse events (74,691).

Data Analysis

Mean and percentages of baseline characteristics were calculated for the study participants for age, gender, race, disease duration, time from symptom onset to diagnosis (diagnostic delay), site of onset (bulbar vs. limb), vital capacity, ALS Functional Rating Scale- Revised (ALSFRS-R), and riluzole use. Baseline was defined as the time of trial entry.

Survival was calculated as time until death. Cox proportional hazards regression models were used to estimate the adjusted effect of urate levels on survival. The following covariates were considered potential confounders and were included in the models: age, gender, time from symptom onset to diagnosis (diagnostic delay), baseline creatinine, and baseline body mass index (BMI). In order to calculate BMI for all individuals, height was imputed when missing by using the average height for the individual’s gender (N=582). We assessed the

potential difference between imputed BMI and actual BMI in participants with both height and weight available. The mean difference was −0.02 (p=0.66, 95% CI: −0.11, 0.07). Correlations between uric acid, BMI, and creatinine were calculated by Pearson's correlation coefficient.

Effects of uric acid on the change in ALSFRS-R from the study baseline were estimated from a random-slope linear mixed model with a fixed effect for time, uric acid, and time × uric acid and random participant specific intercepts and sloped with unstructured covariance. Sex, diagnosis delay, age, BMI, creatinine and their interaction with time were also entered as fixed effects to control for chance differences. The mean model was unstructured in time, whereas the covariance model assumed participant-specific linear deviations from the means.

Results

Study participants

At the time of this analysis, PRO-ACT included longitudinal data from 10,723 people with ALS from 23 separate clinical trials. Baseline characteristics are provided in Supplementary Table 1. Urate levels were available in some but not all trials included in PRO-ACT. For the present study, we included individuals for whom urate levels and potential confounders of urate levels (age, gender, diagnostic delay, creatinine, and BMI) were available (N=1,736). Clinical and demographic characteristics of study participants are summarized in Table 1. Baseline urate was significantly correlated with BMI (r= 0.30, p<0.001) and creatinine (r= 0.19, p=<0.001).

Survival and functional decline by urate levels

In an adjusted Cox proportional hazards analysis, controlling for potential confounders, there was an 11% reduction in risk of death during the study (HR 0.89, 95% CI [0.82,0.97], p < 0.01) for each unit (mg/dL) increase in baseline urate (N=1,736) (Table 2). An initial Cox model was fit with an interaction between urate level and gender to see if the effect of urate on survival was different based on gender. The gender-urate interaction was removed for the final model when the interaction was found non-significant (p=0.76). Urate levels were not significantly different between individuals on riluzole and participants who were not on riluzole (p=0.24).

Figure 1 shows the predicted survival from the Cox proportional hazards model if all study participants had their urate levels set to 3 or 7mg/dL compared to the baseline survival. The cut-off of 7mg/dL was chosen because the current trials of urate elevation in PD and ALS are aimed at raising urate levels above 7mg/dL (NCT02642393; NCT02288091). The model predicts a 36% decrease in the risk of dying at any time point when urate levels are set to 7 mg/dL compared to when they are set to 3 mg/dL.

A mixed model estimated a −1.5 point change in ALSFRS-R per month in our cohort (N=1,736; 95% CI: −1.8, −1.1; p < 0.001). The estimate for the rate of change in ALSFRS-R scores per month slowed by 0.041 (p=0.028) per unit (mg/dL) increase in baseline urate levels, with higher levels associated with improved outcomes. The same model estimated a

−4.9% (95% CI: −6.1, −3.6; p < 0.001) change in vital capacity (VC) per month in the 1,285 individuals in whom longitudinal VC values were available. The estimate for the rate of change in VC scores per month slowed by 0.12% (p=0.06) per unit (mg/dL) increase in baseline urate levels.

Discussion

Our pooled analysis provides further support for urate as a predictor of ALS outcomes. Urate has been proposed as a prognostic factor for ALS by some, but not all authors[32–37]. Here we leveraged the expansion of PRO-ACT, the largest aggregation of ALS clinical trials, to examine the relationship between urate levels at study entry, survival, and functional decline. Our results showing a small, but significant association between urate and ALS outcomes are consistent with a growing literature supporting urate as a prognostic and potential neuroprotective agent in neurologic disease[9,11–14,42–45]. Of note, previous epidemiological studies on this topic ranged in size from 86 to 942 participants[32–39] and it is possible that the reported lack of an association between urate and ALS survival in some series may have been due to lack of statistical power. Alternatively, differences in statistical methods and study populations or relatively small effect size may explain these discordant results.

Urate, creatinine, and BMI have all been identified as possible predictors of ALS prognosis[40, 41, 46]. Yet, whether these three variables are independent or reflect shared pathophysiologic mechanisms has been debated. Here we have shown that when controlling for both creatinine and BMI, urate was a significant predictor of ALS survival and functional decline as assessed by the ALSFRS-R. Another topic of debate in the literature is whether urate is a prognostic factor in both men and women, given the gender differences in physiologic urate concentration. In our study, the gender-urate interaction was found to be insignificant.

The PRO-ACT database has several limitations. There may be differences in participants of ALS clinical trials when compared to clinic-based populations (i.e. clinical trials tend to include younger ALS patients with more frequent limb onset and thus better prognosis)[47] leading to selection bias. In addition, not every trial included the same variables thus limiting the number of individuals that could be included in the final analyses.

This study confirms the utility of the PRO-ACT database as a powerful epidemiological tool to analyze biomarkers of prognostic value in ALS[40, 41] given the large amount of data that has been aggregated into a single database. PRO-ACT is a dynamic database; data from more clinical trials are being deposited and will serve to increase statistical power even further. It is expected that ALS researchers will continue to leverage PRO-ACT to further investigate ALS phenotypes and prognostic features when effect sizes are small. These analyses may in turn assist clinical trial design as identification of potential sub-populations of treatment responders upon stratification by biomarker, gene, or phenotype may also be possible.

As with any epidemiologic study, association does not imply causation and the possibility of unknown confounders cannot be excluded. However, the consideration of urate as a prognostic factor in ALS may have therapeutic implications and provides a foundation for relevant future avenues of research. Interestingly, pre-clinical studies of urate level modulation have already been performed in several models of neurodegeneration and supported urate as a neuroprotectant[9,11–14,42–45]. Pre-clinical studies on the role of urate in cellular and animal models of ALS are ongoing. These studies are of great translational potential. Indeed, urate modulation via its precursor inosine is rapidly advancing from the bench to the bedside in PD where a phase 2 clinical trial has demonstrated the safety and tolerability of urate-modulation[15, 48]. Clinical trials of urate elevation in ALS are ongoing (NCT03168711). Results from these studies will clarify whether urate modulation may be a valuable treatment for ALS. Ultimately, work on urate neurobiology may unravel novel therapeutic targets along urate-mediated pathways that may affect oxidative stress and damage and, in turn, ALS disease progression.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ALS	amyotrophic lateral sclerosis
ALSFRS-R	ALS functional rating scale - revised

BBB	blood-brain barrier
BMI	body mass index
CI	Confidence Interval
CNS	Central Nervous System
CSF	cerebrospinal fluid
HR	hazard ratio
PD	Parkinson’s disease
PRO-ACT	Pooled Resource Open-Access ALS Clinical Trials
N	number
SD	standard deviation
VC	vital capacity
Uox	urate oxidase

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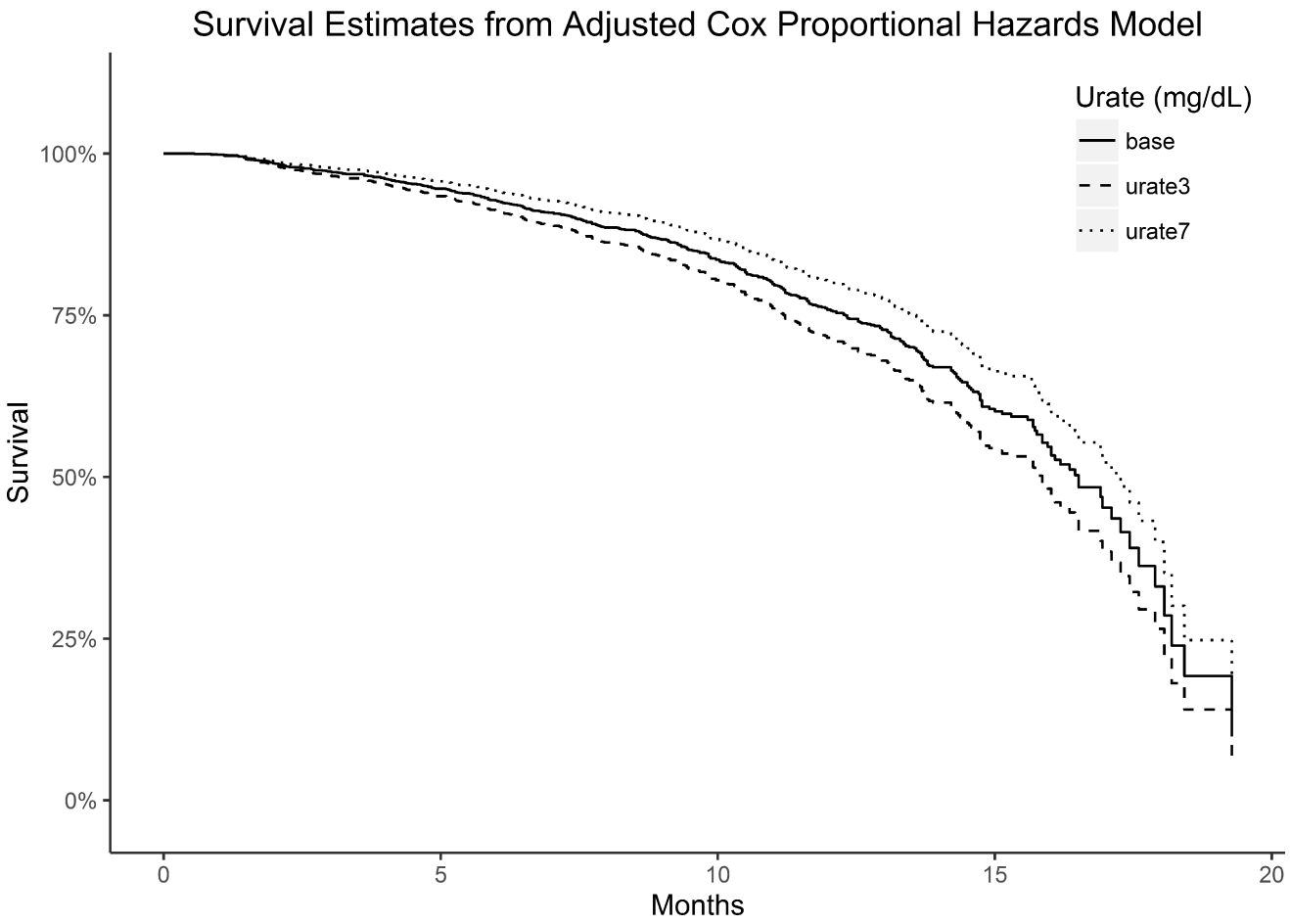

Figure 1. Predicted Survival from Cox Proportional Hazards Model

The predicted survival if all study participants had their urate levels set to 3 mg/dL or 7mg/dL compared to baseline survival (solid line; participants had a mean urate level of 5.0 mg/dL).

Table 1

Characteristics of study participants (N=1,736)

Characteristic	Percent or mean (±SD)
Age	55.0 (±12.1) years
Gender	36.7% Female
Diagnostic delay	10.5 (±8.7) months
BMI	25.3 (±4.5) kg/m^2
Creatinine	0.9 (±0.2) mg/dL
Urate	5.0 (±1.3) mg/dL

BMI: Body Mass Index. N: number. SD: standard deviation.

Table 2

Hazard Ratios from Cox Proportional Hazards Model

	HR	se.HR	p
Uric Acid (mg/dL)	0.89	0.043	0.0098
Gender (Male)	1.017	0.11	0.88
Diagnostic Delay (months)	0.99	0.007	0.042
Age (years)	1.030	0.004	< 0.001
Creatinine (mg/dL)	5.36	0.23	< 0.001
BMI (kg/m^2)	0.91	0.013	< 0.001

BMI: Body Mass Index. HR: hazard ratio.