doi:10.1093/brain/awr248 Brain 2011: 134; 3451–3454 | 3451

BRAIN
A JOURNAL OF NEUROLOGY

The risk to relatives of patients with sporadic amyotrophic lateral sclerosis

Martha F. Hanby,[1] Kirsten M. Scott,[1] William Scotton,[1] Lokesh Wijesekera,[1] Thomas Mole,[1] Catherine E. Ellis,[1] P. Nigel Leigh,[1,2] Christopher E. Shaw[1] and Ammar Al-Chalabi[1]

1 MRC Centre for Neurodegeneration Research, Institute of Psychiatry, Department of Clinical Neuroscience, King's College London, London SE5 8AF, UK
2 Brighton and Sussex Medical School, Trafford Centre for Biomedical Research, University of Sussex, Falmer, East Sussex BN1 9RY, UK

Correspondence to: Ammar Al-Chalabi,
MRC Centre for Neurodegeneration Research,
Institute of Psychiatry P 041,
London SE5 8AF, UK
E-mail: ammar.al-chalabi@kcl.ac.uk

Amyotrophic lateral sclerosis is a neurodegenerative disease of motor neurons with a median survival of 2 years. Most patients have no family history of amyotrophic lateral sclerosis, but current understanding of such diseases suggests there should be an increased risk to relatives. Furthermore, it is a common question to be asked by patients and relatives in clinic. We therefore set out to determine the risk of amyotrophic lateral sclerosis to first degree relatives of patients with sporadic amyotrophic lateral sclerosis attending a specialist clinic. Case records of patients with sporadic amyotrophic lateral sclerosis seen at a tertiary referral centre over a 16-year period were reviewed, and pedigree structures extracted. All individuals who had originally presented with sporadic amyotrophic lateral sclerosis, but who subsequently had an affected first degree relative, were identified. Calculations were age-adjusted using clinic population demographics. Probands ($n = 1502$), full siblings ($n = 1622$) and full offspring ($n = 1545$) were identified. Eight of the siblings and 18 offspring had developed amyotrophic lateral sclerosis. The unadjusted risk of amyotrophic lateral sclerosis over the observation period was 0.5% for siblings and 1.0% for offspring. Age information was available for 476 siblings and 824 offspring. For this subset, the crude incidence of amyotrophic lateral sclerosis was 0.11% per year (0.05–0.21%) in siblings and 0.11% per year (0.06–0.19%) in offspring, and the clinic age-adjusted incidence rate was 0.12% per year (0.04–0.21%) in siblings. By age 85, siblings were found to have an 8-fold increased risk of amyotrophic lateral sclerosis, in comparison to the background population. In practice, this means the risk of remaining unaffected by age 85 dropped from 99.7% to 97.6%. Relatives of people with sporadic amyotrophic lateral sclerosis have a small but definite increased risk of being affected.

Keywords: amyotrophic lateral sclerosis; sporadic case; family history; risk to relatives
Abbreviations: ALS = amyotrophic lateral sclerosis

Introduction

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 fronto-temporal dementia also occurs in some (Fallis and Hardiman, 2009; Byrne and Hardiman 2010). Founder studies show that

Received April 6, 2011. Revised July 14, 2011. Accepted July 25, 2011. Advance Access publication September 20, 2011

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

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

A daughter had a subsequently affected mother, and a father had subsequently affected monozygous twins, both of which affect counts in the table.

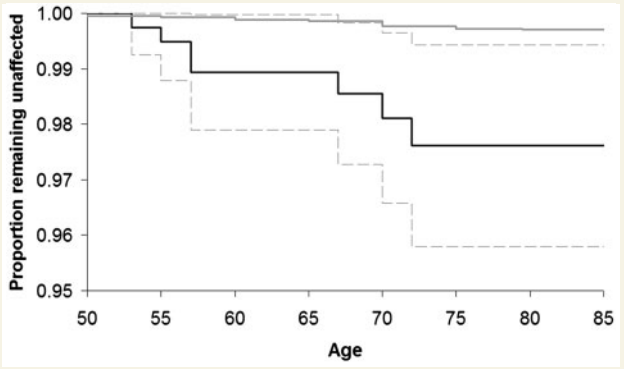

Figure 1 Proportion of siblings remaining unaffected in the clinic population compared with the background population risk. Siblings represented by black line with 95% confidence limits as thinner dashed lines. Risk to local population shown by upper grey line. Note the *Y* axis starts at 0.95, not zero.

Discussion

Over 16 years we found that 0.5% of siblings and 1% of offspring of patients with apparently sporadic ALS subsequently developed ALS. The crude risk of a diagnosis of ALS per year for first degree relatives was about 0.1%. These results highlight a practical dilemma and require careful interpretation. This could be regarded as a misclassification study, estimating the rate at which familial ALS is misdiagnosed as sporadic ALS. However, like all complex diseases, ALS also demonstrates familial clustering without necessarily showing Mendelian inheritance (Fang *et al.*, 2009), as well as presenting an increased risk to relatives of several neurodegenerative 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 (Thijs *et al.*, 2000; Magnus *et al.*, 2002, Czaplinski *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 $24 \times 10\% \times 1/338$, 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.

Acknowledgements

We thank Professor Carmel Armon for his helpful and thoughtful review of this manuscript. We thank the Medical Research Council, Motor Neurone Disease Association, ALS Association and the NIHR Biomedical Research Centre for Mental Health and the Heaton-Ellis trust for their support of research at King's College London.

Funding

European Community's Health Seventh Framework Programme [(FP7/2007-2013), (259867 to A.A.C. and C.E.S.)]; the British Geriatric Society (to M.F.H.).

References

Al-Chalabi A, Andersen PM, Chioza B, Shaw C, Sham PC, Robberecht W, et al. Recessive amyotrophic lateral sclerosis families with the D90A SOD1 mutation share a common founder: evidence for a linked protective factor. Hum Mol Genet 1998; 7: 2045–50.

Al-Chalabi A, Fang F, Hanby MF, Leigh PN, Shaw CE, Ye W, et al. An estimate of amyotrophic lateral sclerosis heritability using twin data. J Neurol Neurosurg Psychiatry 2010; 81: 1324–6.

Anderson KG. How well does paternity confidence match actual paternity?: Evidence from worldwide nonpaternity rates. Chicago, IL, ETATS-UNIS: University of Chicago Press; 2006.

Armon C, Guiloff RJ, Bedlack R. Limitations of inferences from observational databases in amyotrophic lateral sclerosis: all that glitters is not gold. Amyotroph Lateral Scler Other Motor Neuron Disord 2002; 3: 109–12.

Byrne S, Hardiman O. Familial aggregation in amyotrophic lateral sclerosis. Ann Neurol 2010; 67: 554.

Byrne S, Walsh C, Lynch C, Bede P, Elamin M, Kenna K, et al. Rate of familial amyotrophic lateral sclerosis: a systematic review and meta-analysis. J Neurol Neurosurg Psychiatry 2011; 82: 623–27.

Czaplinski A, Yen AA, Appel SH. Amyotrophic lateral sclerosis: early predictors of prolonged survival. J Neurol 2006; 253: 1428–36.

Edwards JH. The simulation of mendelism. Acta Genet Stat Med 1960; 10: 63–70.

Falconer DS. The inheritance of liability to certain diseases, estimated from the incidence among relatives. Ann Hum Genet 1965; 29: 51–76.

Fallis BA, Hardiman O. Aggregation of neurodegenerative disease in ALS kindreds. Amyotroph Lateral Scler 2009; 10: 95–8.

Fang F, Kamel F, Lichtenstein P, Bellocco R, Sparen P, Sandler DP, et al. Familial aggregation of amyotrophic lateral sclerosis. Ann Neurol 2009; 66: 94–9.

Johnston CA, Stanton BR, Turner MR, Gray R, Blunt AH, Butt D, et al. Amyotrophic lateral sclerosis in an urban setting: a population based study of inner city London. J Neurol 2006; 253: 1642–3.

Magnus T, Beck M, Giess R, Puls I, Naumann M, Toyka KV. Disease progression in amyotrophic lateral sclerosis: predictors of survival. Muscle Nerve 2002; 25: 709–14.

Talman P, Forbes A, Mathers S. Clinical phenotypes and natural progression for motor neuron disease: analysis from an Australian database. Amyotroph Lateral Scler 2009; 10: 79–84.

Thijs V, Peeters E, Theys P, Matthijs G, Robberecht W. Demographic characteristics and prognosis in a Flemish amyotrophic lateral sclerosis population. Acta Neurol Belg 2000; 100: 84–90.