Review

The epidemiology of ALS and the role of population-based registries

Ettore Beghia, Giancarlo Logroscino, Adriano Chiò, Orla Hardiman, Douglas Mitchell, Robert Swingler, Bryan J. Traynor on behalf of the EURALS Consortium

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a degenerative disorder characterized by loss of upper and lower motor neurons, culminating in respiratory insufficiency and death after 3–5 years. The disease has several peculiarities: it is fairly rare, its natural history varies with age and sex, its etiology is unknown, it cannot be prevented, and there are few if any options for the treatment of the disease and its complications.

2. ALS is a worldwide rare clinical condition

Until the mid-1990s, with the exception of the Western Pacific high-risk foci, the worldwide incidence of ALS was reported to range from 0.4 to 2.6 per 100,000 population per year [1–5] (Table 1). There are several explanations for the reported variability in the incidence. These include, among others, the variable (mostly small) sample size of the source population, completeness of case ascertainment, heterogeneity across countries, use of different diagnostic criteria, and the inclusion or exclusion of the disease variants.

The use of multiple sources of cases is fundamental to optimize case finding. The capture-recapture method is one statistical method for assessing, and adjusting for, ascertainment bias. This method has been used extensively to adjust demographic estimates in wildlife populations and has a high potential for epidemiological studies in humans [6,7]. At present, two epidemiological studies have been conducted with this methodology [8,9]. However, the use of capture-recapture methodology requires a number of assumptions, including the equal probability of ascertainment of each case in the population and the independence of the sources. By contrast, the incidence rates calculated from patients enrolled in population-based registries of ALS are fairly homogeneous, ranging from 1.7 to 2.3 cases per 100,000 per year [10–15]. There are several reasons for the higher and more homogeneous incidence rates of ALS, as reported in these population-based registries. First, in each registry there was a prospective inception of cases (with consequent minimization of patients’ losses). Second, all registries referred to multiple sources for case ascertainment (which brought to an almost complete identification of the affected individuals who received medical attention). Third, there was a continuous surveillance of the disease, based on the

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intrinsic mechanisms of the registration process. Last, similar diagnostic criteria were adopted, with one exception (the Scottish registry used slightly different criteria until 1994, the year of dissemination of the El-Escorial criteria) [16].

3. Unanswered questions in the epidemiology of ALS

Several questions on the epidemiology of ALS still remain unanswered. (1) Is the incidence of ALS really increasing? (2) Is ALS an age-related or an aging-related disease? (3) Is the incidence of ALS in women lower than in men? (4) Are there environmental risk factors for ALS? (5) Do we know the full spectrum of ALS? 6. Can we identify early prognostic predictors?

4. Is the incidence of ALS increasing?

There are several observations in the literature supporting the concept of an increasing incidence of ALS. To verify this assumption, a prolonged observation of a defined population is required. This was done in Scotland by monitoring the incidence rates during the decade 1989–1998. As shown in Fig. 1, there are several fluctuations of the incidence of the disease both in men and in women (mostly explained by the small sample size) without a consistent trend over the decade. This observation was confirmed by the studies done in the Rochester population [17,18] and supports the concept that the apparent increase in the incidence of ALS depends on an increasing case ascertainment based on a better diagnostic assessment of the disease, especially in women and in the elderly, in the context of the aging general population (see below).

5. Is ALS an age-related clinical condition?

ALS is extremely rare under age 30 and almost unheard under 20. In contrast, the disease is commoner in patients in...
their 50s and 60s with a clear increase with age until the seventh decade. However, there is still insufficient evidence to conclude that ALS is an age-related or an aging-related disease. The difficulty in ascertaining ALS in the elderly makes this question even more difficult to answer. This difficulty arises from problems with differential diagnosis between ALS and other clinical conditions in the elderly and the likelihood of a different (and less easily ascertained) course of the disease in this age group (a population with numerous comorbidities affecting muscle strength and motion). The elderly are also less likely to encounter neurological services. Differences in care for the elderly were mentioned in the Scottish register, where subjects older than 80 were less likely to be visited by a neurologist and be prescribed riluzole [19]. Musculoskeletal pain and fatigue are the most commonly reported symptoms by older adults [20]. In contrast, delivery of routine medical services is suboptimal in this population [21]. More specifically, misdiagnosis of ALS appears to be more common in patients above age 60 [22]. All these issues may explain under ascertainment of ALS in the elderly. However, we cannot exclude the possible relevance of an exposure to one or more unknown environmental factors with a specific latency period in the pathogenesis of ALS. It is possible that subjects who survive beyond the age of 80 are protected against motor neuron damage either because they are genetically unsusceptible to the putative causative influence or the exposure occurred after a critical age [23]. A careful examination of well-designed population-based studies seems to provide an explanation for an age-related increase in the incidence of ALS. The only study (done in Rochester, Minnesota, US) [24], which showed an exponential increase in the incidence of the disease was performed in a small sample of patients. A more recent study (when the calculations were made on a larger sample) showed a peak in the 60-to 69-year age group, consistent with several other populations [18].

6. Is there an increasing incidence of ALS in women?

Table 2 presents the results of several studies in the last 40 years [12]. Comparing the oldest to the most recent publications, there is a significant decrease in the male/female ratio, which falls from 2.6 to 1 (in the decade 1965–1974) to 1.1 to 1 (in the 1990s). Data from Rochester, Minnesota [18,24] also show a slight decrease in the male/female ratio over a 73-year period (ranging from 1.2 in the period 1925–1984 to 1.0 in 1998). These differences can be explained in part by different study design (retrospective in the oldest and prospective in the most recent studies) and by the different geographic distribution of the studies. A higher ascertainment rate could be also expected in women in the most recent studies, based on the higher chance of (older) women than men to seek medical advice [25]. However, an increasing exposure of women to the same (unknown) environmental factors as those postulated for men cannot be excluded. This assumption may be justified by the changing lifestyle of women, which has become more similar to that of men. Following socioeconomic changes during the last century, women are increasingly exposed to occupational and environmental risk factors, which may differ across geographic areas. An increased risk for ALS was found among smokers [26,27], and a cohort study showed an increase in risk among women but not men [28].

7. Is the mortality of ALS increasing?

This question implies an assumption that the incidence of ALS is increasing. Table 3 shows a consistent increase over time in the mortality of ALS comparing different periods of observation in the same populations [3]. This finding supports the observation of a decline in survival of patients in a 10-year prospective, population-based registry of the disease in Scotland [29] and the 50% increase of mortality reported from the US National Center for Health Statistics during the period 1969–1998 [30]. These trends could be explained by the increasing reliability of death certificates coupled with an increased awareness of the disease among physicians and lay people. However, there are still several concerns regarding the quality of death certification, especially when different geographic areas are compared. In a recent study in Italy comparing the North and the South of the country, the rate of the true positives (i.e., the ratio between the cases with ALS documented in the death certificates and those in which the disease was confirmed in the medical records) was 66.7 vs. 51.6% [31]. Another possible explanation is the so-called Gompertzian effect (i.e., the conflict among different causes of death, which means a change in the causes of death with the aging of the general population). Alternative explanations include an increasing ALS mortality in elderly women (as above indicated), and a change in the prevalence of some (unknown) environmental factors.

The effects of the increasing age of the general population are the best explanation for the increase in mortality from ALS, which was found in Norway during the period 1961–1994 [32]. In that study, the increase was entirely confined to patients aged 65 years or older. This is in keeping with other reports, which
showed an increase in ALS mortality in the elderly, particularly in women [33,34].

8. Environmental risk factors in ALS

The assessment of the environmental risk factors in ALS is still far from optimal, as shown by the high number of observations of uncertain etiological significance [35]. These include conjugal ALS (i.e., the disease has occasionally been reported in husband and wife), correlation with antecedent poliomyelitis or concurrent neoplasms (adenocarcinoma, lymphoma, adenoma), exposure to (heavy) metals (including lead, mercury and selenium), to solvents or to electrical or electromagnetic fields, mechanical trauma, heavy physical activity, and living in rural areas or using chemical substances in agriculture. These and other factors were examined by Carmel Armon [36] (Table 4), who performed a systematic review of the published literature and selected the five studies supported by the best methodology. Three of these studies were conducted in the United States (in the Washington State, in the New England, and the Mayo Clinic), one in Scotland and one in Italy.

For each factor, the evidence was graded from I (best) to IV (worst). As shown by the table, most of the available evidence was at best fair (grade III). Interestingly, cigarette smoking was the only risk factor supported by fairly good epidemiological evidence (two of three studies providing grade II evidence). This observation supports the assumption that the increasing incidence of ALS in women can be explained by changing lifestyles and increasing exposure to risk factors previously limited to males. Despite these findings, some recent observations have re-linked the interest of ALS researchers in environmental risk factors. A recent note in the Lancet Neurology discussed observations on professional sports and the risk of ALS [37]. Of 24,000 Italian soccer professionals who played between 1960 and 1997, eight died from ALS. The number of cases expected in the same cohort was 0.61, giving a tenfold increase in risk among soccer players. This observation was confirmed, although with more conservative figures, by a more recent study looking at mortality from ALS in a cohort of 7325 male football players followed for 137,078 person–years [38]. Five ALS cases were found in this cohort. The number of expected cases was 0.77, the overall standardized morbidity ratio was 6.5. The risk was 7.5 in the age classes 15–49 years and 13.8 among professionals playing during the decade 1980–1989. The position played was significantly correlated to the disease risk, with midfield players ranking highest (12.2). As well, the risk was highest in individuals playing 5 years or longer (15.2). These epidemiological findings appear biologically plausible because soccer as a professional sport is characterized by heavy physical activity, repeated traumatic events, and exposure to toxic contact agents or noxious drugs. In fact, there is indirect evidence of an increased production of reactive oxygen species (ROS) when combining strenuous exercise with other factors (dietary habits, drugs, ischemia followed by reperfusion) [39]. Oxidative stress can potentially induce detrimental changes in crucial metabolic functions including nucleic acid damage [40,41].

However, despite these apparently striking findings, the strength of the association between physical activity, soccer and other professional sports and ALS is still ill-defined [42–46]. In contrast to clinical findings in man, prolonged vigorous exercise does not promote onset or progression of motor neuron degeneration in SOD-1-mediated ALS in experimental animals [47]. In this context, a large multicenter study combining the data from population-based registries may provide definite evidence in favor or against a true causal association.

9. The ALS spectrum of severity

ALS is a severe clinical condition with a high mortality rate. Different studies have consistently shown that 70–80% of cases die within 5 years [48] (Fig. 2). However, the slope of the curves

<table>
<thead>
<tr>
<th>Variable</th>
<th>WA, USA</th>
<th>NE, USA</th>
<th>Scotland</th>
<th>Mayo</th>
<th>Italy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical activity</td>
<td>(II)</td>
<td>+ (IV)</td>
<td>− (III)</td>
<td>+ (II)</td>
<td>− (II)</td>
</tr>
<tr>
<td>Chemicals</td>
<td>+ (II)</td>
<td>+ (III)</td>
<td>− (II)</td>
<td>(II)</td>
<td>+ (II)</td>
</tr>
<tr>
<td>Sport</td>
<td>+ (II)</td>
<td>+ (III)</td>
<td>(II)</td>
<td>(II)</td>
<td>+ (II)</td>
</tr>
<tr>
<td>Family hx (*)</td>
<td>− (II)</td>
<td>(II)</td>
<td>+ (IV)</td>
<td>(II)</td>
<td>− (II)</td>
</tr>
<tr>
<td>Trauma</td>
<td>(II)</td>
<td>+ (II)</td>
<td>(II)</td>
<td>(II)</td>
<td>+ (II)</td>
</tr>
<tr>
<td>Electric shock</td>
<td>(II)</td>
<td>(II)</td>
<td>(II)</td>
<td>(II)</td>
<td>(II)</td>
</tr>
<tr>
<td>Rural area</td>
<td>(II)</td>
<td>(II)</td>
<td>(II)</td>
<td>(II)</td>
<td>(II)</td>
</tr>
<tr>
<td>Cigarette</td>
<td>+ (II)</td>
<td>(II)</td>
<td>(III)</td>
<td>(II)</td>
<td>(II)</td>
</tr>
<tr>
<td>Alcohol</td>
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<td>− (III)</td>
<td>− (II)</td>
<td>(II)</td>
<td>− (II)</td>
</tr>
<tr>
<td>Diet</td>
<td>+ (V)</td>
<td>+ (V)</td>
<td>+ (V)</td>
<td>+ (V)</td>
<td>+ (V)</td>
</tr>
<tr>
<td>Metals</td>
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<td>+ (II)</td>
<td>+ (II)</td>
<td>+ (II)</td>
<td>+ (II)</td>
</tr>
<tr>
<td>Manual work</td>
<td>+ (III)</td>
<td>+ (III)</td>
<td>+ (III)</td>
<td>+ (III)</td>
<td>+ (III)</td>
</tr>
<tr>
<td>Poliomyelitis</td>
<td>− (IV)</td>
<td>− (IV)</td>
<td>− (IV)</td>
<td>− (IV)</td>
<td>− (IV)</td>
</tr>
</tbody>
</table>

(*) Family history of neurodegenerative diseases.
+ = found to be a risk factor; − = not found to be a risk factor; +/- = evidence was uncertain.
(II) Cohort studies with parallel controls with exposure established before/without knowledge of diagnostic status; population-based case-control studies with putative risk factor occurring before probable biologic onset of disease and complete case ascertainment.
(III) Bias or confounding may account for the findings regarding risk factor, but not to the extent that would invalidate findings.
(IV) All other studies with controls with risk factor occurring before biological disease onset; results not attaining statistical significance; results of post-hoc analyses, uncorrected for multiple comparisons.
(V) Studies with risk factor most likely occurring after biological disease onset or uncontrolled data.
WA = Washington; NE = New England.
Source: [36].
of progression, site of symptom onset (bulbar vs. spinal), severity with the differential diagnosis between ALS and other motor neuron disorders [16] may explain the variability of the disease severity in a well-defined population. Several prognostic predictors have been implicated. These include age at onset of symptoms, age at diagnosis, disease duration, rate of symptom progression, site of symptom onset (bulbar vs. spinal), severity of respiratory impairment, and the use of enteral nutrition and/or assisted ventilation. However, the only variables found to independently predict the outcome of ALS include age [17,50–55], site of onset [50,53–58], and the speed of symptom progression [54,59]. In a recent US study [55], the role of several prognostic factors was assessed in predicting 12-month survival. In this study, better survival was predicted by a younger age, spinal onset, less severe disease at the time of the first visit, body mass index loss lower than 5%, and a life lived with a partner. Significantly younger age at onset and predominance of pure upper motor neuron signs at presentation characterized the long-term survivors in another large referral ALS population [60]. Enteral nutrition and assisted ventilation are the possible explanation of the tendency to longer survival of ALS, which was documented in a recent study done in Italy in a small sample of patients from a population-based registry. Every diagnostic classification of ALS must include a correct definition of the population at risk, the selection of the proper sources of cases, and the choice of correct diagnostic criteria.

If one considers that a predefined proportion of cases are affected by the disease in question, some patients may escape as being asymptomatic. Although we do not know if this is the case with ALS, it cannot be excluded that some individuals may show pathological signs of motor neuron degeneration in the absence of clear clinical symptoms and signs. These cases fall into the category “asymptomatic”. Some of these patients may be traced at the time of a medical examination for other unrelated clinical problems. Not all symptomatic patients are seen in medical facilities. The oldest patients or those with milder variants may even escape medical detection. A few additional cases may be traced through death certificates and/or autopsy series. This implies the need to refer to multiple sources (as above indicated) when trying to obtain the best ascertainment of ALS cases in a given population.

The sources of ALS patients are multiple and include hospital records, outpatient records, neurophysiology archives, general practitioners’ archives, disability records, lay associations’ files, ad-hoc comprehensive health care facilities (ALS centers), death certificates, and administrative files (e.g., hospital discharge diagnoses, HDD). Hospital records, neurophysiology archives, death certificates and HDD are among the best sources of cases for a population-based registry of ALS.

The choice of the best ALS diagnostic criteria is another relevant problem at the time of implementation of a disease registry. Every diagnostic classification of ALS must include signs of involvement of the upper (UMN) and lower (LMN) motor neuron, evidence of disease progression, and exclusion of other clinical conditions, which may explain the clinical picture. As new classification of ALS was devised in 1990 in El Escorial, Spain, which is now broadly used for the diagnosis of the disease for research and practical purposes. According to this classification [16], four diagnostic categories were identified, defining the level of diagnostic accuracy on the basis of the involved regions (bulbar, cervical, thoracic, and lumbo-sacral) and the presence of UMN and LMN signs. Definite ALS is characterized by ULM and LMN signs in at
least three regions; probable ALS is characterized by UMN and LMN signs in at least two regions with upper signs rostral to lower signs; possible ALS is defined by the presence of ULM and LMN signs in one region, UMN signs alone in two or more regions, or LMN signs rostral to upper signs; suspected ALS is defined by lower signs in two or more regions. The classification was revised in 1999 in Airlie House [68] with the inclusion of the category “clinically probable laboratory supported ALS”, which is characterized by the presence of clinical signs of UMN and LMN dysfunction in one region, or UMN signs alone in one region with LMN signs defined by EMG criteria in at least two limbs and exclusion of other causes by clinical laboratory and neuroimaging. In the Airlie House classification, the category “suspected ALS” was deleted. The El Escorial classification and its revised version have several advantages, which include the high specificity, due to the fairly low number of false positives [48,69], and the ease of use in randomized clinical trials, which promotes uniformity of assessment of drug efficacy and permits meta-analysis of different trials. However, this classification has also several disadvantages, which include its difficult application to clinical practice, its excessive rigidity (for example, the category “possible ALS” can be invariably considered ALS only when other exclusion criteria are used), and the assumption that ALS is a single disease entity. The limitations of the El Escorial classification are exemplified by the results of studies on the survival of ALS, which showed that approximately 10% of cases die while still being classified as possible or suspected ALS [48]. Then, in a study assessing the reliability of the El Escorial classification [70], the inter-rater agreement (measured by the kappa statistic) was found to be poor when neurologists from different backgrounds were asked to examine the medical records of a number of patients with ALS or other clinical conditions. The agreement was significantly improved after discussion and training, which means that the El Escorial classification can be correctly used when the caring physicians are appropriately trained.

On this basis, a prospective population-based registry was started in Lombardy, a region of Northern Italy (total population 4,947,554) on 1st January 1998. This Lombard registry is one of the three active Italian population-based registries, which are all included in the European ALS Consortium (named EURALS). EURALS is a consortium of population-based registries (Italy, Scotland, Ireland, England (Lancashire and Cumbria)) and clinic-based cohorts (Russia, Serbia, London, Madrid, Limonges, and Israel). The main aims of EURALS are: (1) to provide an answer to key epidemiological questions (among which the incidence of ALS in the very old, the male/female ratio, and the aggregation of ALS within families); (2) to perform case-control studies on risk factors for ALS; (3) to explore the heterogeneity of ALS and identify the principal phenotypes, which provide the basis for genetic studies.

EURALS was established in October 2004 at a consensus meeting in Amsterdam [71]. When a formal agreement was obtained by the members of the steering committee on the processing of sensitive data, informed consent, use and disclosure of information, and security provisions, a password-protected database was implemented. The database is located in the Mario Negri Institute in Milan. The data are available to the principal investigators of each participating country. The steering committee also manages all the principal collaborative research projects. The website was launched in December 2005 with an ongoing collection of ALS incident cases from the population-based registries. However, in order to ensure proper case registration, a validation study of the El Escorial diagnostic criteria is in course. In this study, up to 30 consecutive ALS patients and 20 controls are recruited by each participating country. Where needed, the medical records

<table>
<thead>
<tr>
<th>Country</th>
<th>ALS Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ireland</td>
<td>5.0 M</td>
</tr>
<tr>
<td>Scotland</td>
<td>5.0 M</td>
</tr>
<tr>
<td>Lancashire &amp; Cumbria</td>
<td>1.8 M</td>
</tr>
<tr>
<td>London</td>
<td>1.0 M</td>
</tr>
<tr>
<td>Italy (all)</td>
<td>13.0 M</td>
</tr>
<tr>
<td>Belgrade</td>
<td>2.0 M</td>
</tr>
<tr>
<td>Madrid</td>
<td>1.0 M</td>
</tr>
<tr>
<td>France</td>
<td>1.5 M</td>
</tr>
<tr>
<td>Russia</td>
<td>14.0 M?</td>
</tr>
<tr>
<td>Israel</td>
<td>7.0 M</td>
</tr>
</tbody>
</table>
of these patients are translated into English and then made accessible to each investigator in the web site. Every case and control will be classified according to the classical and revised El Escorial criteria. The degree of inter-rater agreement will be then tested with the kappa statistic.

The total European population at risk is in excess of 30 million, of which more than 25 million are from the established population-based registries (Fig. 3). Other registries are being implemented in the Russian Federation (about 14 million) and in Israel (7 million). On this basis, at least 500 patients with newly diagnosed ALS could be registered every year by the European population-based registries (and many more from the other sources). This sample has sufficient power to address most if not all the unanswered questions in the epidemiology of ALS.

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References

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