Can Mortality Data Be Used to Estimate Amyotrophic Lateral Sclerosis Incidence?

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Abstract

\textbf{Background:} Because studies of the incidence of amyotrophic lateral sclerosis (ALS) have uncertain feasibility and high costs, mortality rates are often used to provide an estimate. We performed a systematic review of the literature concerning mortality related to ALS. We aimed to use well-known criteria of good epidemiological practice to assess the methodological quality of the studies.

\textbf{Methods:} A MEDLINE and ScienceDirect literature search was performed to identify studies on ALS mortality published from 1971 to 2009. The literature was examined following 6 criteria.

\textbf{Results:} Of the 29 studies examined, almost all presented a clear definition of the population at risk, but 55\% of the papers did not report on the accuracy of death certificates, and the use of both ‘underlying’ and ‘contributory’ causes of death was identified in only 41\% of cases. When comparing ALS mortality data between calendar dates, the codes from the International Classification of Diseases were consistent overall, except in 3 studies. A majority of articles that compared mortality patterns between geographical regions or ethnic groups discussed the key issues of comparability of health care and equality of access. Overall, among the 29 ALS mortality studies, only 3 complied with all the criteria. In 2 of them, the mortality rates were highly consistent with available incidence data.

\textbf{Conclusion:} Only few studies on mortality data followed a high-quality methodology. When studies complied with the criteria, they showed good accuracy with regard to incidence rates. The criteria used in this study could also be used to guide future studies based on mortality data.

Introduction

Amyotrophic lateral sclerosis (ALS) is a rare neurodegenerative disease [1–7] with an incidence of between 1.5 and 2.5 per 100,000 person-years of follow-up in industrialized countries. It is associated with a severe prognosis and a median survival time after diagnosis of about 24 months [8]. In the absence of a population-based register, morbidity studies have rarely been performed to assess the incidence of ALS due to uncertain feasibility and high costs [9]. The characteristics of the disease led researchers to use mortality to indirectly estimate incidence. Mortal-
ity data have also been used in gompertzian analyses to test hypotheses about the evolution of ALS and its pathophysiology [10–17].

The use of mortality data is perceived as a convenient approach by which to estimate the incidence of ALS. Death certificates (DC) are popular sources of information because, in most countries, they carry a record of the causes of death and are readily available [18]. Accurate diagnosis and a well-recognized outcome with a fatal issue are essential if researchers are to use mortality data to assess incidence.

Diagnosis of ALS is recognized to be straightforward in adults [9]. It is a well-defined condition with a variable clinical presentation. The diagnosis requires standard methods that are available and accessible. Differential diagnoses are less common than those of ALS itself, particularly in the bulbar form. Patients suffering from ALS are mostly diagnosed and followed in referral centers, and rates of misdiagnosis are reported to be less than 10% [19, 20] even among those not followed in that way. In a study of the Irish register, 7% of patients had been diagnosed by a neurologist as having ALS with neuropathological investigations suggestive of ALS, but were finally considered to have another disease (ALS mimic syndromes) [21]. In the Scottish register, 8% of cases were false positives. Re-evaluation of the diagnosis was mostly prompted by absence of symptom progression, development of atypical features and inconsistent investigation results [22].

Within the time period, there were no major changes in diagnosis methods [23]. This point is particularly true for the period that used the El Escorial criteria. Despite the 1998 revision of the El Escorial criteria in Airlie House [24], and the fact that the new criteria are considered to be more precise adding a probable form based on paraclinical data, the impact of these changes was not of great importance [25].

Riluzole was found to increase survival by roughly 3 months in a clinical trial [26] and observational studies. Overall, treatment and medical care of ALS (noninvasive ventilation and multidisciplinary approaches) have not shown additive effects on life expectancy across the whole ALS population [27], probably because their impact on survival is limited or restricted to a small number of selected cases. Recent data indicate that survival has improved over time among placebo controls enrolled in clinical trials since 1990 [28].

ALS is rapidly and invariably fatal [9, 10], with only about 10% of patients living longer than 5–8 years [27, 29]. It is therefore assumed that all patients diagnosed with the condition will eventually be identified via a DC, and that the incidence pattern for a given year will be reflected in the mortality pattern 2–4 years later. The late presentation is quite uniform in that three quarters of patients die from respiratory failure [30–32]. The homogeneous profile of death from ALS facilitates the identification of cases and the coding of DC. Misclassification when ALS is quoted as a cause of death is possible but less likely than for other neurodegenerative disorders such as Parkinson’s disease or dementia [33]. In autopsy-based studies, false positives are very rare [32, 34].

Despite specificities that favor the use of mortality data to assess incidence, potential sources of bias have to be acknowledged, checked and discussed in mortality-data-based studies.

We performed a systematic review of the literature concerning mortality related to ALS. Our aim was, using well-known criteria of good epidemiological practice, to discuss the methodological quality of studies. As the vast majority of mortality studies are at least partially based on DC, we focused our presentation on them. Here, ALS is considered to be synonymous with motor neuron disease (MND).

Materials and Methods

Literature Search

A Medline and ScienceDirect literature search was performed to identify studies on ALS mortality published from 1971 to June 2009. We used the following medical subject heading terms: ‘amyotrophic lateral sclerosis’, ‘motor neuron disease’, ‘epidemiology’, ‘mortality’, ‘death’ and ‘incidence’. Additional references were identified from article citations. Only papers published in English were reviewed. The literature search was performed by 1 author (B.M.). The other members of the group were consulted regarding the eligibility of an article when needed. References included in this review were validated by the group.

Literature Analysis

The literature analysis was also performed by 1 author (B.M.) with the support of the other authors. During the comprehensive analysis, we identified methodological variations among study designs, applied usual criteria of good epidemiological practice when using mortality data and assessed the extent to which articles complied with them. The criteria are presented in table 1.

Presentation of Data

Parameters of interest in this article (true positivity rate, positive predictive value, false negatives and false positives, proportion of ALS quoted as primary and secondary causes of death) were calculated as percentages with 95% confidence intervals (95% CI), using exact methods on the basis of the absolute numbers presented in articles. When absolute numbers were not given, they were calculated from the total number of cases in the study and the percentages given.
Results

Twenty-nine articles dealing with ALS mortality rates based on DC data were included in this study. Our literature search retrieved 2,008 articles, but 1,858 were discarded on the basis of titles and abstracts (references not focused on ALS, mortality or incidence rates) and 121 were considered ineligible on the basis of the full text. Reasons for rejection were as follows: 26% were focused on ALS incidence only, 20% were literature reviews of ALS (with reviews of mortality and incidence studies) or editorials, 18% were focused on ALS mortality either not used to calculate rates or not based on DC, 12% dealt with diagnostic issues, 10% focused on the accuracy of DC, 5% reported clusters, 3% reported causes of death when suffering from ALS, and 6% were excluded for other reasons. Table 2 shows the extent to which mortality studies based on population DC complied with criteria of good epidemiological practice.

Table 1. Good practice epidemiological criteria for ALS mortality studies

<table>
<thead>
<tr>
<th></th>
<th>Definition of the population at risk (Def Pop)</th>
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<tbody>
<tr>
<td>1</td>
<td>The population at risk should be well defined</td>
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<tr>
<td>1.1</td>
<td>Careful criteria for exclusion of cases</td>
</tr>
<tr>
<td>2</td>
<td>Accuracy of DC (Acc DC)</td>
</tr>
<tr>
<td>2.1</td>
<td>Data on accuracy in the concerned country and for the relevant period of time should be investigated, either by conducting a substudy or consulting existing reports</td>
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<tr>
<td>2.2</td>
<td>This information should be available for the overall population and stratified by age</td>
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<tr>
<td>3</td>
<td>Mortality data should be based on ‘underlying’ and ‘contributory’ causes (Und &amp; Contrib)</td>
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<td>4</td>
<td>Examination of ALS rate time trends</td>
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<td>4.1</td>
<td>To compare ALS mortality among calendar dates, data coded with different ICD codes have to be consistent (ICD Consist)</td>
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<tr>
<td>4.2</td>
<td>Evolution of health care system over a long period of time should be considered</td>
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<td>5</td>
<td>When examining ALS variations between geographical regions, it is essential to confirm that the health care and DC systems are comparable and of high quality (Geo Access)</td>
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<tr>
<td>6</td>
<td>When examining ALS variations between ethnic groups, critical consideration of ethnic factors and access to health care is needed (Ethno Access)</td>
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</tbody>
</table>

Definition of the Population at Risk (Def Pop)

The Population at Risk Should Be Well Defined

In such studies, accurate demographic information about the population at risk must be available so that an appropriate denominator can be used. This may be a particular problem in developing countries where censuses are infrequent or where significant undercounting occurs. All but one study presented in table 2 fulfilled the definition of the population at risk (Def Pop) criterion by either indicating sources of data on the population at risk or presenting the size of the population.

Careful Criteria for Exclusion of Cases

In studies based on mortality data, it is not unusual to exclude young people under 20 years old recorded as having died from ALS [10, 35, 36]. It is worth bearing in mind that excluding young people might lead to an underestimation of incidence (albeit with low impact). On the other hand, it reduces the likelihood of false-positive cases of ALS. Some slow progressors are also sometimes excluded from mortality studies when DC data are mixed with hospital data. The use of El Escorial criteria [24, 37] is helpful as progression of the motor deficit is required to define ALS.

Accuracy of DC (Acc DC)

Data on Accuracy in the Country Concerned and for the Relevant Period of Time Should Be Investigated either by Conducting a Substudy or Consulting Existing Reports

In the literature on ALS, 2 types of study provide information about the accuracy of DC (Acc DC). Overall, they show that DC are of satisfactory quality in most countries but some variations may occur. Their results suggest that some physicians who complete DC of ALS patients may not have full knowledge of the medical history [38].

The first and less common type of study (design type A in table 3), is based on scrutiny of the national DC system in order to retrieve cases with ALS quoted as an underlying or contributory cause of death [34, 39]. In those studies, researchers used data from hospital databases or registers to assess the accuracy of DC. This approach has achieved estimated positive predictive values of 72.4% in Japan, 72.0% in the USA and 90.4% in Scotland. Other than those surveys, the literature contains reports of several morbidities leading to death that was erroneously attributed to ALS. These false-positive cases were, in fact, bulbar or pseudobulbar palsy, cerebrovascular disease [40], multiple sclerosis (MS) [39] or progressive muscular atrophy [41].
The second type of study is based on morbidity data and retrieval of DC for patients with ALS known to have died [39, 42–47] (design type B in table 3). Estimations of true positivity rates showed variations from 95% to 49% between countries, and regional differences within a given country [45]. They also provided information about the ICD codes used when ALS was not recorded, for example cardiac disease, MS, pulmonary disease, cerebrovascular disease, muscular dystrophy and neuropathy or cancer [44, 46]. Similar patterns were presented by Noonan et al. [48], who showed that when ALS was quoted as a contributory cause of death, the most common underlying causes were ischemic heart disease, cerebrovascular disease and pneumonia [46, 48]. Accordingly, Leone et al. [49] noticed that among the 21.2% of the 18,924 DC mentioning ALS as an immediate, associated or contributory cause, the most frequent underlying causes were cardiocerebrovascular diseases, influenza, pneumonia and malignant neoplasm.

Thus, depending on the study design, the information of interest is: the proportion of cases in which ALS is reported as the primary cause of death, secondary cause, or contributory cause.
**Table 3.** DC-based studies of ALS presenting information on accuracy of death certificates

<table>
<thead>
<tr>
<th>Ref. No.</th>
<th>First author</th>
<th>Country</th>
<th>Years</th>
<th>Design</th>
<th>Number of deaths</th>
<th>Primary cause in DC, %</th>
<th>Secondary cause in DC, %</th>
<th>Not mentioned in DC (FN), %</th>
<th>TPR, %</th>
<th>Number of DC</th>
<th>PPV, %</th>
<th>FP, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>34</td>
<td>Kondo</td>
<td>Japan</td>
<td>1952–1971</td>
<td>A</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>72.4</td>
<td>709</td>
<td>92.6</td>
<td>95.4</td>
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<td></td>
<td></td>
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<td>68.9–75.6</td>
<td>66.3 (61.7–70.6)</td>
<td>33.7 (29.3–38.3)</td>
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<td>82.9 (77.8–87.3)</td>
<td>95.4 (91.1–98.0)</td>
<td>17.0 (12.7–22.2)</td>
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<td>4.6 (2.0–8.8)</td>
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<td>39</td>
<td>Chancellor</td>
<td>Scotland</td>
<td>1989–1990</td>
<td>A, B</td>
<td>95</td>
<td>NM</td>
<td>NM</td>
<td>7.4 (3.0–14.6)</td>
<td>92.6</td>
<td>281</td>
<td>90.4</td>
<td>9.6</td>
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<td>95.4 (91.1–98.0)</td>
<td>72.4 (68.9–75.6)</td>
<td>27.6 (24.4–31.1)</td>
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<td>40</td>
<td>Kurtzke</td>
<td>USA</td>
<td>1963–1967</td>
<td>A</td>
<td>NA</td>
<td>NM</td>
<td>NA</td>
<td>NA</td>
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<td>709</td>
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<td>41</td>
<td>Jokelainen</td>
<td>Finland</td>
<td>1969–1973</td>
<td>B</td>
<td>157</td>
<td>92.4 (87.0–96.0)</td>
<td>3.8 (1–8.1)</td>
<td>3.8 (1–8.1)</td>
<td>96.2</td>
<td>50</td>
<td>72.0</td>
<td>28.0</td>
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<td>42</td>
<td>Dean</td>
<td>England</td>
<td>1963–1978</td>
<td>A</td>
<td>95</td>
<td>NM</td>
<td>NM</td>
<td>37.4 (33.4–41.6)</td>
<td>62.5</td>
<td>96</td>
<td>94.6</td>
<td>4.6</td>
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<td></td>
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<td>1979–1985</td>
<td>B</td>
<td>225</td>
<td>74.5 (69.9–79.6)</td>
<td>13.1 (9.3–17.7)</td>
<td>12.4 (8.7–16.8)</td>
<td>87.6</td>
<td>96</td>
<td>9.6</td>
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<tr>
<td>43</td>
<td>O’Malley</td>
<td>Ireland</td>
<td>1960–1972</td>
<td>B</td>
<td>265</td>
<td>68.3 (62.3–73.9)</td>
<td>11.3 (7.8–15.8)</td>
<td>20.4 (15.7–25.7)</td>
<td>79.6</td>
<td>42</td>
<td>79.4</td>
<td>4.6</td>
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<td>44</td>
<td>Chio</td>
<td>Italy</td>
<td>1970–1995</td>
<td>A</td>
<td>65</td>
<td>47.7 (35.1–60.5)</td>
<td>1.5 (0.03–8.3)</td>
<td>50.8 (38.1–60.4)</td>
<td>49.2</td>
<td>50</td>
<td>72.0</td>
<td>28.0</td>
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<td>45</td>
<td>Ragonese</td>
<td>Italy</td>
<td>1970–1995</td>
<td>A</td>
<td>566</td>
<td>64.3 (55.3–72.6)</td>
<td>12.7 (7.4–19.8)</td>
<td>23.0 (16.0–31.3)</td>
<td>77.0</td>
<td>50</td>
<td>72.0</td>
<td>28.0</td>
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<td>north 411</td>
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<td>64.3 (55.3–72.6)</td>
<td>12.7 (7.4–19.8)</td>
<td>23.0 (16.0–31.3)</td>
<td>77.0</td>
<td>50</td>
<td>72.0</td>
<td>28.0</td>
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<td>46</td>
<td>Hoffman</td>
<td>USA</td>
<td>1958–1963</td>
<td>A</td>
<td>72</td>
<td>66.7 (54.6–77.3)</td>
<td>5.5 (1.5–13.6)</td>
<td>27.8 (17.9–39.6)</td>
<td>72.2</td>
<td>50</td>
<td>72.0</td>
<td>4.6</td>
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<td>61.9–71.2</td>
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<td>47</td>
<td>Hudson</td>
<td>Canada</td>
<td>1978–1982</td>
<td>A</td>
<td>130</td>
<td>34.0 (25.8–42.7)</td>
<td>66.0 (57.3–74.2)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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</tbody>
</table>

FN = False negative; TPR = true positivity rate; PPV = positive predictive value; FP = false positive; NA = not applicable; NM = not mentioned. Design A: from DC national information system to hospital data or multiple sources. Design B: from hospital data to DC national information system. Design C: DC national information system only.

Imputed from the period of study. Imputed from the data. Absolute numbers of deaths in each category that were used for CI calculation were imputed from the total number of deaths and percentages of categories. Only primary causes of death were used.
and not mentioned at all; the true positivity rate; the positive predictive value, and the proportion of unknown causes of death overall.

This Information Should Be Available for the Overall Population and Stratified by Age

It is important to pay special attention to the accuracy of data on the elderly. Some biases in the ascertainment of ALS cases could lead to underestimated mortality because ALS diagnosis is recognized to be more difficult in older people.

As the age-specific ALS incidence peaks at over 65 years, this issue is of major importance. People in whom the disease onset occurs at an older age are less likely to see a neurologist, and death is more rapid (the median survival is around 6 months shorter among patients aged more than 80 years) [50]. In addition, elderly populations have more comorbidities [51] and exhibit many nonspecific ALS symptoms [9].

The identification of ALS from records is also more difficult in an elderly population; an older age at death and longer intervals between the clinical onset and death have been shown to correlate with reduced DC accuracy [45]. Furthermore, an old patient with comorbidities may die from other causes, with ALS being recorded as a contributory cause of death or ignored. For example, ALS was more likely to be listed as a contributing cause in the elderly because of the increased frequency of intervening diseases [51]. In this population, a modification of competitive causes of death also impacts on mortality data [9, 52, 53].

Due to increased life expectancy and aging of the population, the number and proportion of old people with ALS will rise progressively. In this context of aging of populations, issues of accurate diagnosis and reliable DC information are even more important.

Of the 29 studies presented in table 2, approximately 45% considered these points and reported accuracy information (Acc DC criteria) referring either to the study data or to earlier work in the same country [54]. However, none stratified results by age group to assess whether or not quality decreased for older patients.

Mortality Data Should Be Based on Underlying and Contributory Causes (Und & Contrib)

It is essential that mortality studies use underlying and contributory causes in DC (Und & Contrib) [23, 33, 35, 54, 55]. Indeed, depending on death circumstances and patient characteristics, ALS may be included under either heading. This issue is particularly important in elderly people, as reported by Gunnarsson et al. [51], who showed that the proportion of cases in which ALS was a contributory cause of death increased after 65 years of age from 10 to about 30% by the age of 80 years and above. The proportion of cases in which ALS was recorded as an underlying cause varied between studies from around 90% [9, 42, 56] to 34% [57] (design type C and some of type B in table 3).

Some studies are based on data covering only underlying causes; the reason for that is either not mentioned or stated to be unavailability of contributory causes of death [33, 36, 44, 54, 58]. Thus, the impact on the results of using only primary causes of death will vary with the proportion of cases in which ALS was recorded as a primary or a secondary cause or as unknown.

Some authors have postulated that ALS is recorded as a primary cause more often than for other neurological disorders such as Alzheimer’s disease, Parkinson’s disease [23] and MS. O’Malley et al. [43] presented data relative to ALS and MS mortality. MS was less likely to be mentioned in part I of the DC (underlying cause of death), i.e. in 45.5 versus 68.3% for ALS. Furthermore, MS was not mentioned on the DC of 26.4% of patients who had it; the figure for ALS was 20.4%. Lastly, in this study, 4 patients originally diagnosed as having ALS had MS recorded as the main cause of death, and 1 patient had both MS and MND as primary causes. Of 29 studies, 12 used both primary and secondary causes of death, 6 used only primary causes [12] and 11 did not include that information [15, 59, 60].

Examination of ALS Rate Time Trends

To Compare ALS Mortality among Calendar Dates, Data Coded with Different ICD Codes Have to Be Consistent (ICD Consist)

DC are filled out using the ICD, which has changed over time (table 4). Evolution in mortality rates cannot be attributed to modification in the ICD if the ways of coding primary and secondary causes were not impacted by the ICD changes [23].

Modifications in ICD classifications followed modification in terminology and classifications. Before approximately 1975, the nomenclature of motor neuron disorders was confusing. Progressive muscular atrophy (PMA), progressive bulbar palsy (PBP) and progressive lateral sclerosis (PLS) were considered as particular forms of MND and different from ALS. After that date, these clinical descriptions were grouped within the term MND considered as synonymous with ALS. Thus, when mortality data are based on different ICD classifications, re-
searchers have to use consistent ICD codes (ICD Consist). For example, considering the respective codes of 356.1, 348.0 and 335.2 could be misleading [9] as the two first (for ICD-7 and -8) consider the specific subtype of ALS (excluding PMA, PBP and PLS), while the ICD-9 code 335.2 considers ALS overall (including PMA, PBP and PLS).

In the literature, the most frequently used method when considering time trends with data coded according to ICD-7, -8 and -9 was to use items 356, 348 and 335.2, respectively. While acceptable, this method is not the most appropriate. Indeed one has to remember that item 356 of the ICD-7 indicated 'motor neurone disease and muscular atrophy', i.e. it contains muscular atrophies that have subsequently been separated from MND. The best approach in this context is, like Chio et al. [36], to use the following codes: 356.0 and 356.1 for ICD-7; 348.0, 348.1 and 348.2 for ICD-8, and 335.2 for ICD-9.

Thus, among 24 studies for which ICD codes were detailed in the methods section, 2 studies using ICD-7, -8 and -9 were considered as using inconsistent codes [9, 12], and another was considered as not suitable for the study of ALS or MND because it focused on MND with the G12 code of ICD-10 'spinal muscular atrophy and related syndromes' [25].

Evolution of Health Care Systems over a Long Period of Time Should Be Considered

Changes in health service provision and practitioner awareness may lead to overestimation of mortality. Improvements over recent years in ALS diagnosis may (with aging of the population) at least hypothetically explain the rise in death rates [23, 61]. The time to diagnosis has shortened in recent studies [62], perhaps reflecting improved knowledge of ALS among physicians [63]. Lastly, as extensively discussed in Seljeseth et al. [38], health care systems are better organized than they were, particularly in terms of improved access to neurologists [38, 63] and increased resources to diagnose ALS in elderly people [9]. Besides, in this Dutch study, it is postulated that an improvement in the accuracy of DC could be an explanation for the identified rise in mortality rates, and that previous underreporting of ALS in women could explain differences in ALS mortality rates by gender.

When Examining ALS Variations between Geographical Regions, It Is Essential to Confirm that the Health Care and DC Systems Are Comparable and of High Quality (Geo Access)

Variations between studies – such as in their presentation of results or, particularly, in the methods used to collect causes of death – influence the interpretation of the results or quality of the data collected. For example, in Italy, differences in ALS mortality rates between north and south have been shown to be related to differences in organization of the national health policies, which influenced DC recording [45]. Of course, this can pose real problems when comparing mortality data between countries or regions.

For example, it is difficult to accurately compare mortality data from developing countries and Europe or the USA. Thus, mortality data are better suited to comparison over time within the same country rather than between countries [64]. Most papers that report variations

Table 4. ICD codes for ALS and MND by year of publication

<table>
<thead>
<tr>
<th>Publication date</th>
<th>ICD-6, -7</th>
<th>ICD-8</th>
<th>ICD-9</th>
<th>ICD-10</th>
</tr>
</thead>
<tbody>
<tr>
<td>MND (i.e. ALS)</td>
<td>1948, 1955</td>
<td>1965</td>
<td>1977</td>
<td>1990</td>
</tr>
<tr>
<td>Subtype of ALS</td>
<td>356, 348</td>
<td>356.0, 348.0</td>
<td>included in 335.2</td>
<td>included in G12.2</td>
</tr>
<tr>
<td>Progressive muscular atrophy</td>
<td>356.1, 348.0</td>
<td>356.0, 348.2</td>
<td>included in 335.2</td>
<td>included in G12.2</td>
</tr>
<tr>
<td>Progressive bulbar palsy</td>
<td>none, 348.1</td>
<td>included in 335.2</td>
<td>included in G12.2</td>
<td></td>
</tr>
<tr>
<td>Progressive lateral sclerosis</td>
<td>none, none</td>
<td>included in 335.2</td>
<td>included in G12.2</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>356.3, 348.9</td>
<td>included in 335.2</td>
<td>included in G12.2</td>
<td></td>
</tr>
<tr>
<td>Spinal type of muscular atrophy</td>
<td>356.2, excluded from MND</td>
<td>excluded from MND</td>
<td>excluded from MND</td>
<td></td>
</tr>
</tbody>
</table>

* For ICD-6 and -7 mentioned as ‘motor neurone disease and muscular atrophy’.
* Also including the spinal type of muscular atrophy.
in mortality between or within countries emphasize the crucial point of access to care. As presented in table 2, authors considered the possible impact of geographical variations in rates of access to a neurologist or physician on diagnosis [42, 48, 51, 61, 65–67], accuracy of DC [68] and racial demographics (Geo Access) [69].

When Examining ALS Variations between Ethnic Groups, Critical Consideration of Ethnic Factors and Access to Health Care Is Needed (Ethno Access)

Comparison of ALS rates between ethnic groups is a relevant area in ALS research [64, 70]. The results of such studies [48, 49, 69] showed consistently that ALS mortality was higher in white people (close to 2/100,000) than among Hispanic and African-American people. Matsumoto et al. [68] in Hawaii compared ALS incidence and mortality between people of Caucasian, Japanese and Filipino origin and identified a slightly higher mortality in the latter group. Conclusions drawn from these studies should consider the ways in which ethnic data have been collected, comparative access to health care among ethnic groups, and the impact of socioeconomic status on access to diagnosis and, consequently, on information about causes of death (Ethno Access). In the USA, Sejvar et al. [69] addressed the possibility that greater access to care and more accurate and frequent diagnosis of ALS among white people could explain the rate difference. Leone et al. [49] raised the issue of underreporting of ALS in DC for black people. Lastly, Dean and Elian [66] compared mortality data from New Zealand, South Africa and Australia, and addressed the ethnic issue in their discussion section. Five of the 8 articles dealing with variations among ethnic groups discussed this point [49, 66, 68–70].

Synthesis

Finally, when we applied these 6 criteria (Def Pop, Acc DC, Und & Contrib, ICD Consist, Geo Access and Ethno Access) to the 29 studies (the last 2 criteria being applied when indicated), only 3 were considered ideal [40, 55, 70]. It has to be noted that the mortality rates reported by Dean [40] and Fong et al. [55] were highly consistent with incidence rates presented in the articles for the same countries and periods of time (table 5). This point indirectly reinforces the usefulness of these criteria for identifying well-suited studies and accurate results. Results from Zaldivar et al. [70] relative to mortality rates between ethnic groups in Cuba could not be compared due to lack of incidence data. Five studies tended to comply with these criteria but had to be rejected due to a lack of information in the article about ICD codes, and about whether authors used underlying and contributory causes [15, 16, 34, 51, 68].

Conclusion

The readily availability of DC data gives researchers a convenient opportunity to determine the mortality associated with ALS and thereby (given the rapidly and invariably fatal course) estimate its incidence. Mortality data are of particular value when investigating changes in ALS over time in a particular country – assuming confirmation of a homogenous system for the period of inter-

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<table>
<thead>
<tr>
<th>Country</th>
<th>Mortality rate</th>
<th>Incidence rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>first author</td>
<td>ref. No.</td>
</tr>
<tr>
<td>England</td>
<td>Dean</td>
<td>40</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>Fong</td>
<td>55</td>
</tr>
<tr>
<td>Cuba</td>
<td>Zaldivar</td>
<td>70</td>
</tr>
</tbody>
</table>

* Mortality rates could not be compared due to lack of data.

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Table 5. Comparison between mortality rates presented in studies who complied with the 6 criteria for well-suited mortality studies and incidence rates
est (from a logistical point of view and regarding compatible ICD classifications) and data of sufficient quality.

In this article we examined the ALS mortality literature using 6 good epidemiological practice criteria. We showed that a minority of articles complied with all of them. However, when studies did apply these methods, mortality rates were highly consistent with incidence rates. Criteria used in this study could be used to guide future studies based on mortality data. It could be interesting to conduct a prospective multicenter study relating mortality data to medicoadministrative data. This would have the double advantage of the possibility of evaluating the accuracy of DC and of gathering complementary data that can permit epidemiological analyses, notably survival analyses.

Acknowledgments

We thank Sandra Gresiak and Elisabeth Grelier for their help in obtaining the papers, and William Francis for editing the manuscript.

References


