Published in final edited form as:

Amyotroph Lateral Scler Frontotemporal Degener. 2014 March ; 15(0): 114–118. doi: 10.3109/21678421.2013.837930.

Racial differences in motor neuron disease

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Abstract

Our objective was to compare and contrast clinical features of black and white patients seen in the UAMS ALS/Motor Neuron Disease (MND) clinic from January 2001 to December 2010. Death certificate information was reviewed to determine race of Arkansans who died of ALS/MND between 1999 and 2006. We used a retrospective chart review of patients with ALS/MND seen at least once in our clinic and reviewed state death certificate data. Results showed that from 1999 to 2006, 466 Arkansas deaths were attributed (immediate or contributory) to ALS/MND; 17 (3.6%) were black, four (0.9%) other, and 445 (95.5%) white. During this period, the proportion of black Arkansans was 17%. From 2001 to 2010, we saw 330 patients with ALS/MND: 30 (9.1%) black, six (1.8%) other, 294 (89.1%) white. Average onset age for whites was 58.1 ± 12.4 years, for blacks 52.8 ± 13.0 ($p = 0.038$). Gender, onset site, time from symptom onset to first clinic visit and initial vital capacity were similar between the groups. Initial ALSFRS-R was 37.5 ± 7.2 for whites and 30.8 ± 8.5 ($p = 0.004$) for blacks. A first or second degree relative with ALS/MND was reported by 8.1% of whites and by none of the black patients ($p = 0.15$). Riluzole, PEG and non-invasive ventilation use was similar between the groups. Median tracheostomy-free survival was 36 months for white and 40 months for black patients ($p = 0.475$). In conclusion, although blacks appear relatively spared from ALS/MND, they present at an earlier age and are functionally worse at their first visit. Investigating the genetic make-up of blacks with the disease may help identify genes that modify risk of developing ALS/MND.

Keywords

Epidemiology; race; prognostic

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Declaration of interest: F. Kadlubar is deceased so disclosures are not included for this author. S. Rudnicki has served as a consultant for Knopp Biosciences. The remaining authors have nothing to disclose. The authors alone are responsible for the content and writing of the paper.

Introduction

Recent epidemiological studies of amyotrophic lateral sclerosis (ALS) have focused on identification of genetic and environmental risk factors for development of the disease across different ethnic populations. A better understanding of the heterogeneity in disease susceptibility may potentially allow us to better identify prognostic predictors as well as investigate new therapeutic interventions. Population based registries in Europe and North America reported similar incidences of the disease, ranging from 1.5 to 2.5 per 100,000 person-years with no relevant changes in the clinical and demographic characteristics of Caucasian populations over time (1-7). Epidemiologic data are scarce for non-Caucasian populations; however, a lower incidence rate is suggested among African, Asian and Hispanic groups (8,9). This has at least in part been attributed to under-ascertainment of the cases due to socioeconomic status of these groups resulting in poor access to health care. The clinical features and survival data of ALS patients with different racial origin have not been well described. Our objective was to compare and contrast the clinical and demographic characteristics of black and white patient groups seen in the University of Arkansas for Medical Sciences (UAMS) ALS/Motor Neuron Disease (MND) clinic. We are the only multidisciplinary ALS clinic in a state of just under 3 million inhabitants; our clinic is located in Little Rock, more or less the geographic center of the state.

Methods

After approval by the UAMS Institutional Review Board, a retrospective chart review of patients with ALS/MND seen at least once in our multi-disciplinary ALS clinic between January 2001 and December 2010 was performed. Patients who were referred to our clinic were examined by a neuromuscular specialist (BG, TAL, SAR) who confirmed the diagnosis based on revised El Escorial criteria; patients were included with the diagnosis of clinically definite, probable, or possible ALS (10). Demographic variables obtained for each patient included age of onset, self-reported race, gender, family history, referral source, time from symptom onset to first clinic visit, site of onset, premorbid body mass index (BMI) and BMI at their first visit. Premorbid BMI was determined by asking the patient what their weight was a year prior to any symptoms of ALS, and calculating the BMI from the height measured at the first visit. The ALS Functional Rating Scale-Revised (ALSFRS-R) was used at the initial and follow-up examinations. Forced vital capacity measurements were performed by an experienced respiratory therapist at each visit. Riluzole use, obtaining a percutaneous endoscopic gastrostomy (PEG), and use of ventilation (non-invasive and invasive) were recorded for patients followed longitudinally in whom they were suggested, based upon current guidelines for ALS management (11). Survival times from symptom onset were determined until December 2010 or death.

Continuous variables were described with means and standard deviations (SD), while categorical variables were summarized using counts. Univariate comparisons of the demographic and clinical variables were made with Student's two-sample *t*-tests and Fisher's exact test. Survival curves were estimated by the Kaplan-Meier method (see Figure 1), and the survival distributions of groups were compared using log-rank tests. Multivariate analyses of the risk for death were performed using Cox proportional hazards models that

included gender, age of onset and onset site as independent variables. Statistical analyses were performed with the SAS/STAT software package (SAS Institute Inc, NC, USA).

In addition, we also reviewed state death certificate data to determine race of patients in the state whose death certificate recorded the codes corresponding to ALS/MND as either a primary or secondary cause of death from 1999 through 2006. We did not attempt to match patients in our clinic to the death certificate data.

Results

A total of 330 patients with ALS were seen in the UAMS ALS Clinic between January 2001 and December 2010. Of these, 294 (89.1%) were Caucasian (white) and 30 (9.1%) were of African origin (black). Six patients (1.8%) described themselves as belonging to another ethnic group. According to death certificate data obtained for the years 1999 until 2006, 466 deaths were attributed to ALS/MND in Arkansas. Among these, 445 (95.5%) were white and 17 (3.6%) were black. Four patients (0.9%) were classified as of other racial origin. Population statistics obtained from the Department of Health and Human Services revealed the percentage of Arkansans who were black ranged from 15.4% to 17% for the period 1999–2010. From 2006 through August 2012, nearly 500,000 patients were seen in all outpatient clinics at our institution; of those, 24% were black and 70% were white.

The comparison of demographic and clinical characteristics of the ALS patients with different racial origin is tabulated in Table I. The average age of onset was 52.8 ± 12.9 years in black patients and was significantly earlier compared to the white patients with an average age of 58.1 ± 12.4 years ($p = 0.02$). There was no statistically significant difference in gender, referral source or time from symptom onset to first clinic visit between the two groups. There was also no statistically significant difference in time to first visit comparing blacks and whites as a function of site of onset, although blacks with bulbar onset had the shortest time to diagnosis for all groups (8.8 ± 3.7 months) and this represented a significantly shorter diagnostic delay compared to blacks with extremity onset (16.5 ± 10.8 months, $p = 0.028$). Site of onset was similar between black and white patients. Although there was not a statistically significant difference in the presence of a positive family history in white compared to black ALS patients, none of our black ALS patients had a positive family history, while 8% of the white ALS patients had a positive family history. Blacks had significantly higher premorbid BMI compared to whites (31.2 ± 6.4 compared to 28.4 ± 5.3 , $p = 0.01$). However, the decrease in premorbid BMI to the value determined at the first clinic visit was significantly greater in blacks than whites (4.26 ± 3.0 vs. 1.79 ± 3.0 , $p = 0.0003$). The ALSFRS-R performed for each patient at their first clinic visit documented a worse score for black patients (30.7 ± 8.7) compared to whites (37.4 ± 7.2 , $p = 0.0002$). Despite the poorer functional status among blacks, initial vital capacity was similar between the two groups.

Treatment modalities were also examined for each patient group and the results are summarized in Table II. The numbers of patients who elected to take riluzole, used non-invasive ventilation, and obtained a PEG were recorded for the two racial groups. These data were reported only for those in whom these treatment modalities were recommended based

upon current guidelines for care of ALS patients and shown as the denominator in the table. The tracheostomy data also include only those patients who reached the endpoint of tracheostomy or death. Statistical analysis did not find a significant difference in the use of these treatments in the patient groups.

Survival times from time of symptom onset for black and white ALS patients found hazard of death for black subjects is approximately 16% less than hazard of death for white subjects; this did not reach statistical significance. Median survival time was 40 months (95% confidence interval 31–118) for black patients and 36 months (95% CI 34–105) for whites ($p = 0.45$). While the Cox proportional hazards model presented in Table III found the effect of race was still not significant after adjusting for age at onset, gender, and site of disease onset, the direction of the race effect did change. After adjustment, hazard of death for black subjects is approximately 9% more than hazard of death for white subjects (n.s.). Age and bulbar onset were significantly associated with the risk of death in these subjects. For each five-year increase in the age of onset, the risk of death increased by approximately 19%. Similarly, the risk of death was approximately 33% higher in subjects with a bulbar site of onset compared to those with extremity onset.

Discussion

We found fewer blacks in our ALS clinic than would be predicted by the racial distribution of our state, with similar findings in a death certificate review from the state of Arkansas. While the possibility has been raised by others that paucity of blacks with ALS could be a referral bias, we think this is unlikely for several reasons. Our institution historically has provided health care to patients of all races; approximately one-quarter of patients who received care in our institution's outpatient clinics was black over the past six years. In addition, black patients did not have a delay in being seen in our clinic compared to whites, and if it was indeed harder for a black patient to access health care in our ALS clinic, one would expect to see this. The percentage of black patients with ALS seen in our clinic was greater than the percentage of black patients who died from ALS statewide, again suggesting our clinic is reasonably accessible to patients independent of race. In the study on the incidence of ALS among those veterans who served during the Gulf War, blacks made up 20.3% of all veterans included in the study, but only 13.1% of those who developed ALS; given the VA system, this difference cannot be ascribed to access to health care (12).

Our study demonstrated a trend toward black patients being younger at symptom onset, having lost more of their premorbid BMI by their first visit, and presenting with a lower ALSFRS-R score compared to white patients with ALS. A recent study from Africa also confirmed that the mean age at onset of ALS is earlier in subjects from African origin compared to Caucasians and Japanese (13), and a recent paper from an ALS clinic in Alabama found blacks to have a younger age of onset than whites (14). It is possible that younger age in black ALS patients is influenced by the fact that a greater percentage of whites living in Arkansas are 35 years of age and older compared to blacks (57.6% compared to 43.2%) and the median age for a black Arkansan is approximately 9–10 years younger than for a white non-Hispanic Arkansan (15). Although we accept that more severely affected patients might be preferentially referred to our center, there is no reason to

think that would only be true for blacks and not also whites. In addition, our clinic is supported by the Muscular Dystrophy Association, so patients without insurance can attend the clinic free of charge.

Despite this young onset ALS trend among black patients, there was no statistically significant difference in overall survival between the ethnic groups. In part this may be related to breathing, since both groups have a similar vital capacity at their first clinic visit. Riluzole use was similar between races. Although there may be a trend towards more use of tracheostomy and potentially less use of a feeding tube in blacks compared to whites, the differences were not statistically significant. Differences between the groups could be driven by personal choice or, alternatively, how the information was presented to patients and families. With such small numbers of black patients, it may require data from a multicenter trial or a national registry to determine if treatment choices differ between patients of different races.

In a Cox proportional hazard model, we demonstrated that older patients and those with bulbar-onset disease have worse survival, which has been found in multiple other studies; however, unlike at least some other studies, we did not find that females had a worse prognosis than males (16,17).

Our study has limitations; even by looking at a 10-year epoch, we identified relatively few blacks with ALS, so numbers available for comparison are fairly small. Larger numbers could potentially resolve modest differences in clinical features or treatment decisions that smaller numbers may have missed. Although there was substantial overlap in the time-frames, we also did not use identical years in our chart review, death certificate data or state population statistics as we were limited by available data. For this reason, we did not carry out statistical analysis comparing percentages of blacks in our ALS clinic to the population at large. We also acknowledge that death certificate data are notoriously inaccurate regarding cause of death.

Why might black patients be less likely to have ALS? Given that none of our black patients had a family history of ALS, the paucity of genes causing ALS in the black population may decrease the absolute numbers of patients who develop the disease. This is supported by a previous report showing decreased frequency of the most common A4V mutation in SOD-linked familial ALS cases in a black population in North America (18). It is also possible that blacks may be more likely to have genes that may in some way be neuroprotective. Parkinson's disease, like ALS a neurodegenerative disease, is also less likely to occur in blacks in the US compared to whites (19,20), although blacks may have a greater risk of Alzheimer's disease compared to similarly aged whites (21).

Conclusion

Our study allowed us to make some observations in characteristics of ALS among black subjects: 1) lower than expected numbers of blacks with ALS in our state; 2) younger age at onset with possibly more aggressive clinical progression compared to whites. How genes or environmental risk factors may play a role in these differences is unknown. Further research

from different regions in United States and African countries including genotyping of blacks with ALS could enable researchers to clarify these points. Better understanding of both risk factors for developing the ALS, as well as possible factors that may help prevent the disease, may ultimately lead to better treatments of a disease that currently remains nearly universally fatal.

Acknowledgements

Research was supported in part by the Kathryn and J. Thomas May ALS Research Fund and by the Translational Research Institute (TRI), through the NIH National Center for Research Resources and National Center for Advancing Translational Sciences. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

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Figure 1.
Kaplan-Meier survival curves for black and white ALS patients from symptom onset.

Table I

Comparison of demographic/clinical characteristics of ALS patients.

Variable	Black (n = 30)	White (n = 294)	p-value
Age of onset (years) ^b	52.8 ± 12.9	58.1 ± 12.4	0.02
Gender			0.57
Male	15 (50%)	163 (55%)	
Female	15 (50%)	131 (45%)	
Family history of ALS in first or second degree relatives ^a	0	24 (8%)	0.14
Referral to ALS Clinic by: ^a			0.36
PCP/Other	9 (30%)	65 (22%)	
Neurologist	21 (70%)	229 (78%)	
Time from symptom to first clinic visit (months) ^b	15.3 ± 10.4	12.9 ± 9.6	0.24
Onset site ^a			0.53
Bulbar	7 (23%)	89 (30%)	
Non-bulbar	23 (77%)	205 (70%)	
Time to diagnosis by site of onset (months)			
Bulbar	8.8 ± 3.7	11.6 ± 9.4	0.763
Non-bulbar	16.5 ± 10.8	13.5 ± 9.7	0.234
Pre-morbid BMI2	31.2 ± 6.4	28.4 ± 5.3	0.01
BMI at first clinic visit ^b	27.0 ± 6.9	26.6 ± 5.2	0.79
Decrease in BMI ^b	4.26 ± 3.0	1.79 ± 3.0	0.0003
ALSFRS-R at first clinic visit ^b	30.7 ± 8.7	37.4 ± 7.2	0.0002
VC at first clinic visit ^b	68.2 ± 29.8	73.0 ± 22.0	0.48

^aFisher's exact test.^bStudent's two-sample *t*-test.

Table II

Comparison of treatment modalities between racial groups.

Variable	Black	White	<i>p</i> -value ^a
Riluzole use ever	13/28 (46%)	148/281 (53%)	0.55
NIV use ^b	20/24 (83%)	192/219 (87%)	0.52
Tracheostomy ^c	3/20 (15%)	10/223 (4%)	0.10
PEG obtained ^b	8/15 (53%)	131/190 (69%)	0.25

NIV: non-invasive ventilation; PEG: percutaneous gastrostomy.

^a Fisher's exact test.^b Includes only those patients in whom NIV/PEG was recommended.^c Includes only those patients who had reached endpoint of tracheostomy or death.

Table III

Cox proportional hazards model.

Variable	Hazard ratio	95% CI	p-value
Black	1.085	0.68–1.73	0.733
Age (5 years)	1.188	1.12–1.25	<0.001
Male	1.244	0.96–1.61	0.100
Bulbar	1.326	1.05–1.83	0.022