The risk to relatives of patients with sporadic amyotrophic lateral sclerosis

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Amyotrophic lateral sclerosis (ALS) shows complex inheritance (Al-Chalabi et al., 2010). Although ~5% of cases have a clear family history of ALS in first degree relatives, a family history in more distant relatives or of diseases suggestive of ALS or frontotemporal dementia also occurs in some (Fallis and Hardiman, 2009; Byrne and Hardiman 2010). Founder studies show that...
even individuals who do not realize they are related may share a common genetic cause for ALS because of a common ancestor (Al-Chalabi et al., 1998). Given that many people do not know their family history beyond first degree relatives and that causes of death are even less likely to be known, it is difficult to define exactly what is meant by sporadic ALS.

A recent population-based study has estimated the increased risk of ALS to first degree relatives as between 9 and 17 times, but did not distinguish between those with and without a family history (Fang et al., 2009). Furthermore, a specialist ALS clinic population is typically biased compared to a population-based sample in containing younger, motivated patients and those with atypical forms of ALS (Armon et al., 2002). It is common to be asked in such a clinic whether there is an increased risk to relatives. We therefore sought a practical estimate of the risk in a clinic setting to relatives of individuals with sporadic ALS.

Materials and methods

Inclusion criteria

Ethically approved, written informed consent was obtained from all patients. The diagnosis of ALS was made by two neurologists after exclusion of other conditions. Patients with a diagnosis of ALS, flail arm variant of ALS, primary lateral sclerosis or progressive muscular atrophy were included.

Data collection

Detailed pedigree information was reviewed for every patient seen between 1994 and 2009 in a tertiary referral clinic with a catchment population of ~ 3 million. An in-depth search was undertaken to identify any family member who had also been seen in the clinic. Patients with a family history were excluded. Only relatives alive at the time the proband was first seen were included in the analysis. Any patient seen in the clinic who was the second person in their family to be diagnosed was identified and the initial relative flagged as reclassified from sporadic to familial ALS.

Statistical methods

Demographic characteristics were compared using t-tests. Age of onset data were transformed to normal before analysis. The Fisher’s exact test was used to test the independence of gender and having an affected relative. The unadjusted risk was calculated as the ratio between observed cases in siblings and offspring and the total number of siblings and offspring at risk. For the subset of siblings whose ages were known, age-adjusted incidence rates were calculated by adjusting to the clinic population demographics.

The risk of ALS to a sibling of a proband was compared to that of the background population from an ALS population register drawn from the area surrounding the clinic and analysed with Kaplan-Meier product limit distribution over the 16-year observation period of the study. All P-values were two-sided. Calculations were performed in SPSS (version 16.0, SPSS Inc.).

Results

Patients with ALS (n = 1502) seen between 1994 and 2009 met the inclusion criteria. They had 1622 siblings and 1545 offspring (Table 1).

There was no difference between the characteristics of probands with unaffected and subsequently affected first degree relatives for gender (Fisher’s exact test, P = 0.68) and average age of onset (two-sided t-test, P = 0.37). Eight new cases of ALS were identified in siblings and 18 in offspring of probands, giving an unadjusted risk of ALS of 0.5% in siblings and 1.0% in offspring.

Age information was available for 478 siblings and 824 offspring. For this subset the overall crude incidence was 0.11% per year (0.05–0.21%) in siblings and 0.11% per year (0.06–0.19%) in offspring.

Age-adjustment using the clinic population gave an incidence rate for siblings of 0.12% per year (0.04–0.21%). By age 85, siblings had an 8-fold increased risk of ALS compared with the background population, with a risk of 2.4% (0.6–4.2%; Fig. 1). For offspring, because 90% of the offspring did not reach the median age of ALS diagnosis by the end of the study period, an accurate age-adjusted incidence rate was not possible. Where age was available, of 607 offspring aged below 50 years, seven were subsequently diagnosed with ALS and of 68 offspring aged greater than 56 years, 11 were subsequently diagnosed with ALS. There was no difference between the average age of disease onset of siblings and offspring (two-sided t-test, P = 0.31).

Table 1 Mean age at onset in years for probands and relatives

<table>
<thead>
<tr>
<th>Gender</th>
<th>Males (n)</th>
<th>Females (n)</th>
<th>Total (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proband</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>56.7 (939)</td>
<td>58.9 (563)</td>
<td>57.6 (1502)</td>
</tr>
<tr>
<td>Siblings</td>
<td>65.5 (653)</td>
<td>68.2 (969)</td>
<td>66.6 (1622)</td>
</tr>
<tr>
<td>Offspring</td>
<td>41.3 (922)</td>
<td>38.9 (623)</td>
<td>38.1 (1545)</td>
</tr>
<tr>
<td>Proband with relatives remaining unaffected</td>
<td>56.7 (924)</td>
<td>58.9 (552)</td>
<td>57.5 (1476)</td>
</tr>
<tr>
<td>Proband with relatives subsequently diagnosed</td>
<td>58.2 (15)</td>
<td>62.0 (11)</td>
<td>60.5 (26)</td>
</tr>
<tr>
<td>Proband with siblings subsequently diagnosed</td>
<td>57.5 (6)</td>
<td>42.0 (2)</td>
<td>53.6 (8)</td>
</tr>
<tr>
<td>Proband with offspring subsequently diagnosed</td>
<td>64.3 (9)</td>
<td>63.0 (8)</td>
<td>63.8 (17)</td>
</tr>
<tr>
<td>Affected siblings</td>
<td>57.0 (2)</td>
<td>63.8 (6)</td>
<td>62.1 (8)</td>
</tr>
<tr>
<td>Affected offspring</td>
<td>57.8 (10)</td>
<td>50.5 (8)</td>
<td>54.5 (18)</td>
</tr>
</tbody>
</table>

A daughter had a subsequently affected mother, and a father had subsequently affected monozygous twins, both of which affect counts in the table.
out necessarily showing Mendelian inheritance (Fang et al., 2009), but do demonstrate familial clustering with familial ALS misdiagnosed as sporadic ALS. However, like all degenerative diseases (Fallis and Hardiman, 2009), the distinction between familial and sporadic ALS is therefore to some extent artificial, although convenient.

The age adjusted risk of a subsequent diagnosis of ALS in siblings was estimable at 0.12% per year (0.04–0.21%). Comparison with the population risk of ALS showed that by age 85, siblings had an 8-fold increased risk of ALS. This should however be put in context. The actual risk was just 2.4% (0.6–4.2%), which means that the risk of remaining unaffected by age 85 had dropped from 99.7% to 97.6% (Fig. 1). In other words, siblings are still overwhelmingly likely to die of heart disease, stroke or cancer, rather than ALS. We could not accurately estimate the risk to offspring because the numbers at risk in the older age groups are small, there is considerable censoring of data and a small denominator.

This study should not be regarded as a population estimate of the risk to relatives of those with ALS. We have deliberately studied a clinic population because this is biased and yet is the context in which the clinical (as opposed to research) question is asked. The age of onset, diagnostic delay, distribution of bulbar onset and median survival of our clinic population is similar to that of other published clinic populations from tertiary referral centres (Thijss et al., 2000; Magnus et al., 2002, Capplinski et al., 2006, Talman et al., 2009), but is likely to be different from that of a general neurology clinic or healthcare systems that do not provide free universal access. Nevertheless, the conclusion that there is a small but definite increased risk to first degree relatives is likely to be valid.

Complex diseases like ALS, which show familial clustering and heritability, can be explained genetically with the Liability Threshold Model, in which multiple risk factors lead to a normal distribution of disease risk in the population, but for which disease only occurs once a threshold of risk burden is reached (Falconer, 1965). Under this model, one expects that first degree relatives have an increased risk that is approximately the square root of the population risk (Edwards, 1960). For ALS, the cumulative lifetime risk by age 85 is about 1 in 338 in our local population (Johnston et al., 2006), giving an expected risk to first degree relatives of 5.4%, which is of the same order of magnitude as our observed value.

A weakness of this study is that we relied on affected relatives coming to the same clinic as the proband, since we did not actively follow-up every family of those with sporadic ALS. This can be expected to lead to under-ascertainment. In addition, the age-adjustment was performed only on the proportion of siblings with age information. Affected relatives are more likely to have age information than the unaffected, which represents a further source of bias.

Non-paternity might be expected to confound our findings. Estimates of non-paternity rates vary widely, but a rate of about 1.6% for the UK is reasonable (Anderson, 2006), so about 24 of the probands in our sample might be children with different biological fathers from the expected. The risk of familial ALS in the population is 5–10% of the lifetime risk of ALS as a whole (Byrne et al., 2011). A liberal estimate is therefore 24 × 10% × 1/338, so the probability of this affecting our study is <1%.

This study differs from previous Swedish work estimating the risk to relatives (Fang et al., 2009) in two important respects. First, the Swedish study was population based, whereas this study is clinic based. Second, the Swedish study made no distinction between those with familial and sporadic ALS, whereas we have specifically examined the population with sporadic ALS.

We have shown a small but definite increased risk to relatives of patients with sporadic ALS seen in a tertiary referral clinic in the UK. The increase in risk should be seen in the context of other causes of death and could be regarded as a measure of uncertainty in family histories obtained in a specialist centre.

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