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Rate of familial amyotrophic lateral sclerosis: a systematic review and meta-analysis

Susan Byrne,1,3 Cathal Walsh,2 Catherine Lynch,1 Peter Bede,1,3 Marwa Elamin,1,3 Kevin Kenna,3 Russell McLaughlin,3 Orla Hardiman1,3

ABSTRACT

Background The population rate of familial amyotrophic lateral sclerosis (FALS) is frequently reported as 10%. However, a systematic review and meta-analysis of the true population based frequency of FALS has never been performed.

Method A Medline literature review identified all original articles reporting a rate of FALS. Studies were grouped according to the type of data presented and examined for sources of case ascertainment. A systematic review and meta-analysis of reported rates of FALS was then conducted to facilitate comparison between studies and calculate a pooled rate of FALS.

Results 38 papers reported a rate of FALS. Thirty-three papers were included in analysis and the rate of FALS for all studies was 4.6% (95% CI 3.9% to 5.5%). Restricting the analysis to prospective population based registry data revealed a rate of 5.1% (95% CI 4.1% to 6.1%). The incidence of FALS was lower in southern Europe. There was no correlation between rate of FALS and reported SOD1 mutation rates.

Conclusion The rate of FALS among prospective population based registries is 5.1% (CI 4.1 to 6.1%), and not 10% as is often stated. Further detailed prospective population based studies of familial ALS are required to confirm this rate.

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease which was first described by Charcot in the mid-nineteenth century. It is predominantly a sporadic disease but a small percentage of cases occur within kindreds.1

In 1955, Kurland et al published a case series of 58 patients in which 10% reported a family history of ALS.2 Although subsequent publications have reported varying rates of familial amyotrophic lateral sclerosis (FALS), the figure of 10% remains as the accepted population frequency of FALS.3–7

There is no definitive definition for FALS. It is generally accepted that the presence of ALS in either a first or second degree relative of the index case constitutes the familial form of the disease. Genes known to be associated with FALS include SOD1, TARDBP, FUS and ANG.8 The frequency of SOD1 mutations has been estimated to account for 10–20% of all FALS cases.6 This estimate is not population based and most studies preferentially recruit patients with familial ALS.9 10 To date only one population based estimate of SOD1 frequency has been carried out, reporting a rate of 13.6%.6 Estimation of the rates of SOD1 related FALS is also confounded by the occurrence of mutations in up to 5% of the sporadic population, some of whom represent familial disease with incomplete penetrance.12 The population frequency of the other known causative genes within populations has not been established.

We performed a systematic review and meta-analysis of all studies that presented original data reporting a rate of FALS (ie, the proportion of familial cases among all ALS cases, either in a defined population or in a case series). Analysis of the population based frequency of FALS was then undertaken and, where possible, a geographic comparison was made with the frequency of known SOD1 mutations.

METHODS

Systematic search

A Medline literature search was performed to identify all published studies on FALS, in addition to ALS incidence and prevalence studies from 1966 to October 2009. The MeSH terms ‘ALS’, ‘amyotrophic lateral sclerosis’, ‘FALS’, ‘familial amyotrophic lateral sclerosis’, ‘familial motor neuron(e) disease’, ‘motor neuron(e) disease’, ‘MND’, ‘incidence’, ‘prevalence’ and ‘mortality’ were used. Additional references were sought from cited articles. Where no information was reported on the rate of FALS in a population based study, the corresponding author was contacted where possible. Unpublished up to date data from the Irish ALS prospective population based register was also used.

Eligibility criteria and data collection

All studies presenting original data that reported a rate of FALS (ie, the proportion of familial cases within a defined cohort) were included in the systematic review. Only studies that demonstrated complete enrolment, either in the form of population based registry or in sequential case series, were analysed. Studies with non-random enrolment or cohorts enriched for familial disease were not included in analysis.

Studies fulfilling inclusion criteria were grouped together according to the type of data presented: (1) prospective registry based studies that aim to capture all cases within a given geographic region in order to define incidence and prevalence; (2) retrospective studies that attempt to capture all cases in a given geographic region with the aim of estimating incidence and prevalence; (3) prospective cases series; and (4) retrospective case series.
Table 1  Comparison of the type of study, rate of familial amyotrophic lateral sclerosis, source of case ascertainment and case inclusion criteria for each study

<table>
<thead>
<tr>
<th>Country</th>
<th>Years</th>
<th>FALS Total ALS</th>
<th>% FALS</th>
<th>Ascertainment</th>
<th>Diagnosis</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Puglia, Southern Italy</td>
<td>1998–1999</td>
<td>2 130</td>
<td>1.50</td>
<td>A, B, C, D, G, K</td>
<td>Bi, H, J, L, N</td>
<td></td>
</tr>
<tr>
<td>Piemonte, Northern Italy</td>
<td>1995–2004</td>
<td>53 1260</td>
<td>4.20</td>
<td>A, D, H</td>
<td>Bi, N</td>
<td></td>
</tr>
<tr>
<td>Uruguay</td>
<td>2002–2003</td>
<td>6 143</td>
<td>4.20</td>
<td>A, B, H, J</td>
<td>Bi, I, K, M</td>
<td>States based on detailed family history</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group 2: retrospective population based study</th>
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</thead>
<tbody>
<tr>
<td>Rochester, USA</td>
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<tr>
<td>Modena, Italy</td>
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<tr>
<td>Middle Finland</td>
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<tr>
<td>Northern Sweden</td>
</tr>
<tr>
<td>Cantabria, Spain</td>
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<tr>
<td>Sardinia, Italy</td>
</tr>
<tr>
<td>South-West Greece</td>
</tr>
<tr>
<td>Belgrade, Yugoslavia</td>
</tr>
<tr>
<td>Northern Denmark</td>
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<tr>
<td>Hordaland, Norway</td>
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</table>

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<tr>
<th>Group 3: prospective case series</th>
</tr>
</thead>
<tbody>
<tr>
<td>Texas, USA</td>
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<tr>
<td>New York, USA</td>
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<tr>
<td>Colorado, USA</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Group 4: retrospective case series</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brazil</td>
</tr>
<tr>
<td>London, UK</td>
</tr>
<tr>
<td>Rochester, USA</td>
</tr>
<tr>
<td>Lazio, Italy</td>
</tr>
<tr>
<td>Novia Scotia, Canada</td>
</tr>
<tr>
<td>Leuven, Belgium</td>
</tr>
<tr>
<td>Israel</td>
</tr>
</tbody>
</table>

**Key**

- **A**: Prospective register
- **B**: All neurologists
- **C**: Multicentre hospital records
- **D**: Multicentre discharge records
- **E**: Single centre hospital records
- **F**: Single centre discharge records
- **G**: ALS association records
- **H**: Death certificates
- **I**: Compulsory reporting
- **J**: EMG archives
- **K**: Control drug registry
- **L**: Private neurologists
- **M**: Questionnaire

**Diagnostic criteria**

- **A**: Post mortem
- **B**: El Escorial criteria
- **C**: EEC definite, probable
- **D**: EEC definite, probable, suspect
- **E**: Simplified EFN criteria
- **F**: Diagnosed by neurologist pre-criteria
- **G**: ALS rated using institutions own scoring system
- **H**: SMA included
- **I**: SMA excluded
- **J**: PMA included
- **K**: PMA excluded
- **L**: PLS included
- **M**: PLS excluded
- **N**: EMG >80% patients
- **O**: EMG <80% patients

ALS, amyotrophic lateral sclerosis; EEC, El Escorial criteria; FALS, familial amyotrophic lateral sclerosis; PMA, progressive muscular atrophy; PSP, progressive supranuclear palsy; SMA, spinal muscular atrophy; WFN, World Federation of Neurology.
Statistical analysis
In each study the rate of FALS is reported as the number of familial cases among all cases of ALS. Statistical analysis was carried out to combine proportions using the Meta function of R (R Development Core Team (2009). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0 http://www.R-project.org/).

The inverse variance method was used to pool proportions. Both fixed and random effects models were estimated and 95% CIs were calculated.

RESULTS
Systematic review
Fifty-four epidemiological studies provided original information on cohorts of patients with ALS. A rate of FALS was reported in 38 of these studies, although in no case was FALS ascertainment the primary objective. Five studies were not included in the analysis. Of these, two were undertaken to genotype mutations in the ALS population. Both studies exhibited enrolment bias. Three studies reported data on more than one occasion and therefore only the most recent study was included in the meta-analysis. Reports from geographical areas with high incidence clusters (Guam/Kii Peninsula of Japan) were excluded.

Of the 33 studies analysed, eight reported incidence data from prospective population based registers, 14 reported retrospective incidence and prevalence data, three reported data from prospective case series of disease progression, and eight reported data from retrospective case series. Only two studies stated how they defined FALS. In total, 575 cases of FALS were recorded among 11 221 reported cases of ALS.

The type of study, rate of FALS, source of case ascertainment and case inclusion criteria are outlined in table 1.

Meta-analysis
Pooled analysis of all studies generated a rate of FALS of 4.6% (95% CI 3.9% to 5.5%) (table 2).

A degree of heterogeneity was noted between reported rates of FALS in the prospective population based registers available for analysis. The pooled result for rate of FALS for these studies was 5.1% (95% CI 4.1% to 6.1%). In the 14 retrospective population based studies, the pooled result for rate of FALS was 3.7% (95% CI 2.9% to 4.7%).

Figure 1 demonstrates a Forrest plot of the results.

The individual rate of FALS for each country in Europe was plotted on a map to determine a possible geographic pattern (figure 2).

Regions of relatively homogenous genetic origin, such as Ireland and Scotland (both of which both have large prospective databases of over 1200 patients) exhibit almost the same rate of FALS. Lower rates are reported in the more diverse populations of southern Italy and the Balkan Peninsula. Variations in the distribution of families with SOD1 mutations have also been identified. The population based rate of SOD1 mutations in Italian FALS patients is 13%, and the rate in sporadic ALS in 0.7%. This contrasts sharply with rates of 1.9% in a Dutch FALS group and 0.44% in Dutch sporadic ALS patients. The true population based rate of SOD1 gene mutations in other countries remains unclear, as the majority of studies performed to date have been neither prospective nor population based. Moreover, we were unable to identify a geographic correlation between FALS rates and reported SOD1 mutation rates for the same region.

DISCUSSION
Our analysis indicates that the commonly accepted frequency of 10% for FALS represents an overestimation of the dominantly inherited Mendelian form of ALS. The population based frequency of 5.1% is likely to represent the most accurate estimation of rate of FALS, as population based studies include all patients in a defined geographic area in a given period of time. Accordingly, reported rates of FALS of 10% from previous studies are likely to have been biased by ascertainment from populations enriched by FALS cases.

Geographic variation in the rate of FALS in Europe (figure 2) may reflect true population based differences across different regions. Heterogeneity in the genetic substructure of European populations has been demonstrated recently. These geographic differences may occur because of variability in the underlying genetic structure of the European population. However, difficulties in case ascertainment could also account for this difference. Evidence for population based differences is emerging for SOD1: a founder effect for the A4V mutations in SOD1 has been recently identified in the USA and this mutation is rare in Europe. Mutations in OPTN seem to be primarily in Japanese populations. The existence of geographic variability for TARDP and FUS has not yet been established. As more causative genes are identified in FALS, detailed analysis of the frequency of various mutations within individual FALS populations will become available.

The meta-analysis is limited by the absence of a clear definition of FALS. While most groups define FALS as the presence of ALS in at least two members of an extended kindred, the degree of relatedness and the size of the extended kindred are rarely considered. Given that the lifetime risk of ALS is 1:450 for women and 1:350 for men, there is an increasing probability of two affected members with sporadic ALS occurring in the same kindred as the size of the kindred increases. Therefore, ensuring segregation of mutations within kindreds is also difficult.

Table 2 Meta-analysis results: subgroup analysis and pooled analysis

<table>
<thead>
<tr>
<th>Study type</th>
<th>Proportion FALS cases (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No of studies</td>
</tr>
<tr>
<td>Group 1: prospective population based registry</td>
<td>8</td>
</tr>
<tr>
<td>Group 2: retrospective population based study</td>
<td>14</td>
</tr>
<tr>
<td>Group 3: prospective case series</td>
<td>3</td>
</tr>
<tr>
<td>Group 4: retrospective case series</td>
<td>100</td>
</tr>
<tr>
<td>Population based studies (groups 1 and 2)</td>
<td>22</td>
</tr>
<tr>
<td>Case series studies (groups 3 and 4)</td>
<td>11</td>
</tr>
<tr>
<td>Pooled results for all studies (groups 1→4)</td>
<td>33</td>
</tr>
</tbody>
</table>

FALS, familial amyotrophic lateral sclerosis.
important, as exemplified by a recent report of two apparent SOD1 kindreds in which the disease did not segregate with a known pathogenic SOD1 mutations.²⁴

In conclusion, we have demonstrated that the rate of FALS across population based studies rarely exceeds 5% of all cases of ALS. This contrasts with the generally accepted figure of 10%, which originates from a paper written in 1955.

Careful prospective population based analysis of kindreds using validated criteria for a diagnosis of FALS is required to confirm that 5% represents the true population based rate of familial ALS, and to determine whether the documented geographic variation in rates of FALS is corroborated.

REFERENCES


