Incidence of Amyotrophic Lateral Sclerosis Among American Indians and Alaska Natives

Paul H. Gordon, MD, PhD; Jason M. Mehal, MPH; Robert C. Holman, MS; Lewis P. Rowland, MD; Andrew S. Rowland, PhD; James E. Cheek, MD, MPH

Importance: More thorough evaluation of amyotrophic lateral sclerosis (ALS) and motor neuron disease in unique populations could provide clues to etiologies for these idiopathic conditions, and educational programs for American Indian and Alaska Native (AI/AN) people and health care professionals on reservations could improve awareness, understanding, diagnosis, and treatment. In the ongoing search for susceptibility genes, studying particular racial groups, such as AI/ANs, might facilitate the identification of new mutations.

Objective: To provide better understanding of ALS and secondarily of motor neuron disease among AI/AN people by estimating the incidence and prevalence among AI/ANs served by the Indian Health Service health care system.

Design and Setting: Analysis of electronic records for AI/ANs with ALS and with motor neuron disease separately for the calendar years 2002-2009 using inpatient and outpatient visit data from the Indian Health Service, which provides health care to eligible AI/ANs nationwide.

Participants: Cases were defined by at least 2 inpatient or outpatient visits with the diagnosis.

Main Outcome Measures: Crude and age-adjusted incidence and prevalence rates were calculated.

Results: Seventy-one AI/ANs were diagnosed with ALS, yielding an average annual crude incidence rate of 0.65 cases per 100 000 and an age-adjusted incidence of 0.92. The median age at onset was 56.0 years and was higher among women than men (62.0 vs 55.0 years; P=.06). Age-specific incidence increased to 70 to 74 years. The crude and age-adjusted point prevalence rates were 2.00 and 4.12, respectively. The crude and age-adjusted incidence rates for motor neuron disease were 1.08 and 1.50, respectively. The annual rates were unchanged across the study period.

Conclusions and Relevance: The incidence of ALS among AI/ANs appears to be lower than that reported for white populations, a finding congruent with reports of other minority populations. Community-based studies are important to confirm these findings and to examine reasons for the low rate of ALS among AI/ANs.


Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder of unknown cause that leads to destruction of motor neurons and death in an average of 30 months from onset. Incidence rates range from 1.2 to 4.0 cases per 100 000 in developed countries. Few studies, however, have examined rates in American minority populations and, to our knowledge, no previous study has estimated rates among Native Americans.

American Indians and Alaska Natives (AI/ANs) are among the poorest people in the United States. Health disparities associated with poverty and rural living are major problems among AI/AN communities. Few neurologists serve on reservations, which means that neurological diseases may be underrecognized and undertreated, adversely affecting the health of AI/ANs. Despite ethnic variation in the occurrence of neurodegenerative illnesses, most variants have not been studied comprehensively among AI/AN populations. A better description of neurodegenerative illness among AI/ANs could improve awareness and understanding, as well as the allocation of resources and treatment for those living on reservations.

The goal of this analysis was to provide a better understanding of ALS and secondarily of motor neuron disease (MND) in AI/ANs by estimating the incidence and prevalence among AI/ANs served by the Indian Health Service (IHS) health care system.
METHODS

The IHS, an agency of the US Department of Health and Human Services, provides health care to members of federally recognized tribes throughout the continental United States and Alaska, with most facilities located on rural reservations. Approximately 1.9 million AI/ANs were eligible for IHS and tribal health services in 2009.14

We determined the average annual incidence and point prevalence rates of ALS and MND among AI/ANs receiving IHS/tribal health care for the calendar years 2002-2009. Data for AI/ANs who received care directly from the IHS/tribal health care facilities or who were referred for hospital care services were obtained from the IHS National Patient Information Reporting System. These data include all hospital discharge and outpatient visit records from IHS-operated and tribally operated medical facilities, as well as facilities and providers that contract to provide health care services.13-16 Hospital discharge data for locations in the IHS West region (California, Oregon, Washington, and Idaho) were excluded from the study because there were no IHS-operated or tribally operated hospitals in those states and data on contract health service were incomplete.13,16

The unit of analysis for this study was the patient. Data for records with the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes for ALS or MND (335.20 and 335.2, respectively) listed as one of up to 15 diagnoses for AI/ANs were selected.17 The code for MND included progressive muscular atrophy, progressive bulbar palsy, pseudobulbar palsy, and primary lateral sclerosis in addition to ALS. For ALS and MND incidence estimates, patients were required to have at least 2 ALS- or MND-associated inpatient or outpatient visits during the period 2002-2009 with no such visits during 2001. The ALS and MND point prevalence estimates were calculated as of the midpoint in the study period, December 31, 2005, and included all patients with at least 2 ALS- or MND-associated inpatient or outpatient visits during 2001-2005 who were presumed to be alive on December 31, 2005. A patient was considered alive only if he or she had a visit of any kind in the IHS health care system during 2006-2009. The IHS data sets are not linked to death certificate data. The method used estimates whether a patient was living or dead on the basis of later visits within the IHS health care system. The population used for the denominator on prevalence day was 1.5 million people.

The patient visit records were examined by age group, sex, period, and geographic region. Groups were aged younger than 20, 20 to 49, 50 to 64, and 65 or older. The United States was divided into the following 7 regions: East, Northern Plains East, Northern Plains West, Alaska, Southern Plains, Southwest, and West.18

Incidence and point prevalence rates for both ALS and MND were expressed as the number of cases per 100,000 persons of the corresponding population. For the incidence rate, the population was estimated using the annual IHS user populations, which include all registered AI/ANs who have received IHS-funded health care service at least once during the preceding 3 years.14 The population used for the prevalence rate was estimated by calculating the total number of AI/ANs with an inpatient or outpatient visit record within the IHS/tribal health care system during 2001-2005 who also had at least 1 visit within the IHS/tribal health care system during 2006-2009. Incidence rates and corresponding denominators were also calculated for the periods 2002-2005 and 2006-2009. When examining ALS and MND rates for these periods, a patient meeting the ALS or MND case definition for the study period was included for each period in which he or she had a visit. Poisson regression was used to compare unadjusted rates between groups defined by sex, region, and period.19

Age-adjusted rates were calculated overall and by sex, region, and period using the direct method with the 2000 projected US population as the standard.20,21 Gamma intervals were calculated for comparisons of age-adjusted rates, and those with nonoverlapping intervals were considered statistically different.22,23 P < .05 was considered statistically significant.

This analysis of IHS inpatient and outpatient visit data represents all AI/ANs who received direct or contract health care through the IHS health care system during the study period. The study received institutional review board approval from the IHS, the Centers for Disease Control and Prevention, and the University of New Mexico.

RESULTS

AMYOTROPHIC LATERAL SCLEROSIS

Seventy-one AI/AN patients met the inclusion criteria for ALS; the average annual crude incidence rate was 0.63 cases per 100,000 and increased with age to 70 to 74 years (Table and Figure 1). The median age at first visit was 56.0 years: 62.0 years for women and 55.0 years for men (P = .06). The crude incidence rates did not differ by sex,

| Table. Average Annual Incidence and Point Prevalence Rates by Age Group and Age-Adjusted Incidence and Point Prevalence Rates for ALS and MND Among AI/ANs, 2002-2009, United Statesa |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Age Group, y    | ALS             | MND             | ALS             | MND             |
|                 | Incidence       | Prevalence      | Incidence       | Prevalence      |
|                 | Crude Rateb     | Age-Adjusted    | Crude Rate      | Age-Adjusted    |
|                 | Rate            | Rate            | Rate            | Rate            |
| <20             | 0.38            | 0.98            | 0.15            | 2.35            |
| 20-49           | 2.23            | 8.83            | 3.53            | 16.86           |
| 50-64           | 3.24            | 18.75           | 4.58            | 26.25           |
| >65             | 0.63            | 2.00            | 1.08            | 3.92            |
| All ages        | 0.92            | 4.12            | 1.50            | 7.06            |

Abbreviations: AI/AN, American Indian and Alaska Native; ALS, amyotrophic lateral sclerosis; MND, motor neuron disease.a American Indian and Alaska Native patients using the Indian Health Service direct and contract health service were included according to inpatient and outpatient visit data. Rates are per 100,000 persons of corresponding group. Rates based on fewer than 5 deaths were considered statistically unreliable and were not calculated. For the ALS incidence and prevalence calculations, there were no patients in the case group younger than 20 years.
There was no difference in the age-adjusted rates by sex, and the median age was similar among men and women. The age-adjusted point prevalence was 4.12 cases per 100,000, with no differences by sex or region.

**MOTOR NEURON DISEASE**

The average annual crude and age-adjusted incidence for MND was 1.08 and 1.50 cases per 100,000, respectively (Table). The median age at first visit was 55.5 years overall: 57.0 years for women and 54.0 years for men (P = .01). The corresponding crude and age-adjusted prevalence rates were 3.92 and 7.06 cases per 100,000. The age-specific prevalence increased with age to peak in the oldest age group and was not different by sex or geographic region.

This study, to our knowledge, is the first analysis of ALS among AI/ANs. It is a comprehensive examination of ALS incidence and prevalence in AI/ANs within the IHS/tribal health care system. We used a national clinical database that includes all inpatient and outpatient visits reported within the IHS/tribal health care system in the United States.13,14

The analyses suggest that AI/ANs may have a lower incidence of ALS than whites. Most studies show incidence and mortality rates in white populations from 1.2 to 4.0 cases per 100,000 persons.2-4,24,25 Only a few studies have examined rates of ALS in minority populations. A population-based study in western Washington State yielded age-adjusted rates of 0.74 for African American men and 0.53 for African American women.3 The absolute number of members of minority groups with ALS was small, but the rates were comparable with those found for AI/ANs in our study. Similarly, an analysis of ALS mortality data in the United States, which can be used as a surrogate for incidence of ALS,23,26 yielded a relative risk (95% CI) of 0.62 (0.60-0.64) for African Americans and 0.42 (0.40-0.46) for races listed as “other” compared with white Americans.27 Analysis of the rates in MND, a broader ICD-9 category, was done for comparison purposes. Incidence rates for MND in this study paralleled those for ALS and were lower than reports of MND incidence in other populations.8 Taken together, these data suggest that the incidence of ALS may be lower in some non-white groups than in whites.

It is not known why the incidence and prevalence rates of AI/ANs appear lower than those for people of white race. Different populations may have different genetic or environmental risks for ALS or, owing to lack of specialty care, may be more likely to receive the diagnosis of competing diseases, particularly in the frail elderly in whom the diagnosis of ALS can be difficult.28 Underdiagnosis or misdiagnosis may partially explain the apparently lower rates for AI/ANs living on reservations.
Competing causes of death, particularly in young people, in combination with younger expected age of death could reduce the pool of people at risk for ALS.\(^{29}\) The life expectancy for AI/ANs is currently estimated to be approximately 5.2 years less than that for the general US population (72.6 years vs 77.8 years).\(^{30}\) The risk of dying is higher among AI/ANs for alcohol-related diseases (ratio of mortality rates = 6.1), tuberculosis (6.0), diabetes mellitus (2.8), trauma (2.4), homicide (1.9), and suicide (1.8).\(^ {30}\) The contrasting life expectancy results in substantive age-related differences between the 2 populations.\(^ {31}\) Whereas 73.7% of the US general population die after age 65, only 26.3% of the AI/AN population die after that age, reducing the population of AI/ANs at risk for ALS, a disease that occurs with advancing age. There are also differences in age-related mortality patterns within the AI/AN population; 60.3% of AI/AN men die before age 65 compared with 47.4% of AI/AN women, possibly creating differential risks on the basis of sex.

Varying incidence according to race could also support the possibility of genetic influences in the pathogenesis of the disease. The incidence of ALS is generally considered to be uniform across white populations in the United States and Europe,\(^ {31}\) although only limited research has been done on socioeconomic or other risk factors that might expose differences. Rates of ALS may be lower in black African, Asian, and Hispanic populations.\(^ {27,31,32}\) Africans have greater variability in expression of some genes than their European descendants, which is one possible explanation for the higher risk of ALS among whites in North America and Europe than among African Americans. Asians, the presumed ancestors of today's AI/ANs, also have greater variability in the expression of some genes and appear to have a lower incidence of ALS than whites.\(^ {32,33}\) In the ongoing search for susceptibility genes, studying particular racial groups, such as AI/ANs, might facilitate the identification of new mutations.\(^ {31}\)

Underascertainment and health disparities could also contribute to the lower rates detected in this study.\(^ {34}\) The geographical area of all reservations is approximately 55.7 million acres (225 410 km\(^2\)), representing 2.3% of the area of the United States. There were 836 physicians serving the eligible population in 2010. The physician to patient ratio is approximately one-sixth of the US national average (0.44 physicians/1000 population compared with 2.42 physicians/1000 population).\(^ {35,36}\) The number of neurologists is unknown but is a small subset of the overall number of physicians.

Women were older than men at the time of first visit during the study period and, in contrast to other reports,\(^ {2,25,26}\) the rates were similar in men and women, which could also be owing to unique risk factors, uniquely susceptible populations, or ascertainment bias by sex or systematic late diagnosis in women. The age-adjusted rates did not differ by period or geographic region, possibly because of truly stable rates across time and area or because there were not enough patients identified to detect differences.

Our study has important limitations. Miscoding or inaccurate hospital diagnoses may have occurred and may have varied by region. Rates based on health data may underestimate the frequency of ALS and MND; cases that would be captured in door-to-door surveys may be missed.\(^ {34}\) Community interviews were not possible in this study, so we were not able to determine the extent to which late diagnosis or underdiagnosis in women contributed to the findings. Patients within the IHS health care system may also receive care outside the system, which would result in underascertainment of cases. In addition, Native Americans who live on or near reservations might not use the IHS system. In 2009, approximately 1.5 million AI/ANs had used the IHS system in the previous 3 years, whereas an estimated 1.9 million people lived on or near a reservation.\(^ {37}\) Various population estimates for AI/ANs exist, including the census population, the estimated number of all self-reported AI/ANs residing in the United States; the IHS service population, the estimated number of AI/ANs who live on or near a reservation based on census data; and the IHS user population, the number of AI/ANs who have used the IHS system in the previous 3 years.\(^ {14,37,38}\) We did not use the census population as our denominator because approximately 43% of AI/ANs are integrated throughout the United States and do not reside in geographic locations where the IHS has responsibilities.\(^ {31}\) However, the age and sex distribution of the user population that we studied closely approximates that obtained by census estimates of the entire AI/AN population (eFigure). We did not use the service population as the denominator because the estimate is extrapolated from the number of AI/ANs possibly in a county with a reservation and is not a true ascertainment of the number of AI/ANs in the catchment area.\(^ {30}\) In addition, the mobility of the population and inaccurate reporting on the census renders estimates of the service population less reliable; the service population is an approximation based on combining census data from different states, whereas the user population is concrete. The user population approximates those Native Americans who actually use the IHS system\(^ {14,37,38}\) and who would be at risk, in this study, for having an ALS-associated visit. Ethics boards restricted our access to identifiable data on individual people, so information on the number of patients with a family history of ALS was unavailable. Finally, we did not have access to death certificates. Therefore, we cannot be certain whether or when a patient died. The method used to determine point prevalence estimated whether a patient was living or dead on the basis of later visits within the IHS health care system.

This study suggests that the incidence of ALS in AI/ANs may be lower than that reported in whites. Future community-based studies are needed to confirm the rates and to determine risk factors for ALS in AI/ANs. More thorough evaluation of ALS and MND in unique populations could provide clues to etiologies for these idiopathic conditions, and educational programs for AI/ANs and health care professionals on reservations could improve awareness, understanding, diagnosis, and treatment.

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Author Affiliations: Indian Health Service, US Department of Health and Human Services, Northern Navajo Medical Center, Shiprock (Dr Gordon), and Public Health Program, Department of Family and Community Medicine, University of New Mexico Health Sciences Center,
Albuquerque (Drs A. S. Rowland and Cheek), New Mexico; Division of High-Consequence Pathogens and Pathology, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia (Messrs Mahal and Holman); and Department of Neurology, Columbia University, New York, New York (Dr L. P. Rowland).

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Correspondence: Paul H. Gordon, MD, PhD, Northern Navajo Medical Center, Medical Staff Office, Hwy 491 N, Shiprock, NM 87420 (paul.gordon@ihs.gov).


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Online-Only Material: The eFigure is available at http://www.jamaneuro.com.

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