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Epidemiology of amyotrophic lateral sclerosis: A review of literature

P. Couratier [a,b,*], P. Corcia [c], G. Lautrette [a], M. Nicol [a], P.-M. Preux [b], B. Marin [b]

[a] Centre de compétence SLA-fédération Tours-Limoges, CHU de Limoges, 2, avenue Martin-Luther-King, 87000 Limoges, France
[b] Inserm UMR1094, neuroépidémiologie tropicale, université de Limoges, 2, rue du Dr.-Marcland, 87025 Limoges cedex, France
[c] Centre de compétence SLA-fédération Tours-Limoges, CHU de Tours, 37044 Tours cedex 9, France

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ABSTRACT

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease of motor neurons, resulting in worsening weakness of voluntary muscles until death occurs from respiratory failure. The incidence of ALS in European populations is two to three people per year per 100,000 of the general population. In Europe, crude prevalences range from 1.1/100,000 population in Yugoslavia to 8.2/100,000 in the Faroe Islands. Major advances have been made in our understanding of the genetic causes of ALS, whereas the contribution of environmental factors has been more difficult to assess and large-scale studies have not yet revealed a replicable, definitive environmental risk factor. The only established risk factors to date are older age, male gender and a family history of ALS. Median survival time from onset to death is usually 3 years from the first appearance of symptoms. Older age and bulbar onset are consistently reported to have poorer outcomes. However, there are conflicting data regarding gender, diagnostic delay and El Escorial criteria. The rate of symptom progression has been revealed to be an independent prognostic factor. Psychosocial factors and impaired cognitive function are negatively related to ALS outcome, while nutritional status and respiratory function are also related to ALS prognosis. The effect of enteral nutrition on survival is still unclear, although noninvasive positive pressure ventilation (NIPPV) has been found to improve survival. These findings have relevant implications for the design of future trials.

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease of motor neurons that results in relentlessly progressive paralysis. Death is usually from respiratory failure, typically within 3 years of disease onset. Diagnostic criteria assume that clinical presentations are subdivided into bulbar-onset and spinal-onset disease, and by the degree of upper and lower motor neuron involvement [1]. However,

* *Corresponding author*. Service de neurologie, CHU de Limoges, 2, avenue Martin-Luther-King, 87000 Limoges, France.
E-mail address: philippe.couratier@unilim.fr (P. Couratier).
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these criteria are facing some criticism. Recent population-based epidemiological research has confirmed the existence of many different subtypes of ALS, comprising a wide clinical and pathological spectrum [2]. In addition to the presence of subcategories of ALS based on phenotype and genetics, there are also pathological subtypes of ALS that partially overlap with the clinical phenotype and genetic substrate. Most patients with ALS have ubiquitinated inclusions that stain for transactive response (TAR) DNA-binding protein 43 (TDP-43) [3]. Those with mutations in either *SOD1* or *FUS* have different pathological signatures, with inclusions staining for the relevant mutated protein. Repeat expansion in *C9orf72* is associated with a characteristic signature, with more extensive deposition of TDP-43 and p62 in the frontal region and in neurons of the CA4 region of the hippocampus [4].

Recent population-based studies have analyzed the rates of incidence and prevalence of ALS within populations of European extraction. However, the search for risk factors (lifestyle, environmental factors) has been more challenging because of the risk of methodological biases. Yet, the study of prognostic factors appears absolutely crucial not only for clinical practice, but also for determining the design of future therapeutic trials. The objective of the present literature review is to provide an update of the key data from epidemiological studies of ALS.

2. Incidence and prevalence

Nearly all population-based epidemiological studies of ALS have been conducted in Europe, and the findings are relatively consistent [5–9]. ALS is generally more common in men than in women by a factor of between 1.2 and 1.5 [10]. The incidence of ALS in European populations is two to three people per year per 100,000 general population [11]. In France, data are collected by the FRALim ALS registry [12], which showed that the crude ALS incidence in Limousin was 3.19/100,000 person-years of follow up (PYFU; 95% CI: 2.81–3.56). After standardization on the European population, the incidence was 2.58/100,000 PYFU (95% CI: 2.27–2.89) and the standardized incidence gender ratio was 1.3. ALS incidence showed a progressive rise with age, culminating in a large peak between ages 65 and 85 years of $>$ 10/100,000 PYFU. The highest value was seen in the 75 to 79-age band (11.53/100,000 PYFU). Also, incidences did not evolve in parallel in males (M) *vs* females (F); the gender incidence ratio (M:F) was 1.3 overall, but 1.1 in those aged $<$ 65 years, 1.7 between ages 65 and 75 years, and 1.9 in those aged $>$ 75 years. According to these results, it may be speculated that three to four incident ALS cases are diagnosed every day in France. While there is no definitive evidence that the age-adjusted rates of ALS are increasing with time, subtle changes in period and cohort effects make retrospective comparisons difficult.

Prevalence estimates from prospective studies were higher (median [interquartile range, IQR]: 7.89 [6.25, 7.98]) than estimates from retrospective studies (median [IQR]: 4.04 [3.92, 4.70]). In Europe, crude prevalence rates ranged from 1.1/100,000 population in Yugoslavia [13] to 8.2/100,000 in the Faroe Islands [14]. In France, depending on the duration of evolution, the number of ALS patients is approximately 6000. ALS rates outside of populations of European descent are less well characterized. Prospective population-based studies from South America have been confined to Uruguay, the population of which is primarily of European origin, and ALS rates there were similar to those of southern European countries [15]. There is also some evidence that the frequency of ALS may be lower in populations with greater degrees of admixtures, and lower rates have been reported in those of mixed ancestry in Cuba [16]. Nevertheless, insufficient data are available to determine the true rates of ALS in large parts of the world, including Africa, Russia, India, large parts of Asia and other countries in South America. A particularly high frequency of ALS that often presents with parkinsonism and dementia was described in the Chamorro tribe, who live on the Pacific island of Guam [17]. A similarly high frequency of ALS has been reported in two separate areas in the Kii Peninsula of Honshu island in Japan, although the higher rates observed there may be partly attributable to a confounding effect of the *C9orf72* mutation [18].

Demographic and phenotypic comparisons across geographical populations are limited by a paucity of high-quality data, although European studies have suggested subtle variations in the frequency of bulbar-onset disease with a possible north–south gradient [19]. The worldwide population-based frequency of cognitive and behavioural impairment in ALS has not been established. A population-based incident study from Ireland reported that 13% of cases have ALS–frontotemporal dementia (FTD), and a further 40% have evidence of cognitive impairment [20]. Those with the *C9orf72* repeat expansion were more likely to exhibit cognitive changes and, as *C9orf72* expansion is not uniformly distributed around the world, it is likely that rates of cognitive and behavioral impairment will also vary. In addition, other genetic factors with local confounding effects and particular phenotypes cannot be discounted, as demonstrated in North Africa, where high rates of recessive disease have been noted; in Sardinia, where the majority of familial ALS cases can be attributed to variants in *TARDBP* and *C9orf72*; in Finland, where repeat expansion in *C9orf72* accounts for the majority of ALS cases; and in Sweden, where a high frequency of the recessive Asp90Ala *SOD1* variant is observed [21].

Aggregation of other neurodegenerative diseases within ALS kindreds has been reported in European populations. While the clinical phenotypes associated with the *C9orf72* repeat expansion account for a large proportion of this aggregation, increased rates of neuropsychiatric disease have also been reported in non-*C9orf72* kindreds, suggesting that, in some populations, ALS may share genetic susceptibilities with neuropsychiatric illnesses [22].

2.1. *Geographical clustering*

The best-known examples of such clusters of ALS cases are those observed on the island of Guam (which have now dropped to average incidence levels) and the Kii Peninsula. The phenotype of ALS seen in these areas might be somewhat atypical, as it can occur with Parkinson's disease and dementia. Also, other population-based studies have found clustering of ALS cases beyond what would be expected by chance. In Finland, a study examining ALS incidence clusters