Investigation of Amyotrophic Lateral Sclerosis in Corrales, NM, 2000 - 2015

Background

On October 1, 2015, Peter Kowalski, a staff member with the Agency for Toxic Substances and Disease Registry (ATSDR) contacted the New Mexico Department of Health (NMDOH) about an e-mail from a community member. This community member asked for an epidemiologic analysis to compare the amyotrophic lateral sclerosis (ALS) prevalence rate in Corrales to the national ALS prevalence rate. The NMDOH evaluated the request and by the end of October, agreed to pursue it. Because ALS is not a notifiable condition, a methodology to identify residents with ALS needed to be developed and a comparison rate needed to be identified.

Amyotrophic lateral sclerosis (ALS) is a progressive neurological disease that typically lasts from two to five years but is always fatal due to failure of respiratory muscles. According to a review by Kiernan et al. (2011), only 20% of patients will survive between 5 and 10 years after the initial onset of symptoms. With ALS, both upper motor neurons (UMNs) and lower motor neurons (LMNs) are affected. Roland and Shneider (2001) describe symptoms of disease in the UMNs as overactive tendon reflexes, Hoffmann signs (sudden flexing of the thumb and/or index finger), clonus (involuntary muscle spasms), and Babinski signs (in adults, upward flexing of big toe when sole of foot scraped), while in the LMNs, symptoms include muscle atrophy, weakness, and fasciculation (spontaneous muscle contractions).

One important risk factor for ALS is genetics, as approximately 5% - 10% of cases are classified as familial (heritable), while the remaining cases are classified as sporadic because there is no consistent pattern that has been identified (Kiernan et al., 2011). Al-Chalabi and Hardiman (2013) reviewed the genetic and environmental risk factors for developing ALS and listed 30 genes that may cause or increase the risk of ALS. The authors propose the gene-time-environment (GTE) model for developing ALS. With this model, individuals are born with genes that have different levels of risk for developing ALS. This risk level is combined with time (how long an individual lives) and environmental exposures. For example, a low-risk gene without any environmental exposures would predict the highest possible age at onset of ALS. If someone had a low-risk gene but did have environmental exposures, the age at onset would be younger.

The potential contribution of various environmental exposures has been explored in the literature, but there is not consensus on which exposures influence the development of ALS and to what extent. For example, Malek et al. (2014) conducted a case-control study to look at both environmental and

occupational exposures by comparing ALS patients identified through neurology clinics to controls. Questions were asked about occupation as well as hobbies and behaviors. Occupational exposure to metals and pesticides demonstrated an increased risk of ALS after controlling for smoking and education. In contrast, Al-Chalabi and Hardiman (2013), in their review of the literature, concluded that there is no evidence of a causal relationship between heavy metal exposure and ALS. They did identify one review of exposure to chemicals that concluded pesticides increase the risk of ALS. Talbott et al. (2016), in their review of the literature, indicated that there was evidence of increased risk for exposure to metals (e.g. lead, mercury) and pesticides and insecticides (among other exposures). Al-Chalabi and Hardiman (2013) indicate that there is conflicting evidence about smoking as a risk factor for ALS, while Talbott et al. (2016) indicate that smoking was one factor that increases the risk of developing ALS. Al-Chalabi and Hardiman (2013) suggest there is mixed evidence for increased risk of ALS among armed services personnel while Talbott et al. (2016) indicated there is increased risk of ALS among military personnel. There is mixed evidence for increased risk of ALS among those exposed to cyanotoxins (Al-Chalabi and Hardiman, 2013) and physical activity (Al-Chalabi and Hardiman, 2013; Talbott et al. (2016)).

Methods

The primary purpose of this investigation was to describe the number and prevalence rate of ALS among residents of Corrales over a defined period that was long enough for adequate numbers to be collected but also realistic in terms of the availability of medical records (old records are typically destroyed or are harder to access) and how much time would be needed to request and obtain medical records. Therefore, all records were restricted to the time-period from January 1, 2000 to December 31, 2015.

A secondary purpose of this investigation was to determine whether the number of ALS cases observed among residents of Corrales differs from what might be expected based on the published prevalence rate of ALS patients by age group in the United States. For this report, the number of ALS patients observed in Corrales was compared to the number of expected ALS patients in the United States based on prevalence rates by age category from the ATSDR's National ALS Registry, which was implemented in 2009. The Registry is the only current data source that can provide a national estimate of ALS prevalence in the United States. National prevalence rates from the Registry have been estimated from 2010-2011, 2012, and 2013 data (https://www.cdc.gov/media/releases/2016/p0804-als-registry.html). For this report, the 2013 data served as the comparison population and the prevalence rate from which the expected number of ALS patients was calculated. This year was selected because it is the most recent year of available data from the Registry and because the methodology used for these data

reflects an improved algorithm compared to previous years which resulted in more "definite ALS" cases being detected (Mehta et al., 2016). An observed-to-expected ratio could then be calculated (more detail about calculations provided on page 6).

To gather a preliminary list of potential ALS patients from Corrales, hospitalization data, death certificates, and self-reports were utilized. For the hospitalization data and death certificates, residence in Corrales was established either by city of residence (various spellings examined) and/or a Zip code listed as 87048, because this Zip code is unique to Corrales. After this list was generated, medical records from outpatient clinics, including hospice, were consulted so that we could utilize our ALS case definition. More details can be found in the case definition section on page 4.

Hospitalization Data

The NMDOH Epidemiology and Response Division's (ERD) Health Systems Epidemiology Program (HSEP) currently collects, maintains, and analyzes the Hospital Inpatient Discharge Database (HIDD). The database includes hospitalizations from all non-federal hospitals. Therefore, it does not include hospitalizations from the Veterans Administration or Indian Health Service, which are federal hospitals. Records from 2000-2015 were requested from HSEP. The diagnoses requested included the International Classification of Diseases, Ninth Revision (ICD-9) code 335.20 or the International Classification of Diseases, Tenth Revision (ICD-10) code G12.21 (which began to be used in hospitals on October 1, 2015) in any diagnosis fields available. From 2000-2008, there were 8 diagnosis fields available in the hospital data; from 2009-2015 there were 18 diagnosis fields available. From 2000-2008, the code 335.20 was not found in any of those files. The closest approximation to this code was 335.2 and was therefore utilized. However, because the correct ICD-9 code could not be used, for residents identified during this period, additional medical records (such as outpatient visits) were required to confirm that there was in fact an ALS diagnosis.

Death Certificate Data

The NMDOH ERD's Bureau of Vital Records and Health Statistics collects, maintains, and analyzes mortality data. Death certificate data from 2000 to 2015 were requested with the ICD-10 code G12.2 listed as an underlying or contributing cause of death. The specific text string listed on the death certificate was also requested because before October 1, 2015, G12.2 was used not only for ALS but also other motor neuron diseases and supra nuclear palsy (Sejvar et al., 2005) and the text string provides

more solid evidence of an ALS diagnosis (personal communication, Wendy Kaye, PhD)[1]. After receiving the data, records were restricted to those listing Corrales as the city of residence and/or the Zip code as 87048.

Self-reports

Because the request came from a community member, residents of Corrales were informed about the study and how to participate through an article (March 13, 2017) in the local newspaper, *Corrales Comment*, and through the New Mexico chapter of the ALS Association, which notified constituents and clinicians (October 11, 2016). The latter included the Adult Neurology Clinic at the University of New Mexico (UNM). Community members were asked to provide the NMDOH with the following information: first name of patient, last name of patient, date of ALS diagnosis, name of primary care physician, name of specialty physicians such as neurologists. For community members who had passed away, a relative could serve as a proxy and provide this information.

Outpatient Clinics

After obtaining the name and date of birth of a potential ALS patient from either hospitalization, death certificate records, and/or self-reports, patients were cross referenced with patients at the UNM Adult Neurology Clinic and/or primary care physicians identified in the hospitalization record. This was done to obtain additional medical records with enough information collected to determine if the case definition of ALS could be met (see below). When a primary care physician could not be identified from the hospitalization record and there was also a death certificate, the certifying physician on the death certificate was contacted. This often led to medical requests submitted to hospice organizations.

Case Definition

To identify ALS patients in a consistent manner and based on expert consensus, a case definition was developed. For all residents identified as potentially having ALS, additional medical records were requested to evaluate if they met the case definition. Because the case definition was used to generate: 1) the expected number of ALS patients in Corrales and 2) a Corrales ALS prevalence rate (number of residents with ALS per 100,000 population) which would in turn be compared to a national prevalence rate, the Registry was chosen, as it has the only US population-based estimate. The goal was to have the

[1] McKing Consulting Corporation, Atlanta, Georgia and co-author of "Prevalence of Amyotrophic Lateral Sclerosis-United States, 2012-2013," Morbidity and Mortality Weekly Report (see references section for complete citation).

Corrales case definition match the national case definition as closely as possible. For the National ALS Registry, the ATSDR developed an algorithm to classify people into three categories: "definite ALS," "possible ALS," and "not ALS." People with ALS were identified through records of a visit to a physician, a hospitalization, x-ray or laboratory test associated with an ALS diagnosis, a death certificate listing ALS as a cause or contributing cause of death, and a prescription of the ALS medication Riluzole (see Mehta et al., 2016[i] for detailed algorithm). Overall, ATSDR relied primarily on administrative datasets from Medicare, Medicaid, the Veterans Health Administration, and the Veterans Benefits Administration to identify prevalence of ALS. They also solicited self-reports from patients.

New Mexico also used the categories "definite ALS," "possible ALS," and "not ALS." However, NMDOH did not have access to Medicare and Medicaid data or to Veterans' data. Therefore, the case definition excluded criteria with those data sources. Because New Mexico did have access to text string confirmation on the death certificate, this was included as a new criterion (b). Individuals were classified as having definite ALS if:

a) Any two of the following: 1) An encounter (hospitalization and/or outpatient clinic visit) coded for ALS in one or more years in the same source or 2) a death certificate listing ALS as a cause of death or 3) a prescription for Riluzole;
b) An encounter (hospitalization and/or outpatient clinic visit) coded for ALS in one or more years in the same source and a death certificate listing ALS as a cause of death with text string confirmation; OR
c) An encounter coded for ALS at least two years and a neurologist visit in the same in the same source; OR
d) An encounter coded for ALS in one or more years for which at least one visit must be with a neurologist in the same source and an encounter coded for ALS in another source; OR
e) An encounter coded for ALS in 1 year and five or more neurologist visits in the same source.

Those included in the "not ALS" category met one or more of the following criteria:

a) No encounter coded for ALS in any source and no prescription for Riluzole; OR
b) An encounter coded for ALS in only one year but no neurologist visits in the same source: OR
c) A person aged <18 years

Those included in the "possible ALS" category included everyone not determined to be either "definite ALS or "not ALS." Each patient was classified according to the algorithm.

Population, Calculation of Rates, Ratios and Confidence Intervals

Corrales is located in Sandoval County, New Mexico. According to estimates from the United States Census Bureau, there were 8,353 residents of Corrales at the time of the United States Decennial Census in 2010. This includes two census tracts (35043010601, 35043010602). A higher percentage of all residents in Corrales (19.4%) were aged 65 or over compared to the United States overall (13.0%) in 2010.

To asses if Corrales had a higher, lower, or similar burden of ALS compared with the United States, we performed several calculations as part of our primary analysis. First, we calculated the number of cases that would be expected to occur in a population of the size and demographic characteristics of Corrales for adults ages 18 and over, because this is the at-risk population for ALS. The expected number of cases was calculated by multiplying the ATSDR Registry's age-specific national ALS prevalence rates by the corresponding population estimates in that age group for Corrales. The average population in Corrales from 2000 to 2015 was used for the population estimate[2]. With this information in hand, we then calculated the ratio of the observed-to-expected number of cases for this community during the specified time-period.

The value of the observed-to-expected ratios may be broadly interpreted as follows. If a given community (such as Corrales) experiences the same rate of ALS as the comparison national rate, then the observed number of cases in that community would be the same as the expected number of cases. In this situation, the observed-to-expected ratio will have a value of one (1.00).

If the community has a rate of ALS that is greater than the comparison national rate, then the observed number of cases in that community will exceed the expected number of cases. The observed-to-expected ratio will be greater than one (>1.00) in such instances. Conversely, the observed-to-expected ratio will have a value less than one (<1.00) when fewer cases are observed in the community of interest than are expected.

Second, we calculated the prevalence rate of ALS in Corrales from 2000 to 2015 by dividing the number of residents in Corrales with ALS over this time-period (counting each resident once) divided by the combined population over age 18 from 2000 to 2015 (16 years).

[2] https://ibis.health.state.nm.us/query/builder/pop/PopTract/Count.html

There will be variation in calculations of any kind, and prevalence rates and observed-to-expected ratios are no exception. For this reason, we calculated 95 percent confidence intervals (CI) for the prevalence rate and observed-to-expected ratio. We may consider the prevalence rate/observed-to-expected ratio as our best estimate of the truth, recognizing that there may be variation. By convention, we assume that the "true" value of the rate or ratio falls between the lower and upper limits of the 95 percent confidence interval most of the time (i.e., in 95 percent of all assessments, the "true" prevalence rate or observed-to-expected ratio will fall within these bounds).

The methods for calculating the 95 percent confidence intervals were based on the Poisson distribution. The Poisson distribution was selected because the number of ALS cases is expected to be relatively small when the community such as Corrales is also relatively small, as compared to the United States.

A prevalence rate for definite ALS in Corrales was calculated from 2000-2015, based on U.S. Census Bureau population data for Corrales in 2010. No adjustment for age was made because this is the way the national rate was calculated. The methods for calculating the 95 percent confidence intervals were also based on the Poisson distribution.

A secondary analysis was performed to explore if conclusions would change if additional residents with some (but insufficient) evidence of ALS according to the case definition were included. These residents were added to those with definite ALS and the same calculations as described above were repeated.

Results

Potential ALS Patients

After reviewing the hospitalization data, death certificate data, and self-reports, there were 9 unique individuals identified as potentially having ALS. Several challenges were identified with the hospitalization data, in particular. For example, some of the earlier years of hospitalization data (before 2006) were problematic because the patient's name and/or date of birth were not always included in the patient's record. Additionally, one year of data did not have city of residence or Zip code of residence for any patient. Therefore, for that year, each hospital in Albuquerque was called for every ALS record and an inquiry was made about each patient's address. No records with a Corrales address were identified. There was also a problem with the diagnosis variables for hospitalization records from 2000-2008, because the appropriate ICD-9 code of 335.20 was not present in any of the records. Although we used 335.2 instead, no patients from Corrales were identified with this diagnosis.

For two individuals, there was a death certificate, but no hospitalization data. Therefore, hospice organizations were contacted to obtain the medical records for these individuals. Of the 9 individuals with potential ALS, 8 had death certificates with an underlying or contributing diagnosis of ALS and all were confirmed through text string literal analysis to have a diagnosis of ALS.

One individual called to report the ALS diagnosis of a family member who had passed away and to provide relevant information. No other community members contacted the NMDOH to provide information about an individual with ALS.

Individuals with Definite ALS, No ALS, and Exclusions

After applying the case algorithm to the 9 residents with potential ALS, 5 met the definition of "definite ALS." Of the four remaining individuals, two were excluded and the other two individuals were classified as "not ALS". The first excluded individual was seen in 2002 and had an ICD-9 code for ALS, but there was no date of birth or patient name and the hospital is no longer in operation. Due to lack of minimal information required, no medical records could be obtained for this individual. The second excluded individual had been living out of state for at least 8 years and was diagnosed in that state. The individual then moved to Corrales. Therefore, any exposures associated with the disease process would likely have occurred out of state. For the third and fourth individuals, there was insufficient encounter data and therefore they met the definition of "not ALS." For example, no medical records could be located for the third excluded individual (only the death certificate was available). The fourth individual had a death certificate and had been seen in the early 2000s at a neurology clinic, but medical records were no longer available because the clinic only retains records for 10 years. Thus, a total of 5 individuals were identified with definite ALS.

Observed-to-Expected Ratios

Based on the number of cases observed during the period of 2000 to 2015 and the expected number of cases from the ATSDR Registry, the observed-to-expected ratio was calculated as 0.61 (Table 1). Thus, the observed-to-expected ratio did not exceed 1.0 for Corrales. The 95 percent confidence intervals for the observed-to-expected ratio included the null value of 1.0.

Table 1. Observed and Expected Number of ALS Cases for Residents of Corrales* for the Time-Period 2000-2015

Disease	Observed No. Cases	Expected No. Cases	Observed-to-Expected Ratio	95% Confidence Interval[3]
ALS	5	8.19	0.61	(0.19 - 1.42)

*Total Population for Corrales from 2000 – 2015 with expected cases for 16 years

Prevalence Rate of Definite ALS

The data were also analyzed to generate a prevalence rate that could be compared to the Registry's estimate. Given the 5 definite cases of ALS, the prevalence rate in Corrales from 2000 – 2015 was calculated as 4.8 per 100,000 population (95% CI 1.6- 11.2). The range of ages at diagnosis was approximately 65 – 75 years. Records did not always include the actual age at diagnosis; therefore, the age on the first available medical visit was utilized. The national prevalence of ALS from the ATSDR Registry for 2013 had a rate of 5.0 per 100,000 (95% CI 4.95-5.11), respectively. Thus, the national rate and the Corrales rate are very similar.

Secondary Analysis to Explore Including Residents with Insufficient Evidence of ALS

Because two residents were classified according to the case definition as not having ALS due to the lack of medical records, but did have some evidence of an ALS diagnosis, a secondary analysis was conducted to include them in the category of residents with definite ALS. In this scenario, the number of residents with ALS increased from 5 to 7. Given a total of 7 residents with ALS, the observed-to-expected ratio increased to 0.85 (95% CI 0.34 – 1.76). The prevalence rate increased to 6.7 per 100,000 population (95% CI 2.7-13.9). Although not a formal test of significance, 95% confidence intervals are typically used in population-based data to determine if there is a significant difference. The Corrales confidence interval (95% CI 2.7-13.9) overlaps with the confidence intervals of the national rate. When 95% confidence intervals for the rates of two independent populations don't overlap, this means there is a statistically significant difference between the two rates. When they do overlap, the opposite is not necessarily the case and additional testing may be required if the rates appear to be different. Therefore, we used the Fisher's exact test, which is a more sensitive test of significance and is adapted to situations with small numbers, such as this. The Fisher's exact test was used to compare the 2013 national rate to the Corrales rate using a p-value of 0.05 to determine significance, as is typical in

[3] SAS Macro used for generating confidence intervals from Daly, Leslie. 1992. Simple SAS macros for the calculation of exact binomial and Poisson Confidence limits. Comput Biol Med, 22(5):351-361.

most scientific literature. When the 2013 national rate was compared to the Corrales rate, the p-value was 0.378, indicating that the two rates are not statistically significantly different.

Discussion

Because ALS is a terminal neuromuscular disease without a cure or a treatment that effectively prolongs life, any case that occurs in a community is significant. When more than one case occurs, community members naturally may wonder if there is a common exposure or cause. With sporadic ALS and perhaps even familial ALS, there appear to be multiple potential exposures that are associated with the disease.

In reviewing this report, it is important to keep several limitations in mind. While every attempt was made to obtain the medical records of potential ALS patients, some of the data sources did not have complete information. Thus, some ALS cases may have been missed. However, we did conduct a secondary analysis to explore how conclusions might change if residents with insufficient evidence of ALS were included. Even if we had been able to obtain all the medical records, this does not mean that there would not be potential errors. There are several possible scenarios for errors which could affect the results:

1. We overestimated the number of ALS cases, but the population estimate is correct. This would mean the observed to expected ratios are actually too high.
2. We underestimated the number of ALS cases, but the population estimate is correct. This would mean the observed to expected ratios are actually too low.
3. We correctly estimated the number of ALS cases, but we underestimated the population. This would mean that the observed to expected ratios are actually too high.
4. We correctly estimated the number of ALS cases, but we overestimated the population. This would mean that the observed to expected ratios are actually too low.

Based on the results from the primary analysis, the estimated number of ALS cases diagnosed in Corrales is similar to what would be expected for a community of this size and age-distribution, based on the number of cases/prevalence rate from the ATSDR Registry in 2013. When we conducted an exploratory secondary analysis to include 2 residents with insufficient evidence of an ALS diagnosis according to the case definition, our conclusions did not change. Thus, the Corrales rate is considered to be similar to the national rate, even after the addition of the two possible cases.

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