

The Epidemiology of Parkinsonism in Alaska Native People

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A thesis

Submitted in partial fulfillment of the

Requirements for the degree of

Master of Public Health

University of Washington

2016

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Program Authorized to Offer Degree:

School of Public Health

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Abstract

The Epidemiology of Parkinsonism in Alaska Native People

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Objective: The purpose of this study was to describe the epidemiology of parkinsonism in Alaska Native people.

Methods: This was a population based, prospective and retrospective, descriptive study of parkinsonism in Alaska Native people. Cases were identified using ICD-9 codes 332.0 and 333.0 within the Alaska Tribal Health System. Records were reviewed and cases of neurodegenerative parkinsonism were included in the study.

Results: Between 1/1/2000 and 12/31/2013 there were 145 cases identified. Mean age of onset was 60.8 ± 13.0 years and 51% were male. Age adjusted prevalence of typical parkinsonism was 238.9 per 100,000 and incidence was 16.2 per 100,000 person years. Prevalence and incidence increased with age through 84 years. Age adjusted prevalence was similar in men than women ($p = 0.12$). There were 129 (89%) typical cases and 16 (11%) atypical cases. A majority of the cohort (63%) lived in rural communities.

Conclusion: This was the first epidemiologic study of parkinsonism in Alaska Native people. The disorder was rare before the age of 50 with a similar occurrence in men and women.

Introduction

The purpose of this study was to describe the epidemiology of parkinsonism in Alaska Native people. Parkinsonism is the second most common neurodegenerative disorder worldwide, only Alzheimer's disease is more common (de Lau & Breteler, 2006). It is a group of progressive neurodegenerative syndromes characterized by tremor, rigidity, bradykinesia (slowness of movement), and postural instability (problems with walking and balance). The parkinsonism syndromes include neurodegenerative Parkinson disease, progressive supranuclear palsy, multiple system atrophy, and corticobasilar degeneration (D. R. Williams & I. Litvan, 2013). Parkinson's disease is the most common form of parkinsonism, with an estimated prevalence between 100 to 200 per 100,000 in people living in the United States over age 50 years (Tanner & Ben-Shlomo, 1999). Prevalence of the other parkinsonism syndromes is less common. Estimates of progressive supranuclear palsy and multiple system atrophy prevalence are each between 4.9 and 3.3 per 100,000, making them 20 times less prevalent than Parkinson's disease (Tanner & Aston, 2000). Population studies indicate that the symptoms of parkinsonism may not always be recognized resulting in an underestimate of the true prevalence of these disorders.

Diagnostic accuracy of the different parkinsonism syndromes is a challenge (Hughes, Ben-Shlomo, Daniel, & Lees, 1992; Tanner & Aston, 2000; D. R. Williams & I. Litvan, 2013). Because there are no tests for parkinsonism, the different syndromes are determined by symptoms, the way they present, response to treatment, and the clinical course of the disease. For example, neurodegenerative Parkinson's disease typically

presents with a resting tremor on one side of the body. When treated with drugs that are precursors for or that act like the neurotransmitter dopamine, symptoms of tremor, rigidity, and bradykinesia improve. This is called a typical parkinsonism disorder. With the other parkinsonism disorders, symptoms either do not respond or respond poorly to dopaminergic therapy. This poor response to dopaminergic therapy, together with other specific symptoms, such as frequent falls, orthostatic hypotension, ideomotor apraxia (loss of the ability to carry out specific motor movements such as pantomiming tool use), make it possible to distinguish the other types of parkinsonism. These disorders are classified as atypical parkinsonism disorders. To make classification more difficult, symptoms may take three years or longer to fully develop, delaying correct categorization. Histopathologic examination of the brain is necessary to make a definite diagnosis of a parkinsonism disorder. Without this confirmation, cases are considered either possible or probable. Unfortunately, most cases do not come to autopsy (Maraganore, Anderson, Bower, McDonnell, & Rocca, 1999). Because the constellation of symptoms may be difficult to categorize, together with a long clinical presentation and infrequent histopathologic confirmation, cases may be misdiagnosed or missed altogether, particularly by clinicians unfamiliar with movement disorders (Hughes et al., 1992; Tanner & Ben-Shlomo, 1999; D. R. Williams & I. Litvan, 2013).

While the distribution and some risk factors are known, the cause is unknown in most cases of parkinsonism and currently there is no cure. For example, parkinsonism is rare before the age of 50 years and incidence increases exponentially with age. The average duration from diagnosis to death ranges from 14 to 24 years in typical parkinsonism and

less than 10 years for the atypical disorders (D. R. Williams & I. Litvan, 2013). We know that parkinsonism is a result of specific damage to the substantia nigra (cells in the midbrain that produce dopamine) as well as other parts of the nervous system. The discovery that 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) induced parkinsonism in several young people in the 1980s led to the idea that an environmental toxicant may cause parkinsonism. An animal model of MPTP induced parkinsonism has been valuable in our understanding the toxic mechanisms underlying neuronal degeneration in the substantia nigra and other areas of the brain that contribute to Parkinson's disease (Langston, 1987; Langston, Ballard, Tetrud, & Irwin, 1983). We know that those who use tobacco, caffeine, anti-inflammatory drugs, or have high uric acid levels in the blood are less likely to develop Parkinson's disease (Tanner, 2010). A diet high in vitamin E, vitamin B6 legumes and nuts may be protective (Tanner, 2010; Tanner & Ben-Shlomo, 1999). Having high cholesterol levels and night shift work have been inversely related with parkinsonism (Tanner, 2010). Pesticide exposure (particularly organochlorines and alkylated phosphates), living in a rural area, history of a head injury, having a relative with Parkinson's disease and consumption of milk may increase risk (Di Monte, 2003; Seidler et al., 1996; Tanner, 2010; Tuchsén & Jensen, 2000). Studies in twins suggest genetics alone plays only a small role in the etiology of Parkinson's disease. Although the causes of parkinsonism appear to be related to the combination of genetic and environmental factors, the precise etiology remains unclear (Calne & Langston, 1983; Tanner, 2003; Tanner et al., 1999; Warner & Schapira, 2003).

Relatively little is known about trends in parkinsonism, particularly in Alaska Native people (Dorsey et al., 2007; Gordon, Mehal, Holman, Rowland, & Cheek, 2012; Langston, 2002). Gordon et. al. reported an age adjusted prevalence of 355.7 per100,000 in American Indian and Alaska Native people, a proportion higher than what is reported here. This was between 2002 and 2009 and the proportion was adjusted to the 2000 U.S. population. Studies of indigenous circumpolar peoples, the Greenland Inuit, suggest that parkinsonism may be common among these groups as well, but the reasons for these potential disparities are unknown (Koldkjaer, Wermuth, & Bjerregaard, 2004; Wermuth, Pakkenberg, & Jeune, 2002). Knowing the incidence of parkinsonism in Alaska Native people would be useful in validating these observations. Understanding trends of parkinsonism in Alaska Native people would also be helpful in allocation of resources and neurologic services to better manage parkinsonism within the Alaska Tribal Health System. By monitoring disease features, comorbid conditions, individual preferences, and the home environment (including both social support and the built environment) management of these disorders can be optimized. For example, early identification and treatment can preserve function and improve quality of life. Optimal management also leads to a better understanding of the disease for patients, caregivers and health professionals. This will become even more important as potential disease-specific treatments become available in the future.

There are many determinants of parkinsonism and these may vary between populations. Determinants can be grouped into environmental, geographic, racial, social and management. This study describes the frequency, distribution and characteristics

associated with parkinsonism in Alaska Native people. on determinants of parkinsonism in Alaska Native people, specifically the amount, gender, age of onset and distribution of the disorder as well as how it is managed in Alaska Native people, figure 1.

Study Goals

This study had three goals. First goal was to estimate the disease frequency of parkinsonism in Alaska Native people. Using data in the Alaska Native Parkinsonism Registry as the numerator and population estimates from the Alaska Department of Labor and Workforce Development for the denominator, age-adjusted incidence and prevalence will be estimated ("Research and Analysis Home Page- Department of Labor and Workforce Development," 2014). Because parkinsonism prevalence has been reported to be high in Greenland Inuit people, another indigenous Arctic people, it may be important to know if prevalence and incidence is high in other Arctic populations.(Wermuth, Pakkenberg, & Jeune, 2004) Knowing how big a problem parkinsonism is would also be helpful in management of the disorder, within the Alaska Tribal Health System.

The second goal was to characterize the variability and subtypes of parkinsonism in Alaska Native people. Even within those with apparent typical Parkinson's disease, there is variability in the primary clinical features (such as age at onset, rate of progression, primary signs, response to therapy) as well as variability in associated problems such as hallucinations, dysautonomia, postural instability, and impact on activities of daily living. Identification of these features aids in treatment and improves outcome. In addition,

characterizing disease features in this population may be useful in understanding determinants, in developing ways to prevent or delay the development of adverse outcomes and to possibly slow the progression of parkinsonism.

The third goal was to assess the influence of individual, geographic and disease severity on the clinical care and management of individuals with parkinsonism. Identifying factors influencing clinical care, such as access to treatment, could result in improved outcome and reduce the human and monetary costs of parkinsonism to individuals, families, and the community health system.

Methods

Study design

This was a population-based, prospective and retrospective, descriptive study of parkinsonism in Alaska Native people living in Alaska.

Protocol approval

Ethical approval for the conduct of this study was obtained from the Alaska Area Institutional Review Board and the Human Subjects Division at the University of Washington. Surveillance of parkinsonism cases was approved by Tribal Boards with jurisdiction over medical records statewide. These include: the Alaska Native Tribal Health Consortium, Arctic Slope Native Association, Bristol Bay Area Health Corporation, Ketchikan Indian Community, Kodiak Area Native Association, Maniilaq Association, Metlakatla Indian Community, Norton Sound Health Corporation,

Southcentral Foundation, Southeast Area Regional Health Corporation, Tanana Chiefs Council and the Yukon Kuskokwim Health Corporation. In order to protect individual identity, the limited data set was reviewed and approved by privacy officers at the Alaska Native Tribal Health Consortium and the Southcentral Foundation.

Case definition

In order to maximize diagnostic specificity and limit diagnostic confusion, parkinsonism was defined as the presence of resting tremor, with asymmetric onset, bradykinesia and rigidity. Only neurodegenerative parkinsonism cases were included, secondary causes of parkinsonism such as drug induced or vascular parkinsonism were excluded. Cases were divided into the following subtypes: neurodegenerative Parkinson's disease, progressive supranuclear palsy, multiple system atrophy and corticobasal degeneration based on presentation and characteristic symptoms. The diagnostic criterion for Parkinson's disease is based on the presence or absence of typical and atypical symptoms, table 1 (Gelb, Oliver, & Gilman, 1999). For progressive supranuclear palsy, multiple system atrophy, and corticobasal degeneration, diagnostic criteria are based on a poor response to dopaminergic therapy, the presence of disorder specific symptoms, and the absence of other causes such as neuroleptic therapy or structural brain lesions table 2 (D. R. Williams & I. Litvan, 2013).

Case ascertainment

Alaska Native or American Indian People living in Alaska who meet diagnostic criteria for neurodegenerative parkinsonism between 1/1/2000 and 12/31/2013 were eligible for

inclusion in this study. According to the United States Office of Management and Budget, An Alaska Native or American Indian is defined as “A person having origins in any of the original peoples of North America, and who maintains cultural identification through tribal affiliations or community recognition..”(“Standards for the Classification of Federal Data on Race and Ethnicity,” 2015) According to the 2010 census, there were 138,312 people who identified themselves as Alaska Native/American Indian, alone or in combination, living in Alaska. This represents 19.5% of the total population of Alaska.(Norris, Vines, & Hoeffel, 2012) There are five major ethnic groups within the Alaska Native population each with its own culture and language. The Yupik people make up 25% of the total Alaska Native population and they are from the West Coast region of the state. The Inupiaq people make up another 24% and are from the North Slope region. The Tlingit/Haida people make up 19% and are from the Southeast region. The Athabascan people make up 16% and they are from the interior part of the state. The Aleut people make up 14% and they are from the Aleutian chain, Alaska Peninsula and Kodiak Island regions. And the Tsimshian people who make up the remaining 2% of the population are from Annett Island in Southeast Alaska.

The population was divided into six regions based on census districts. These regions align fairly well with Alaska Native ethnic distribution and Native Corporations in Alaska.

Population estimates for these regions were taken from the 2010 census.

All members of a federally-recognized tribe have access to the Alaska Tribal Health System, which was the setting for the study. The study sample included individuals with a diagnosis of parkinsonism identified through the Alaska Tribal Health System. This diagnosis may be made by a primary care provider or neurologist anywhere within the

system. However, virtually all Alaska Native people with parkinsonism who seek medical treatment are referred to Alaska Native Medical Center board-certified neurologists, Drs. Brian Trimble and Scot Hines. Treatment occurs either in Anchorage or during periodic visits to the regional hospitals/clinics, and these patients are assigned a diagnosis of parkinsonism in the electronic medical record within the Alaska Tribal Health System. Diagnoses are coded using the *International Classification of Disease 9th edition* (ICD-9) by treating physicians and are entered into the electronic medical record. The investigator reviewed medical records with ICD-9 codes 332.0 and 333.0 and examined most of the individuals with a presumptive diagnosis of parkinsonism and cases with documented, asymmetrical resting tremor, bradikinesia, and rigidity improved with anti-parkinsonism medications were included in the study. While in most cases parkinsonism symptoms and response to treatment were well documented, there were a few cases where inclusion was based only on the presence of cardinal symptoms reduced with anti-parkinsonian medication without an apparent secondary cause (such as being on a medication that causes parkinsonism). Cases of secondary parkinsonism (for example patients on medications that cause parkinsonism) and cases that did not meet clinical criteria for parkinsonism (no mention of parkinsonian symptoms) were excluded. Onset of parkinsonism was determined as the year symptoms were first mentioned in the record. In a few cases the year of onset of symptoms could not be determined. In those cases year of diagnosis minus 2 years (the average time from symptom onset to diagnosis within the system) was used.

Self reported ethnicity was often available in the medical record for most cases. In cases of mixed race, a patient is asked which Alaska Native group they identify with most. In

cases where ethnicity was not specified, Alaska Native was used. Though there are some American Indian people who are beneficiaries of the Alaska Tribal Health System, there were no American Indian cases found. Some Caucasian people with parkinsonism receive care within the Alaska Tribal Health System either because it is the only health system available or because they are commissioned officers in the United States Public Health Service and they were excluded from the study.

Data collection

Cases identified as having neurodegenerative parkinsonism were entered into the Alaska Native Parkinsonism Registry by the principal investigator. This is a secure, web-based registry kept on a server behind the Information Technology firewall at the Alaska Native Medical Center. The Registry contains information on patient demographics, disease characteristics, quality of life measures, medications, and timing of disease onset, diagnosis and duration of disease (see appendix). By having only one person enter data and well-defined criteria for each data element, quality of Registry data was maintained. While every effort was made to identify each Alaska Native person with parkinsonism, a small percentage of cases may be missed. The Alaska Tribal Health System is a pre-paid health system. Unless referred by an Alaska Native Tribal Health System provider, beneficiaries of this system who receive care outside the system must pay for these services or have other health care insurance that covers those services. Nevertheless, health services through the Alaska Tribal Health System are the only health services available in most rural Alaska communities. While some beneficiaries may go outside this system for specialty care they typically receive their

primary care within this system and as a result, parkinsonism would be recorded as a problem in their local medical record. Furthermore, records from outside neurologist are typically available for review in the medical record (through release of information by the patient). As a result, only people receiving all of their health care outside the Tribal Health System would be missed. While there is no way to estimate the number of these cases it is thought to be small. It is also possible for a person early in the course of their disease, when symptoms are mild, not to be recognized or even seek care for parkinsonism and they would be missed. In summary, the methods used probably identified most cases of parkinsonism in the population. Because on average it took two years from the onset of symptoms to being diagnosed, some early cases were probably missed.

Data within the Alaska Native Parkinsonism Registry dataset contains demographic information, age, gender, the presence or absence of the typical and atypical parkinsonism symptoms, severity, year of symptom onset, year of diagnosis, disease progression, functional impairment, medications, response to therapy and medication-related side effects. See the appendix for a complete list of data elements.

Data analysis

All statistical analyses were performed using SPSS (Statistics Package for the Social Sciences) version 19 for Macintosh (IBM Corp., Armonk, NY). A limited data set (data without identifiers such as name or hospital number) was exported from the Alaska Native Parkinsonism Registry and used for this analysis. Data analyses including means, standard error and standard deviations for continuous data, and counts and percentages

for categorical data were used to describe population demographics, region and ethnicity. Regional distribution, table 3, and ethnicity was looked at in order to look at how the disease was distributed within the population. This was done to determine if there are environmental or cultural factors that may influence the occurrence of parkinsonism in the population. Regional distribution was determined using Alaska Native population data for individuals over the age of 35 years from the Alaska Department of Labor ("Research and Analysis Home Page- Department of Labor and Workforce Development," 2014). Mean population estimates for each age strata were determined for Alaska Native men and women for the years 2000 to 2013 and were used for incidence denominators. Ethnic distribution for the population is available starting with the 2010 census as self-reported Alaska Native ethnicity, either alone or in combination with other ethnicities (Norris et al., 2012). In cases where Alaska Native ethnicity was not self-reported, Alaska Native was used. This ethnic distribution was applied to the study population. In order to evaluate regional and ethnic differences, a rate ratio was used to compare observed with expected rates assuming a uniform distribution of regional and ethnic cases. Because no cases with onset under the age of 35 were found, regional population data for Alaska Natives ≥ 35 years in 2010 was from State of Alaska ("Research and Analysis Home Page- Department of Labor and Workforce Development," 2014).

These estimates will be compared to prevalence and incidence rates reported in other population.

$$Regional\ Ratio = \frac{(number\ of\ regional\ cases)/(total\ cases)}{(regional\ population\ \geq\ 35)/(total\ population\ \geq\ 35)}$$

Data for Alaska Native tribal group (Aleut, Athabascan, Inupiaq, Tlingit-Haida, Tsimshian, or Yup'ik), alone or in any combination reported in the 2010 Census (Norris et al., 2012).

$$\text{Ethnic Ratio} = \frac{(\text{number of cases for tribe})/(\text{total cases})}{(\text{total for tribe})/(\text{total Alaska Native})}$$

Age and gender specific prevalence were determined as the number of prevalent cases in July 2013 divided by the estimated Alaska Native population.

$$\text{Prevalence} = \frac{\text{number of cases in July 2013}}{2013 \text{ Alaska Native population} \geq 35 \text{ years}}$$

Age and gender specific incidence rates were determined as number of incident cases between the years 2000 and 2013 divided by the population at risk (The sum of the annual population for each strata divided by 14 to determine the average annual population then multiplied by 14 years of observation) and expressed per 100,000 person-years.

$$\text{Incidence rate} = \frac{\text{number of cases}}{(\text{population at risk}) \times 14 \text{ years of observation}} \times 100,000$$

Mortality rates were determined as the number of deaths between the years 2000 and 2013 divided by the population at risk and expressed per 100,000 person-years.

$$\text{Mortality rate} = \frac{\text{number of deaths}}{(\text{population at risk}) \times 14 \text{ years of observation}} \times 100,000$$

Denominators for prevalence and incident estimates came from the Alaska Department of Labor as recommended by Lisa Bulkow, MS, the biostatistician with the epidemiology department at the Alaska Tribal Health Consortium. ("Research and Analysis Home Page- Department of Labor and Workforce Development," 2014). Prevalence and incidence were age adjusted to the U.S. general population according to the 2010 census (U. S. Census Bureau, 2015).

$$Age\ adjusted\ rate = \sum\ of\ \left[\frac{(number\ of\ cases\ per\ age\ group)}{(population\ per\ age\ group)} \times 100,000 \times \frac{(count\ of\ std\ million\ per\ age\ group)}{(std\ million)} \right]$$

$$Adjusted\ rate = \frac{\sum\ of\ each\ age\ adjusted\ rate}{total\ U.S.\ population} \times 100,000$$

For the purpose of this study, incidence was determined as the year symptoms began. Urban and rural differences in gender, age, disease onset, diagnosis, and quality of life measures were determined. For the purpose of this study, a rural community was considered to have a population less than 30,000 individuals while the rest were considered urban ("Research and Analysis Home Page- Department of Labor and Workforce Development," 2014). Cases were classified as urban or rural based on home of record listed in the medical record at the time data was abstracted. Parkinsonism subtypes were determined based on symptoms and response to medication. Cases were classified as possible or probable typical parkinsonism according to the diagnostic criteria for idiopathic Parkinson's disease listed in table 1. Classification was based on available information at the last abstraction. To determine the potential differences between typical vs. atypical disease and urban vs. rural, Chi square analysis was used for categorical data and T-test was used for continuous and ordinal data.

Death was determined either through mention of death in medical record, obituary, or social security index. People with parkinsonism typically have multiple visits within the Health Care System not only for their parkinsonism but for other comorbidities, particularly at the end of their life. A case was considered a probable death when visits suddenly stop, there was no record of a visit for six months or longer and no report or knowledge by medical staff of a move outside the state (ie. request for medical records).

Results

Between January 1, 2000 and December 31, 2013 there were 141 cases of incident and prevalent parkinsonism identified. Of these, 123 were typical parkinsonism and 18 were atypical, table 3. There were 71 males total (50%), 60 (48.8%) males had typical disease and 11 (61.1%) had atypical disease, $p = 0.45$. The mean age of onset was 61.8 (± 12.9) years for all cases of parkinsonism, 61.1 (± 12.8) years for typical and 66.1 (± 12.8) years for atypical parkinsonism, $p = 0.14$. Mean age of diagnosis 63.7 (± 12.9) years in typical cases and 68.0 (± 12.1) years in atypical cases, $p = 0.18$. The average delay in diagnosis was 2.6 (SE 0.28) years in typical cases and 1.9 (SE 0.38) years in atypical cases, $p = 0.13$.

During the 14 years of surveillance there were 26 confirmed and 11 probable deaths. In 11 cases deaths could not be confirmed in the medical record or Social Security Death Index but because there was no record of moving or visit they were classified as a probable death. No cases came to autopsy so there were no pathologic confirmations of parkinsonism. Assuming a total number of 37 deaths, 30 (24.4 %) were in cases with typical disease and 7 (38.9 %) were in cases with atypical disease, $p = 0.19$. Mortality

rate in cases of typical disease was 4.57 per 100,000 person-years 35 years and older, for atypical it was 1.07 per 100,000 person years, $p = 0.28$.

Geographic and ethnic distribution was uneven with almost twice the expected number of cases occurring in the Southeast region (ratio 1.99) and fewer cases found in the interior (rate 0.52). Ethnic distribution showed more than expected number of cases in people who described themselves as Tsimshian, Tlingit-Haida or Yup'ik. Except for the Yup'ik cases this is similar to the ethno-geographic distribution as the Southeast region is mostly Tlingit-Haida and Tsimshian people.

There were 98 prevalent cases of typical parkinsonism in July 2013. Total age-specific prevalence was 180.1 per 100,000, in males the rate was 200.3 per 100,000 and in females 175.3 per 100,000, $p = 0.46$. When age-adjusted to the U.S. population as the standard, the total rate increased to 238.9 per 100,000, for males 260.5 per 100,000 and for females 226.7 per 100,000. There was an approximate doubling of prevalence every decade after the age of 50 years, figure 2. There were only 11 total prevalent cases of atypical parkinsonism in the same period. Total prevalence for atypical disease was 20.2 per 100,000 with a rate of 22.7 per 100,000 in males and 17.9 per 100,000 in females, $p = 0.98$.

Between 2000 and 2013 there were 95 incident cases of typical parkinsonism, of which 50 were male and 45 were female. The overall annual incidence rate of typical disease in those over the age of 35 years was 11.2 per 100,000 person years, with a rate of 12.2 per 100,000 person years in males and 10.6 per 100,000 person years in females, $p = 0.22$. When age-adjusted to the U.S. population as a standard, annual incidence increased to 16.2 per 100,000 total, 20.4 per 100,000 for males and 16.1 per 100,000 for females.

Again, there was an approximate doubling of incidence between the ages of 35 and 75 after which the rate tended to level off. During the same period there were 16 incident cases of atypical disease (25% progressive supranuclear palsy, 31% multiple system atrophy and 44% undetermined). The overall incidence rate for atypical disease was 1.9 per 100,000 person years, rate in males was 2.4 per 100,000 person years and in females 1.4 per 100,000 person years, $p = 0.78$.

Case characteristics are outlined in table 10. More cases were living in rural communities (62%) than urban communities, table 8. There was a tendency for more males with parkinsonism to live in rural communities, but this did not reach statistical significance, $p = 0.08$. There were no significant differences between urban and rural cases with respect to age of disease onset or age at diagnosis ($p = 0.14$ and $p = 0.18$ respectively). Despite the fact that it takes three years from onset of symptoms to be classified as probable parkinsonism, there was no significant difference in the proportion of probable cases and possible cases living in urban and rural communities, $p = 0.25$.

Treatment characteristics with medication were most evident in typical cases because by definition, typical parkinsonism responds well to treatment with levodopa and atypical cases do not, table 11. Most cases with typical disease were on a combination of levodopa/carbidopa (82%), a central nervous system monoamine oxidase (MAO) inhibitor (43%) and a dopa agonist (29%). In a few cases (3%) treatment was with a dopa agonist and the patients had never been on levodopa. In this practice, amantadine was used occasionally while catechol-O-methyl transferase inhibitors and anticholinergic agents were used infrequently.

Discussion

The purpose of this study was to describe the epidemiology of parkinsonism in Alaska Native people. The main findings of this study were as follows: (1) most cases (87%) were typical parkinsonism or neurodegenerative Parkinson's disease with a mean age at symptom onset of 61.8 (± 12.9 , range 24 to 94) years and mean age at diagnosis of 64.3 (± 12.8 , range 27 to 96) years, (2) The Alaska Native female population was larger than the male population so more female cases were found. However, population rate calculations were higher in men for both incidence and prevalence. (3) The overall age-adjusted prevalence in adults age 35 and older for typical parkinsonism was 238.9 per 100,000, (4) the overall age-adjusted annual incidence rate in adults age 35 and older for typical parkinsonism was 16.2 per 100,000 person years, (5) a majority (62%) of Alaska Native people with parkinsonism live in rural communities, (6) there was no difference in diagnostic certainty between urban and rural cases (7) and 94.3% of people with typical parkinsonism, or Parkinson's disease, were taking L-dopa medication.

Epidemiologic studies that measure burden of disease are useful for determining the need for services and may provide important insights into the etiology of the disorder (Tanner & Ben-Shlomo, 1999). Because people with parkinsonism tend to have a prolonged survival, identification and characterization of the disorder is enhanced. With this understanding, Alaska Native Tribal Health leaders have allowed a population-based surveillance of the disorder. Knowing the burden of disease within the Alaska Native population not only helps health administrators direct services where needed but may yield insights into factors that influence the disease.

Parkinsonism affects older Alaska Native people with a mean age of symptom onset of 61.1 years for typical disease and 66.1 years for atypical. As in other U.S. and European populations, the disorder is rare before the age of 50 years in Alaska Native people and it increases with age (de Lau et al., 2004; Dorsey et al., 2007; Tanner & Ben-Shlomo, 1999; Van Den Eeden et al., 2003). In the Alaska Native population there are more women than men in every age group 35 years and older. As a result, there were more women found with parkinsonism but once adjusted to the population, more men had both typical and atypical disease in each age group. This is similar to what others have reported in other population based studies.(Tanner & Aston, 2000; Tanner & Ben-Shlomo, 1999; Van Den Eeden et al., 2003). Typical parkinsonism was much more common than atypical disease, 123 (87%) vs. 18 (13%), which is also reported by others (Tanner & Aston, 2000). While atypical disease tended to develop a few years later than typical disease, the difference was not significant (61.1 ± 12.8 years for typical disease and 66.1 ± 12.8 years for atypical, $p = 0.14$).

The age-adjusted parkinsonism prevalence of 238.9 per 100,000 was greater in Alaska Native people than what has been reported in other community-based studies (Kuopio, Marttila, Helenius, & Rinne, 1999; Tanner, 1992; Tanner & Ben-Shlomo, 1999; Wermuth, Joensen, Bungler, & Jeune, 1997; Wermuth et al., 2002). Most estimates of parkinsonism in Europe and North America range between 80 and 180 cases per 100,000 (de Lau & Breteler, 2006; Dorsey et al., 2007; Tanner, 1992). Observed prevalence in Alaska Native people is also high when compared to another indigenous circumpolar population, the Greenland Inuit people. Wermuth reported an age-adjusted prevalence of 187.5 per 100,000 in that population (Wermuth et al., 2002). In a study of inpatient and

outpatient visit data for American Indian and Alaska Native people throughout the Indian Health Service, Gordon reported an even greater age-adjusted prevalence of 355.7 per 100,000 (Gordon et al., 2012). In their study, which did include Alaska Native people, case identification was based solely on ICD9 criteria without clinical review. Therefore, secondary causes of parkinsonism were probably included, which might explain the greater prevalence (Hughes et al., 1992). For example, about 10% of cases reviewed for this study were coded as Parkinson's disease but were actually secondary parkinsonism due to neuroleptic use. Despite these methodological differences, there does appear to be a high prevalence of neurodegenerative parkinsonism in Alaska Native people and the cause of this disparity is unclear.

The average, age adjusted annual incidence rate was 160 per 100,000 person years, 171 per 100,000 person years for men and 148 per 100,000 person years for women. These rates are higher than those reported in other populations. For example, a rate of 114.7 per 100,000 person years was reported in Olmsted County, MN, a rate that also included secondary parkinsonism (Bower, Maraganore, McDonnell, & Rocca, 1999). Typical parkinsonism rates range from a high of 490 per 100,000 person years in Rotterdam, Netherlands (de Lau et al., 2004), 84 per 100,000 person years in the United Kingdom (Horsfall, Petersen, Walters, & Schrag, 2013), 32 per 100,000 person years in Singapore (Tan, Venketasubramanian, Jamora, & Heng, 2007), 14.9 per 100,000 person years in Finland (Kuopio et al., 1999) and 11.6 per 100,000 person years in Bulgaria (Hristova, Zachariev, Mateva, & Grozdev, 2010). Age specific incidence rates doubled each decade between 54 and 74 years before leveling off and falling after the age of 84. The age specific rates between 54 and 74 years are higher compared to rates reported in other

studies.(de Lau & Breteler, 2006) Rates ranged between 48 per 100,000 person years in those age 35 to 54 years, to a high of 541 per 100,000 person years in the 75 to 84 years.. Execept for the 54 to 74 year deciles, the annual age-adjusted incident rate of typical parkinsonism in Alaska Native people is similar to that reported in other populations.

People with parkinsonism can live for many years with their disease, particularly in those with onset in their 30s and 40s (Selikhova et al., 2009). Those with typical disease tended to live twice as long as those with atypical disease in this study were average duration of disease was 8.8 ± 7.4 years in those with typical disease and 5.7 ± 3.8 years in atypical cases ($p = 0.02$). This reflects the fact that these are different disorders. Atypical disease has more widespread pathology and limited response to treatment. Data from the Queen Square Bain Bank suggests the average time from diagnosis of Parkinson's disease to death is 14 years (Selikhova et al., 2009). The reason for the shorter duration in Alaska Native people is not clear. One possibility is a lack of supportive services in rural communities, which is were most of Alaska Native people with Parkinson's disease live. With regards to the distribution of cases, the Southeast and Northwest regions had more than expected number of parkinsonism cases. A high number of cases in the Southeast was also reported by Gordon (Gordon et al., 2012). The reason for this disparity is not known. There does appear to be a tendency for more cases to be in coastal areas and fewer cases in the interior. How this might relate to exposure to an environmental toxicant, possibly marine, genetic predisposition or gene-environment interaction requires further study.

According to the urban/rural community definition used in this study, 55% of the Alaska Native population over the age of 35 years lives in a rural community. In this study 63% of parkinsonism cases live in rural communities reflecting this tendency. The high proportion of rural cases raises the possibility there may be a higher exposure to an environmental factor related to parkinsonism in those living in rural Alaska Native communities. This higher prevalence of parkinsonism in rural areas has been observed in other populations and is thought to be related to the agricultural industry (Seidler et al., 1996; Tanner, 1992; Tuchsén & Jensen, 2000). Because of the harsh climate the agricultural industry in Alaska is very small and most agricultural products are imported to the state. What little agriculture there is occurs in the Southcentral part of the state (Resources, 2010), which does not correlate with the observed distribution of parkinsonism cases in this study. If there is an environmental factor linked to parkinsonism, a direct link to the agriculture industry in Alaska is unlikely. The high prevalence of parkinsonism in Alaska Native people, particularly in those living in rural communities needs further study.

The symptoms of parkinsonism can have a detrimental effect on quality of life, particularly with mobility, and often leads to early disability. Walking balance, tremor and getting out of a low chair are among features of the disease that have the most impact on quality of life in both typical and atypical cases. In addition to these, orthostatic lightheadedness is a problem in atypical cases. Living in rural Alaska has many challenges that affect quality of life. For example, some small communities still lack homes with running water (personal experience). Support services, such as physical therapy, are generally not available except in communities with a regional hospital. However, every

community with a population of more than about 50 individuals has a clinic staffed by community health aides¹ (Golnick et al., 2012). The lack of supportive services may also have a negative impact on quality of life and mortality Alaska Native people with parkinsonism living in rural communities.

Treatment of parkinsonism is challenging. As the disease progresses and symptoms become worse frequent adjustments and addition of other medications is often required to maintain motor function and quality of life. While tremor and mobility can improve with treatment in typical cases, postural instability does not (D. R. Williams & I. Litvan, 2013). This can result in falls with a negative impact on quality of life, particularly in atypical cases. Because atypical parkinsonism responds poorly to dopaminergic treatment, often worsening orthostatic hypotension and hallucinations, treatment centers around specific symptoms (D. Williams & I. Litvan, 2013). For example, orthostatic hypotension can improve with support hose and volume expanders to raise blood pressure. Hallucinations can be treated with dopamine blocking agents but this tends to worsen the parkinsonian symptoms of rigidity, bradykinesia and tremor. While medication use in this population reflects local practice, it is similar to the way parkinsonism is managed in the United States and Europe (Leoni et al., 2002). Levodopa is the most effective drug available to treat parkinsonism and 94.3% of typical cases were taking it, table 11. This is typically the initial treatment for Parkinson's disease. Use of MAO inhibitors prolongs the function dopamine in the brain and is often added early on

¹ These are members of the community who are chosen by community members and trained within the Alaska Tribal Health System to provide basic health and medical care to their community. Training consists of four sessions, three to four weeks each, that teach clinical skills. The Community Health Aide Program Certification Board certifies these practitioners.

in the course of treatment. This was used by 48.8% of typical cases. Dopamine agonists act like dopamine in the brain and have fewer motor side effects. They were used in 30.9% of typical cases. Other anti-parkinsonism medications were used infrequently. All these classes of medications are available in regional pharmacies throughout the Alaska Tribal Health System and except for occasional delays due to weather, getting medications to patients living in remote areas (communities with no direct road access) is generally not a problem (personal observation). This is significant as a majority of cases live in rural, sometimes remote communities.

This study has a many strengths. It was a population based, prospective and retrospective study. The Tribal Health System is a spoke and hub system of care where community health aides deliver primary care through community clinics, which are present in nearly every community (Golnick et al., 2012; Sherry, 2004). This facilitates identification and care of people with parkinsonism. Another strength was that all cases were reviewed for diagnostic accuracy and a neurologist examined all cases. Only cases of neurodegenerative parkinsonism were included in the study.

The study also has limitations. Only Alaska Native people were included in the study. The prevalence and incidence in other Alaskan populations is unknown. There are undoubtedly missed cases, which makes under ascertainment in a population with a high estimated prevalence a problem. Because on average it takes two to three years from the time symptoms begin until the diagnosis is made there are symptomatic cases that have yet to be identified. Furthermore, cases that die before they are diagnosed are also missed. Access to care, and in this case neurologic evaluation, within the Alaska Tribal Health System is probably not a limiting cause for case ascertainment (personal

experience). With the spoke and hub system of referral, there are not many barriers to people being seen by a neurologist either in Anchorage or during one of the biannual neurology clinics held at regional hospitals around the state. Finally, the number of cases is small due to the small population size. This impacts the stability of the prevalence and incidence calculations.

This study addressed most of the determinants outlined in the conceptual diagram, figure 1. There may be an association between parkinsonism and the environment. The concentration of cases in coastal regions, particularly in Southeast and Northwest Alaska, is compatible with an environmental risk factor. This may relate to a higher exposure to POPs in these regions, something that needs further study. Though there were ethnic differences observed, the geographic distribution correlates with ethnic distribution of the Native population in the state. Nevertheless, an interaction between genetic and environmental influences may be a risk factor and is something that needs further study (Warner & Schapira, 2003). Despite the geographic challenges of delivering quality care to a vast, sparsely populated area; Alaska Native people with parkinsonism receive treatment similar to what is received in most of developed world.

Neurodegenerative parkinsonism is a problem in Alaska Native people. Compared to other population based studies, parkinsonism is estimated to be more common in Alaska Native people, including than that reported in Greenland Inuit people (Wermuth et al., 2002). The reason for this disparity is not clear. There are regional and possible ethnic differences compatible with current theory that parkinsonism may develop when a genetically susceptible person is exposed to something in the environment. Except for a shorter survival, characteristics of the disorder with regards to gender, age of onset, age at

diagnosis and mortality are similar to that reported in the United States and Europe suggesting the disorder in Alaska Native people is not unique. Despite the vast distances between some communities in Alaska, and the fact that some communities can only be reached by air year round, the Alaska Native Tribal Health System makes access to health care possible, including access to specialists such as neurologist. The fact that parkinsonism is identified just as rapidly in urban areas as it is in rural areas support the fact that there is neurologic access to the entire population. Treatment of Parkinson's disease can be a challenge as visits with a neurologist for some rural cases is only once or twice a year. It is not clear if better access to a neurologist might improve quality of life and survival in people with parkinsonism. Parkinsonism is a problem in Alaska Native people. More study is needed to understand the association with POPs and parkinsonism, particularly in coastal regions. Quality of life for people with parkinsonism as well as mortality might improve if more neurologic services were available for these cases.

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