Analysis of amyotrophic lateral sclerosis as a multistep process: a population-based modelling study

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Summary

Background Amyotrophic lateral sclerosis shares characteristics with some cancers, such as onset being more common in later life, progression usually being rapid, the disease affecting a particular cell type, and showing complex inheritance. We used a model originally applied to cancer epidemiology to investigate the hypothesis that amyotrophic lateral sclerosis is a multistep process.

Methods We generated incidence data by age and sex from amyotrophic lateral sclerosis population registers in Ireland (registration dates 1995–2012), the Netherlands (2006–12), Italy (1995–2004), Scotland (1989–98), and England (2002–09), and calculated age and sex-adjusted incidences for each register. We regressed the log of age-specific incidence against the log of age with least squares regression. We did the analyses within each register, and also did a combined analysis, adjusting for register.

Findings We identified 6274 cases of amyotrophic lateral sclerosis from a catchment population of about 34 million people. We noted a linear relationship between log incidence and log age in all five registers: England r^2=0·95, Ireland r^2=0·99, Italy r^2=0·95, the Netherlands r^2=0·99, and Scotland r^2=0·97; overall r^2=0·99. All five registers gave similar estimates of the linear slope ranging from 4·5 to 5·1, with overlapping confidence intervals. The combination of all five registers gave an overall slope of 4·8 (95% CI 4·5–5·0), with similar estimates for men (4·6, 4·3–4·9) and women (5·0, 4·5–5·5).

Interpretation A linear relationship between the log incidence and log age of onset of amyotrophic lateral sclerosis is consistent with a multistage model of disease. The slope estimate suggests that amyotrophic lateral sclerosis is a six-step process. Identification of these steps could lead to preventive and therapeutic avenues.

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Introduction

Amyotrophic lateral sclerosis is a neurodegenerative disease that mainly affects upper and lower motor neurons. It shows complex inheritance: about 5% of people with amyotrophic lateral sclerosis have a family history of the disease or frontotemporal dementia in a first degree relative and up to 20% have an affected relative in more extensive population-based family studies.[1]

Amyotrophic lateral sclerosis has several intriguing features (many shared with other neurodegenerative diseases) that remain unexplained. First, amyotrophic lateral sclerosis is an adult-onset disorder, even in individuals born with a gene mutation that increases the risk of the disease. Although such a mutation is carried from birth, many people remain healthy into old age and do not develop the disease.[2] Others remain completely healthy until disease onset seems to begin suddenly (typically between the age of 50 and 70 years), and progresses rapidly.[3] It is unknown why a pathological genetic change present from birth is expressed only in adult life, in some people but not others, even for high-penetrance mutations (eg, in the *SOD1* gene), and why, when the mutation is expressed, the pathological process progresses rapidly. Furthermore, several amyotrophic lateral sclerosis genes show pleiotropy, in which the same gene mutation can result in different phenotypes. For example, individuals with expansion of a hexanucleotide repeat in the *C9orf72* gene can remain healthy, or might develop amyotrophic lateral sclerosis, frontotemporal dementia, or amyotrophic lateral sclerosis–frontotemporal dementia. The same mutation might also predispose to schizophrenia, depression, and Parkinson's disease[1] but in every case the burden seems to be specific to a particular subgroup of cells. Additionally, amyotrophic lateral sclerosis seems to start in one neural region and spread,[4] but no genetic or environmental factor has yet been found to decide the site of onset.

Several of these characteristics are shared with cancer, which suggests that, despite the differences between cancer and neurodegeneration (eg, cancer is an uncontrolled proliferation of cells, whereas

neurodegeneration is the result of the death of cells),[5] other shared features remain to be discovered.

Since the 1950s, multistep models have been applied to the study of population patterns of cancer and, although the level of mathematical support remains a matter of debate, they have yielded insights into the likely causes of cancer and in some cases the identification of the steps involved.[6–10] These models generally show that a plot of epithelial cancer incidence against age has an exponential pattern; incidence is proportional to age raised to the power six. This association is consistent with the hypothesis that these cancers are the end result of seven successive mutations.[8–11] Different patterns are reported with some specific cancers—eg, breast cancer, in which cell replication at particular stages of life might have an important role.

Like cancer, amyotrophic lateral sclerosis might be a multistep process in which several sequential steps are needed. For example, a high-penetrance disease-causing mutation would still need the accumulation of the remaining steps to result in disease, which would take time. This scenario would explain both the adult onset and the finding that not every individual carrying a mutation develops disease.

Multistep models have not been used previously in the study of neurodegenerative disease. Therefore, we used a model originally applied to cancer epidemiology to test the hypothesis that amyotrophic lateral sclerosis is a multistep process.

Methods

Model

We used the approach outlined by Armitage and Doll.[11] Briefly, if one assumes that amyotrophic lateral sclerosis is caused in one step, the incidence in a particular year, i, will be proportional to the risk of having undergone that specific step in that year; this risk, u, will depend on the level of exposure to the relevant disease-causing factor. However, without knowledge of that factor and the exposure level, the incidence will be proportional to the average background risk, u, of this step. If instead, the disease needs more than one step (each step with risk u_i), then the chance of undergoing the first step by age t years is u_1t. Undergoing the second step by age t has risk u_2t, and so on, until the state is reached after n–1 steps, in which the person is primed so that the next and final step, which has risk u, would result in disease. Each risk u is assumed to be small because an exposure effect with probability close to 1 makes no difference to the product.

Therefore:

$$i = u_1u_2u_3\ldots u_{n-1}u_n t^{n-1}$$

and

$$\log(i) = (n-1)\log(t) + c$$

(where c is a constant representing $\log(u_1u_2u_3\ldots u_{n-1}u_n)$

The model can be modified to allow for the assumption that the changes need to happen in a specific order, but this assumption does not alter the age-incidence patterns predicted by the model.

Because i is incidence and t is age, a plot of the log of amyotrophic lateral sclerosis incidence against the log of age will be linear if a multistep model applies, and will have slope n–1, one less than the number of steps needed. One exception should be noted: the model predicts that the slope will decrease (and therefore will be less than linear) at the older age groups,[9] a pattern that has been recorded in cancer.

Population registers

To identify population incidence data for amyotrophic lateral sclerosis, we searched PubMed and contacted amyotrophic lateral sclerosis epidemiology research groups. We generated incidence data by age and sex from five amyotrophic lateral sclerosis population registers, which provided incidence and prevalence data broken down by sex and 5-year age groups in Ireland, the Netherlands, Italy (Piedmont), Scotland, and England (South East England amyotrophic lateral sclerosis register [SEALS]).[3,12–17] All participants in the registers had provided written consent for inclusion and subsequent analysis of their data. All five registers try to capture every incident case of amyotrophic lateral sclerosis within a defined catchment area over several years, which allows age and sex-adjusted incidence to be estimated.

To provide a comparison with another neurological disease, we examined population-level data for multiple sclerosis. Data were obtained from a study from Manitoba, Canada.[18]

Statistical analysis

For each register, we used the 2013 version of the European standard population to calculate age-standardised incidence rates for the 25–74 years age range per 100 000 person-years with 5-year age groups (table 1).

We did two different analyses: first, we included data from all ten 5-year age groups from 25–29 years through to 70–74 years; and second, we omitted the youngest and the oldest age groups. We did this because analyses of amyotrophic lateral sclerosis incidence by age, as in cancer, might be imprecise and have measurement errors in extreme age groups. In particular, rates in young people might be imprecise because of the small numbers of cases. Rates in old age groups might be underestimated because of case under-ascertainment or cohort effects (ie, generation differences); for example, this pattern has been recorded for lung cancer incidence because older people had grown up during a period when smoking rates were relatively low.[19] Alternatively, some versions of the multistep model predict that the log(incidence) and log(age) association might be less than linear in the older age groups.[20]

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For the **2013 revision of the European standard population** see http://epp.eurostat.ec.europa.eu/cache/ITY_OFFPUB/KS-RA-13-028/EN/KS-RA-13-028-EN.PDF