Amyotrophic lateral sclerosis mortality rates in Chile: A population based study (1994–2010)

DANIEL VALENZUELA1,2, PEDRO ZITKO3,4 & PATRICIA LILLO1

1Departamento de Neurología Sur, Facultad de Medicina, Universidad de Chile, 2Servicio de Neurología, Complejo Asistencial Barros Luco, SSMS, Santiago, 3Unidad de Estudios Asistenciales, Complejo Asistencial Barros Luco, Santiago, and 4Facultad de Medicina, Universidad Diego Portales, Santiago, Chile

Abstract
Our objective was to describe amyotrophic lateral sclerosis (ALS) mortality rates in the Chilean population over a 17-year period. Chilean death records (1994–2010) were reviewed for the ICD-10 diagnosis G.12.2 (including motor neuron disease and similar conditions), and weighted with population data. Crude and standardized mortality rates by ALS were calculated at the nationwide level and by geographic zone. A risk analysis was performed in successive cohorts from 1910–1919 to 1960–1969, comparing mortality slopes. One thousand six hundred and seventy-one deaths were recorded during 1994–2010, with an average of 1.13 per 100,000, a 1.2:1 male/female ratio, and a statistically significant increase in mortality rate. According to geographical distribution, the Austral area, with a larger population of European origin, showed higher mortality rates compared to the national average. The cohort analysis showed an increasing risk of dying from ALS for all cohorts, and highest above 64 years of age, becoming a competitive cause of death in older ages. In conclusion, as expected, the mortality rate in Chile by ALS is higher than that reported previously in our country, and similar to other Latin American countries. ALS mortality rate has increased over time probably due to the aging of the population and decline in rates for competing causes of death.

Key Words: Amyotrophic lateral sclerosis, motor neuron disease, mortality rates

Introduction
The incidence of amyotrophic lateral sclerosis (ALS) in the European population has been estimated at 1.5–2.5 per 100,000 person-years (1). However, recent evidence has suggested a variable distribution of ALS worldwide. Studies in Hispanic, Latin American and Asian populations have shown a lower incidence of ALS than in Caucasian populations (2–10). As expected, mortality from ALS is also higher in white than mixed populations (3). To date, the lowest mortality rates by ALS have been reported in Chile and Mexico (0.3 per 100,000 population) (2).

At least two considerations should be taken in account in analysing the mortality data from Chile. First, the current mortality rate from ALS was reported in one study based on hospital discharges from 1972 to 1976 and referred exclusively to the Northern Area of the Metropolitan Region (11). Secondly, the population in Chile is admixed. This has been demonstrated by a recent study on the geographical distribution of genes in Chile. The Chilean population has three main stem groups, which are homogenously distributed along the country: native American (44.34 ± 3.9%), European (51.85 ± 5.44%) and African (3.81 ± 0.45) (12). Therefore, it could be expected that a new study including national data from our mixed Chilean population would demonstrate a higher mortality rate from ALS than that previously reported and should be similar to other Latin American countries.

In addition, controversial results about the trends in mortality rates from ALS have been reported worldwide. While in Japan there has been described an increase in mortality rates from 1952 and then a fall 10 years later (13), in others such as England/Wales, Scotland and Italy, the mortality rate has consistently increased over time (14–18). Also, in France and Norway the mortality rate has increased over time especially in elderly people (16,19,20). Chile is
lacking information regarding this issue; therefore we investigate the trend of mortality rates from ALS in our population. In summary, this study aimed to determine the mortality rate in Chile over a 17-year period (1994–2010) using the National Death Registry; to compare mortality rates among the Chilean geographical zones; and to evaluate competing causes of death using birth cohort analysis.

Material and methods

Data resources

ALS mortality rate data for 1994–2010 were obtained from the National Death Registry from the Department of Statistics and Information (INE), Chilean Ministry of Health (MINSAL). For the period 1997–2010, cases were selected if coded as ICD 10/International Classification of Diseases code G12.2. This code includes motor neuron disease, familial motor neuron disease, amyotrophic lateral sclerosis, primary lateral sclerosis, progressive bulbar palsy and progressive spinal muscle atrophy. For the period from 1994 to 1996, cases coded as ICD 9/International Classification of Diseases code 335.2 were selected. This code includes motor neuron disease. Cases younger than 19 years of age were excluded to avoid the inclusion of likely misclassified cases, e.g. hereditary spinal motor neuron disease, as suggested in previous publications (17,21).

The Chilean National Death Registry is based on death certificates, which are compulsory and are validated by the Ministry of Health and The National Statistics Institute of Chile. The last annual statistics report indicated that 99% of deaths received medical certification by a qualified medical doctor, and the misclassification rate was low, at 2.8% (22).

To calculate mortality rate, the intercensus 1992–2002 population projected by INE was considered (excluding those ≤ 20 years of age). Crude mortality rate from ALS was calculated by gender and age for each year. Standardized mortality rate by age was also calculated, using the WHO 2000 population (23) reference (age groups 20–39, 40–49, 50–59, 60–69, 70–79 and 80 and more years).

Poisson regression was used to model the global trend, with restricted maximum likelihood (REML) and 95% confidence intervals.

Mortality rate according to age and gender was calculated using the records for the last five years (2006–2010) and the population at the middle of the period. A five-year period is considered sufficient to: 1) avoid variability from only one year; and 2) allow the capture of the most recent mortality rates, which are less influenced by trends in the last 15 years. This estimation facilitates comparison over time and between studies (16).

Mortality rates in different Chilean geographical areas were calculated using a similar procedure. We divided the country into five zones using the CORFO classification (Corporación de Fomento de la Producción/Chilean Economic Development Agency): Grand North, Middle North, Central, South and Austral.

In addition, an analysis by birth cohort was conducted for the periods from 1910–1919 to 1960–1969, similar to the study published by Chiò et al. (17), to evaluate the impact of environmental factors and competing causes of death. A similar model was developed to test the evolution of the mortality rate based on the birth cohorts’ slopes analysis by successive five-year age bands.

Additionally, the Chilean mortality rate from ALS was compared to results reported from other countries.

Ethics

The Ministry of Health of Chile has authorized this study and no ethics approval was required, as the information is freely available from the INE platform (Department of Statistics and Information of the Chilean Ministry of Health/MINSAL), corresponding to death records and childbirth records. All analyses had confidential character and not individual (MINSAL guarantees that personal records are protected).

Results

Mortality rate

During the 17-year period analysed (1994–2010), 1671 deaths from ALS were recorded, including 926 males and 745 females.

Figure 1 shows that age-standardized ALS mortality rate tended to increase over time ($p < 0.001$) and among both males and females (see detail in Supplementary Figure 1 to be found online at http://informahealthcare.com/doi/abs/10.3109/21678421.2015.1026827). The last five years analysis showed a crude mortality rate of 1.13 per 100,000. Distribution according to gender was 1.2:1 male:female.

Figure 1. Standardized ALS mortality rate in Chile, 1994–2010.
Table I shows Chilean ALS mortality compared to other countries (published in previous studies).

Crude mortality rate by age group is presented in Figure 2. The maximum rate was for the 70–79 years age group (4.78 per 100,000).

Additionally, Supplementary Table 1 to be found online at http://informahealthcare.com/doi/abs/10.3109/21678421.2015.1026827 shows a consistent increase in crude mortality rate by ALS in males and females and for every age band, except at 60–69 and 70–79 years (five-year mobile period analysis). Also, Supplementary Table 2 to be found online at http://informahealthcare.com/doi/abs/10.3109/21678421.2015.1026827 shows the total number of deaths by gender and age.

**Geographical zone distribution**

Analysis of mortality rate by geographical zone did not show a characteristic pattern by latitude. The area with highest rate was the Austral zone (1.47 per 100,000), followed by the Middle North (1.33 per 100,000). The zones with lowest rates were the Grand North and South (0.90 and 1.01 per 100,000 respectively). The Central zone showed an intermediate rate of 1.18 per 100,000.

**Analysis by cohorts**

Figure 3 shows the ALS mortality rate slopes by birth cohort according to successive five-year age bands. In the majority of age groups, the most recent cohorts had a significant increase in risk of dying from ALS compared to previous cohorts, which means that at the same age, persons in the most recent cohorts had the highest risk of dying from ALS. This effect was most significant between 42 and 84 years of age, the interval that included the most groups with a statistically significant coefficient ($p < 0.05$).

**Discussion**

This is the first study reporting broad national mortality rates from ALS in Chile. As we expected, the mortality rate in our country was higher than the previous report, which was based on hospital discharge, and also was similar to other Latin American countries. The geographical distribution through the country did not show a latitudinal pattern, although the highest mortality rate was found in the Austral zone. The birth cohort analysis suggested that the Chilean ALS mortality rate has increased over time.

**Current mortality rates by ALS**

Our analysis showed that the mortality rate in Chile was significantly greater than the previous report which was based on hospital discharge data from 1972 to 1976 (1.13 vs. 0.3 per 100,000) (11). This finding is not surprising, as hospital discharge data have been considered inadequate to case identification and insufficient to estimate prevalence or incidence of ALS (21,24).

The male/female ratio was 1.2:1, which is consistent with other series (3,7,25).

| Authors          | Country | Period      | Mortality rate (x100,000) | Male/female ratio |
|------------------|---------|-------------|--------------------------|-------------------|
| Dean et al. 1994 (14) | England | 1963–1985   | 3.8 M 2.8 F               | 1.4:1             |
| Bostrom, 2012 (40)     | Sweden  | 1990–2010   | 2.98                     | –                 |
| Sejvar et al. 2005 (25) | USA     | 1979–2001   | 1.84                     | –                 |
| Veiga-Cabo et al. 1997* (7) | Spain   | 1951–1990   | 1.49                     | 1.6:1             |
| Valenzuela et al. 2014 | Chile    | 2006–2010   | 1.13                     | 1.2:1             |
| Zdáñizar et al. 2009 (3) | Cuba    | 2001–2006   | 0.83                     | 1.1:1             |
| Matos et al. 2011 (6)  | Brazil   | 2002–2006   | 0.78                     | 1:1               |
| Okamoto et al. 2005 (10) | Japan  | 1995–2001   | 0.74                     | 1.4:1             |
| Chio et al. 1995* (17) | Italy   | 1958–1987   | 0.68                     | 1.4:1             |
| Galdames et al. 1980 (11) | Chile    | 1980       | 0.3                      |                   |

Age-adjusted mortality rate shown for all groups 1995–2001.

*Mortality age- and gender-adjusted to the European population.

*Adjusted to the 1981 Italian population.

![Figure 2. Mortality rate of ALS in Chile distributed by age, 2006–2010.](image)
The highest mortality rate by age was for 70–79 years, followed by a decrease for older people, which may be explained because the diagnosis in the elderly can be more difficult due to coexisting diseases and death from other causes before a possible ALS diagnosis can be confirmed (16).

**Chile in Latin America**

Compared with other Latin American countries, the mortality rate in Chile was similar to Brazil and Cuba. As mentioned previously, this may be explained because of the mixed composition of the Chilean population (12,26,27). Mixed populations in Latin American countries such as Cuba tend to have lower mortality rates from ALS than Caucasian populations (3). Also, studies in South America such as those in Ecuador, Brazil, Uruguay, and Argentina have shown a lower incidence of ALS than in European countries (4–6,9).

**Geographical distribution**

Throughout the country, there was no specific pattern of geographical distribution.

Nevertheless, there was a peak in the Austral zone, which may be explained by a larger proportion of European genetic contribution in that area, as mentioned by Fuentes et al. (12). However, it is not possible to dismiss that an environmental factor may be involved, since the Austral zone is well known for its exposure to red tide (or algal bloom), for example.

In the same way, the higher mortality rate from ALS in the Austral zone was neither related to a major availability of neurologists in that area, nor to a higher population density (28).

Our study did not show a higher mortality rate from ALS in agricultural areas (Central and South zones), nor in mining settlements (Grand North). As is well known, controversial results regarding ALS mortality rates in urban or rural areas have been reported. Whereas Mandrioli et al. (29) showed higher mortality in rural areas, possibly associated with agriculture work and chemical exposure, other authors such as Scott et al. (30) have not found this association. In the same manner, the association between ALS and potential toxic factors such as heavy metals has not been clarified (31). It is important to add that delaying the time of diagnosis does not result in a lower reported incidence of ALS (32,33).

**Increase in mortality rates and cohort analysis**

The mortality rate increased over time during the observed period, which is consistent with results shown in previous studies and may be explained by demographic changes and reduced deaths from competing causes (10,34–36). Since 1910, the Chilean population has experienced a proportional increase in the number of elderly people compared with...
groups of adolescents and young people, and this situation may explain an increase in ALS cases. This change is due to improved environmental conditions, and, since the 1950s, expansion of health services across the country resulted in a lower infant mortality rate (with more children reaching adulthood) and adequate management of potentially treatable conditions such as cardiovascular and infectious diseases (37,38). It is important to note that an improvement in our health system, including better access to medical services and better case ascertainment for ALS diagnosis, may also help to explain the increasing mortality rates over time in Chile.

In the birth cohort analysis, risk of death from ALS (indicated by the slopes) increased over successive cohorts for almost all ages. The most dramatic slopes showing increasing mortality were seen for groups over 64 years of age (belonging to cohorts born before 1946) and may be associated with decreased deaths from competing causes at early ages. This finding is consistent with the study by Chiò et al. (17), which demonstrated by using Gompertzian analysis that rising ALS rates were attributable to effective increases in the susceptible population due to fewer deaths from other causes such as cardiovascular disease. In summary, our findings suggested that the ALS mortality rate is rising within our population, for all ages, but especially for individuals aged 65 years and older. This finding may be related to decreases in competing causes of death, which results in a larger susceptible population.

In terms of study limitations, a 17-year period of mortality records is a short time for a comprehensive cohort analysis as it limits the ability to compare successive cohorts at broader age ranges. However, the quality of the death records, professional coverage of death certification and subsequent review by government statisticians, associated with highly accurate ICD-10 coding, provides confidence that the database was representative of the national population.

Moreover, the cohort approach, which included evaluation of the slopes of increased mortality by age, allowed for comprehensive analysis of mortality, which may be related to effects of changes in other causes of death. Because ALS mortality is almost 100%, it may indirectly reflect incidence values. To date, prospective epidemiological studies in patients with ALS have been conducted in the majority of Europe (8). Future studies to assess clinical aspects of the disease such as survival will lead to a closer analysis of incidence and prevalence of ALS in Chile (39).

Declaration of interest: The authors declare that they have no conflicts of interest.

References
1. Logrosino G, Traynor BJ, Hardiman O, Chio A, Mitchell D, Swinger RJ, et al. Incidence of amyotrophic lateral sclerosis in Europe. J Neurol Neurosurgery Psychiatry. 2010;81:385–90.
2. Cronin S, Hardiman O, Traynor BJ. Ethnic variation in the incidence of ALS: a systematic review. Neurology. 2007;68:1002–7.
3. Zaldívar T, Gutiérrez J, Lara G, Carbonara M, Logrosino G, Hardiman O. Reduced frequency of ALS in an ethnically mixed population: a population-based mortality study. Neurology. 2009;72:1640–5.
4. Bettini M, Vicens J, Giunta DH, Rugiero M, Cristiano E. Incidence and prevalence of amyotrophic lateral sclerosis in an HMO of Buenos Aires, Argentina. Amyotroph Lateral Scler Frontotemporal Degener. 2013;14:598–603.
5. Bucheli M, Andino A, Montalto M, Cruz J, Atassi N, Berry J, et al. Amyotrophic lateral sclerosis: analysis of ALS cases in a predominantly admixed population of Ecuador. Amyotroph Lateral Scler Frontotemporal Degener. 2014;15:106–13.
6. Matos SE, Conde MT, Favero FM, Taniguchi M, Quadros AA, Fontes SV, et al. Mortality rates due to amyotrophic lateral sclerosis in Sao Paulo City from 2002 to 2006. Arquivos de Neuro-Psiquiatria. 2011;69:861–6.
7. Veiga-Cabo J, Almazan-Isla J, Sendra-Gutiérrez JM, de Pedro-Cuesta J. Differential features of motor neuron disease mortality in Spain. International Journal of Epidemiology. 1997;26:1024–32.
8. Chio A, Logrosino G, Traynor BJ, Collins J, Simeone JC, Goldstein LA, et al. Global epidemiology of amyotrophic lateral sclerosis: a systematic review of the published literature. Neuroepidemiology. 2013;41:118–30.
9. Vázquez MC, Ketziaon G, Legnani C, Rega I, Sanchez N, Perna A, et al. Incidence and prevalence of amyotrophic lateral sclerosis in Uruguay: a population-based study. Neuroepidemiology. 2008;30:105–11.
10. Okamoto K, Kobashi G, Washio M, Sasaki S, Yokoyama T, Miyake Y, et al. Descriptive epidemiology of amyotrophic lateral sclerosis in Japan, 1995–2001. Journal of Epidemiology/ Japan Epidemiological Association. 2005;15:20–3.
11. Galdames D, Aguilera L, Riveros JM, Arce C. Epidemiology of amyotrophic lateral sclerosis in Santiago: a retrospective study (author’s transl). Revista medica de Chile. 1980;108:435–9.
12. Fuentes M, Pulgar I, Gallo C, Bortolini MC, Canizales-Quinteros S, Bedoya G, et al. Gene geography of Chile: regional distribution of American, European and African genetic contributions. Revista medica de Chile. 2014;142:281–9.
13. Kondo K, Tsubaki T. Changing mortality patterns of motor neuron disease in Japan. Journal of the Neurological Sciences. 1977;32:111–24.
14. Dean G, Quigley M, Golldacre M. Motor neuron disease in a defined English population: estimates of incidence and mortality. J Neurol Neurosurg Psychiatry. 1994;57:450–4.
15. Buckley J, Warlow C, Smith P, Hilton-Jones D, Irvine S, Tew JR. Motor neuron disease in England and Wales, 1959–1979. J Neurol Neurosurg Psychiatry. 1983;46:197–205.
16. Chancellor AM, Warlow CP. Adult onset motor neuron disease: worldwide mortality, incidence and distribution since 1950. J Neurol Neurosurg Psychiatry. 1992;55:1106–15.
17. Chio A, Magnani C, Schiffer D. Gompertzian analysis of amyotrophic lateral sclerosis mortality in Italy, 1957–1987; application to birth cohorts. Neuroepidemiology. 1995;14:269–77.
18. Logrosino G, Traynor BJ, Hardiman O, Chio A, Courratier P, Mitchell JD, et al. Descriptive epidemiology of amyotrophic lateral sclerosis: new evidence and unsolved issues. J Neurol Neurosurg Psychiatry. 2008;79:6–11.
19. Neilson S, Robinson I, Alperovich A. Rising amyotrophic lateral sclerosis mortality in France 1968–1990: increased life expectancy and inter-disease competition as an explanation. Journal of Neurology. 1994;241:448–55.
20. Flaten TP. Rising mortality from motor neuron disease. Lancet. 1989;1:1018–9.
21. Stickler DE, Royer JA, Hardin JW. Validity of hospital discharge data for identifying cases of amyotrophic lateral sclerosis. Muscle & Nerve. 2011;44:814–6.
Supplementary material available online

Supplementary Figures 1, 2 and Tables I, II.