SHORT REPORT

Cerebrovascular injury as a risk factor for amyotrophic lateral sclerosis

Martin R Turner, Raph Goldacre, Kevin Talbot, Michael J Goldacre

ABSTRACT

Objective To use an unbiased method to test a previously reported association between cerebral arteriovenous malformation (AVM) embolisation and the subsequent development of amyotrophic lateral sclerosis (ALS).

Methods A hospital record linkage database was used to create cohorts of individuals coded as having cerebral and peripheral vessel AVMs, stroke (separately for haemorrhagic and ischaemic), transient ischaemic attack (TIA) and subarachnoid haemorrhage (SAH). The rate ratio for subsequent ALS was compared to a reference cohort.

Results An increased rate ratio for ALS was found in relation to prior AVM (2.69; p=0.005), all strokes (1.38; p<0.001), and TIA (1.47; p<0.001).

Conclusions Cerebrovascular injury from a variety of causes, rather than the presence of AVM or the associated embolisation procedure per se, may be a risk factor for ALS within the context of a more complex multiple-hit model of pathogenesis.

INTRODUCTION

The pathological cascade leading to the fatal adult neurodegenerative disorder amyotrophic lateral sclerosis (ALS) is not yet clear. Cases linked to single genetic mutations are clinically indistinguishable from the vast majority with apparently sporadic disease, and some of the genes linked to hereditary ALS have seemingly disparate functions. It seems, therefore, that ALS involves a common pathway reached by variable upstream routes. No strong epidemiological risk factors have been identified for ALS, other than increasing age. Pathogenesis in a relatively rare disease like ALS is, therefore, likely to involve a multiple-hit model.

A retrospective observational study by Valavanis et al identified seven cases of ALS among 1114 patients seen over a 24-year period (with a median follow-up of 11 years), who had undergone embolisation of a cerebral arteriovenous malformation (AVM). Two further anecdotal cases of ALS, occurring 11 and 14 years after the initial embolisation procedure, respectively, were subsequently reported by another centre. As publication bias is possible in case series, we sought to test this previously unrecognised association in an unbiased fashion using a hospital record-linkage data set and a reference population.

METHODS

An all-England national record-linkage data set of Hospital Episode Statistics and mortality data (1999–2011) was used to undertake studies of cohorts of people with AVM of cerebral vessels (ICD-10 Q28.2), AVM of precerebral vessels (ICD-10 Q28.0) and peripheral AVM (ICD-10 Q27.3) to determine the risks of subsequent ALS relative to a reference cohort. This was repeated for cohorts diagnosed with subarachnoid haemorrhage (SAH) (ICD-10 I60), haemorrhagic stroke (ICD-10 I61-I62), cerebral infarction (ICD-10 I63), and transient ischaemic attack (TIA, ICD-10 G45).

We constructed cohorts of people with each ‘exposure’ condition by identifying every individual in the data set who had a record containing the relevant exposure diagnosis code(s). These individuals were followed up, through record linkage, for any subsequent record of ALS. We restricted ALS outcomes to those diagnosed for 1 year or more after cohort entry to reduce possible bias from misdiagnosis or surveillance. Any individual who had a record of ALS dated earlier than or at the same time as the earliest record of the exposure condition was excluded from the study. For comparison with each exposure cohort, a ‘reference cohort’ was constructed and followed-up in the same way. This cohort comprised over 8.5 million individuals in the data set with no record of ALS—people admitted to hospital for a wide range of mainly minor medical and surgical reasons, including: cataract, inguinal hernia, gallbladder disease, haemorrhoids, varicoce veins, internal derangement of knee, deflected septum, nasal polyp, selected disorders of teeth, upper respiratory tract infections, ingrowing toenail and other diseases of nail, sebaceous cyst, otitis externa/media, bunion, dilation and curettage, appendectomy, hip replacement, and knee replacement. We standardised the cohorts by age, sex, year of admission, region of residence, and social class, and censored the person-days of follow-up for death. We calculated expected numbers of people with ALS in each cohort, compared these with the observed number, and calculated standardised rate ratios. Detailed methods are published elsewhere.

The current programme of analysis of the data has been approved by the English National Health Service (NHS) Central Office for Research Ethics Committees (reference number 04/Q2006/176).

RESULTS

Numbers of people in each cohort are shown in Table 1. Of those in the AVM cohort, 76% were aged 15–64 years and 15% were aged 65 years and above. The corresponding figures for the SAH cohort were 64% and 35%, respectively; 82% of
the stroke cohort and 76% of the TIA cohort were aged 65 years and over. All comparisons between these cohorts and the reference cohort were age-standardised, (see Methods Section). As table 1 shows, significantly elevated rate ratios for ALS were observed in the cohorts of people with AVM (all types combined, age-standardised rate ratio (RR) 2.69; 95% CI 1.23 to 5.12; p=0.005). Although analysis in relation to AVM subtypes (cerebral, pre-cerebral and peripheral) showed a significant association only for cerebral vessel AVM, the statistical power from the smaller numbers involved was felt to be too low to draw firm conclusions with regard to location. Increased rate ratios for ALS were also found in relation to stroke (either haemorrhagic or ischaemic RR 1.38; 95% CI 1.27 to 1.51; p<0.001), and TIA (RR 1.47; 95% CI 1.29 to 1.68; p<0.001). The significance of the increased rate ratio observed for ALS in the cohorts of people with SAH was equivocal (p=0.053).

**DISCUSSION**

Our findings support the published association, albeit small in absolute terms, between the diagnosis of AVM and the subsequent development of ALS, with additional associations noted between ALS and prior non-SAH-related strokes (both ischaemic and haemorrhagic), and TIAs. By considering vascular disease more generally we have previously demonstrated that there is a significant association only for cerebral vessel AVM, the statistical power from the smaller numbers involved was felt to be too low to draw firm conclusions with regard to location. Increased rate ratios for ALS were also found in relation to stroke (either haemorrhagic or ischaemic RR 1.38; 95% CI 1.27 to 1.51; p<0.001), and TIA (RR 1.47; 95% CI 1.29 to 1.68; p<0.001). The significance of the increased rate ratio observed for ALS in the cohorts of people with SAH was equivocal (p=0.053).

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