

Autoimmune disease preceding amyotrophic lateral sclerosis

An epidemiologic study

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ABSTRACT

Objective: To study whether the risk of amyotrophic lateral sclerosis (ALS) is increased in people with prior autoimmune disease.

Methods: An all-England hospital record-linkage dataset spanning 1999–2011 was used. Cohorts were constructed of people with each of a range of autoimmune diseases; the incidence of ALS in each disease cohort was compared with the incidence of ALS in a cohort of individuals without prior admission for the autoimmune disease.

Results: There were significantly more cases than expected of ALS associated with a prior diagnosis of asthma, celiac disease, younger-onset diabetes (younger than 30 years), multiple sclerosis, myasthenia gravis, myxedema, polymyositis, Sjögren syndrome, systemic lupus erythematosus, and ulcerative colitis.

Conclusions: Autoimmune disease associations with ALS raise the possibility of shared genetic or environmental risk factors. *Neurology*® 2013;81:1222–1225

GLOSSARY

ALS = amyotrophic lateral sclerosis; **FTD** = frontotemporal dementia; **MMN** = multifocal motor neuropathy; **MS** = multiple sclerosis; **TDP-43** = transactive response DNA-binding protein 43.

Understanding the risk factors for neurodegenerative disorders, including any pathogenic pathways shared with other diseases, will improve the chances of effective therapeutic development. Amyotrophic lateral sclerosis (ALS) is among the most rapidly progressive forms of neurodegenerative disease, involving a heterogeneous mixture of upper and lower motor neuron loss in conjunction with involvement of extramotor pathways that have clinicopathologic overlap with frontotemporal dementia (FTD). Median survival is 3 to 5 years from symptom onset and 20% survive more than 5 years. The disorder is apparently sporadic in 95% of patients.¹

There is a perception that patients with ALS might be premorbidly “fitter” than the general population, with higher rates among varsity athletes² and professional soccer players,³ although there are many potential confounders relating to increased leisure-time physical activity,⁴ lower body mass index,⁵ and reduced cardiovascular risk,^{6,7} all noted among those with ALS. There have been few studies of comorbidities among patients with ALS. One case-control study showed no significant difference in the frequency of a range of broad disease categories (including endocrine).⁸ In a cohort of 514 patients with ALS,⁹ the prevalence of cardiovascular diseases and cardiovascular risk factors was significantly lower than their prevalence in the general population, confirming previously published findings (discussed in reference 10). Autoimmunity in the pathogenesis of ALS, or perhaps as a mediator of heterogeneity, has long been postulated.¹¹ There are no clear human lymphocyte antigen associations.¹²

METHODS An all-England national record-linkage dataset of Hospital Episode Statistics and mortality data (1999–2011)¹³ was used to undertake studies of cohorts of people with each of a range of autoimmune disorders, compared with a control cohort without these diseases, to determine the risk of subsequent ALS in each cohort. A similar analysis was undertaken on a regional record-linkage dataset, the Oxford record-linkage study, using its data from an earlier period (1963–1998).¹⁴ Details of the methods are given elsewhere.^{13,14}

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RESULTS Observed and expected numbers and rate ratios comparing ALS in each autoimmune group with the control cohort are shown in the table. The rate ratios were significantly high ($p < 0.01$) for ALS associated with a prior diagnosis—at least 1 year before ALS—of asthma, celiac disease, multiple sclerosis (MS), myasthenia gravis, myxoedema, polymyositis, Sjögren syndrome, and systemic lupus erythematosus.

The rate ratios were high for each of these for both males and females although not invariably significantly so (subdivision by sex lowered statistical power). The rate ratio for people with a coded diagnosis of insulin-dependent diabetes was not increased considering people of all ages; however, it was increased for people with a first recorded diagnosis of diabetes aged less than 30 years. The rate ratio for ulcerative colitis was borderline

Exposure	No. observed	Expected no.	RR (95% CI)	p Value
Addison disease	3	4.9	0.62 (0.13-1.81)	0.54
Ankylosing spondylitis	19	14	1.35 (0.81-2.12)	0.23
Asthma, aged 5-54 y ^a	174	119.7	1.60 (1.34-1.91)	<0.001
Autoimmune hemolytic anemia	3	4.1	0.74 (0.15-2.16)	0.78
Chronic active hepatitis	3	2.2	1.37 (0.28-4.01)	0.83
Celiac disease	42	26.9	1.57 (1.13-2.12)	0.005
Crohn disease	54	44.5	1.22 (0.91-1.59)	0.17
Dermatomyositis	3	0.9	3.37 (0.7-9.87)	0.09
Insulin-dependent diabetes: all	216	219.7	0.98 (0.85-1.13)	0.83
<30 y ^a	10	2.7	3.94 (1.84-7.50)	<0.001
Goodpasture syndrome	0	0.4	0.00 (0.00-10.5)	0.80
Hashimoto	3	3.1	0.97 (0.2-2.84)	0.81
ITP	15	11.9	1.26 (0.71-2.08)	0.45
MS ^a	143	34.5	4.25 (3.57-5.02)	<0.001
Myasthenia gravis ^a	36	7.2	5.02 (3.51-6.96)	<0.001
Myxoedema ^a	535	454.5	1.20 (1.10-1.31)	<0.001
Pemphigoid	10	6.2	1.62 (0.77-2.98)	0.18
Pemphigus	1	1	0.98 (0.02-5.45)	0.64
Pernicious anemia	43	33.7	1.28 (0.92-1.73)	0.13
Polyarteritis nodosa	1	1.2	0.81 (0.02-4.52)	0.81
Polymyositis ^a	12	2	6.05 (3.12-10.57)	<0.001
Primary biliary cirrhosis	6	5	1.21 (0.44-2.63)	0.81
Psoriasis	59	50.7	1.17 (0.89-1.51)	0.27
Rheumatoid arthritis	205	191.3	1.08 (0.93-1.24)	0.33
Scleroderma	5	4.8	1.03 (0.34-2.42)	0.88
Sjögren syndrome ^a	17	8.6	1.98 (1.15-3.17)	0.007
Systemic lupus erythematosus ^a	16	8	2.00 (1.14-3.26)	0.008
Thyrotoxicosis	56	55.2	1.01 (0.76-1.32)	0.97
Ulcerative colitis	106	87.2	1.22 (1.00-1.48)	0.05
Pooled analysis ^b	570	502.0	1.15 (1.06-1.26)	<0.001

Abbreviations: ALS = amyotrophic lateral sclerosis; CI = confidence interval; ITP = idiopathic thrombocytopenic purpura; MS = multiple sclerosis; RR = rate ratio.

Shown are number of observed cases of ALS in each autoimmune disease cohort, expected number, and rate ratio of ALS in the cohort with 95% CI. Observed and expected numbers and RRs are based on comparisons with a control cohort and are adjusted, in each comparison, for age in 5-year groups, sex, year of first admission, region of residence, and quintile of the Index of Multiple Deprivation (a standard UK measure of socioeconomic status). RRs are calculated using the formula $\frac{O_{AI}}{E_{AI}}$ divided by $\frac{O_{CON}}{E_{CON}}$, where O and E are the observed and expected numbers of ALS in the autoimmune disease and control cohort, respectively.

^a $p < 0.01$.

^bPooling all autoimmune diseases in the table that were not individually significant ($p > 0.01$).

significant ($p = 0.05$). In a pooled analysis combining all the diseases in the table that were not individually significant ($p < 0.01$), the rate ratio was significantly but modestly elevated. Numbers in the Oxford record-linkage study were much smaller than all-England but there were 2 conditions with significantly high rate ratios: that for MS was 10.9 (95% confidence interval 5.4–19.8, based on 11 observed cases) and for myxoedema was 3.1 (95% confidence interval 1.1–6.7, based on 6 observed cases).

DISCUSSION A previous case-control study found no significant excess of antecedent diseases, including diabetes and thyroid disease.¹⁵ The hospital record-linkage approach has the advantage of large numbers and removal of recall bias that may be a factor in some case-control studies. It is, however, dependent on accurate coding. We suggest that the apparent association of inflammatory muscle disease and myasthenia gravis with ALS is most likely to represent an artifact of diagnostic mimicry. It is also recognized that our study only includes patients for whom hospital admission was required, which may be a source of unmeasurable bias (e.g., younger-onset diabetes).

An association between ALS and MS has been previously suggested. A familial study separately using index cases of ALS and MS reported increased association,¹⁶ and a case series of coincident MS in cases of ALS was associated with expansions of the *C9orf72* GGGGCC repeat.¹⁷ A population-based study of 810 ALS cases observed only 2 with a prior diagnosis of MS, which was believed to be no more than expected by chance, and neither had a *C9orf72* GGGGCC repeat expansion.¹⁸ This latter result would suggest that our findings in relation to MS and ALS may also be confounded by misdiagnosis.

Another hospital record-linkage study considered autoimmune diseases among relatives and spouses of ALS cases. An association was found for MS, but also Behçet disease, ulcerative colitis, and Wegener granulomatosis in the offspring of patients with ALS.¹⁹ However, the basis of these observations in relation to shared pathogenesis remains unclear. Immunologic intervention for ALS, including bone marrow transplant,²⁰ has so far not been effective, despite a large body of evidence linking neuroinflammatory processes to pathogenesis in ALS, in particular oligodendrocyte dysfunction.²¹

In a descriptive study of 1,200 patients with ALS,²² comorbid diabetes (type unspecified) was reported by 9%, and was the most frequent (42%) among diseases reported in first- and second-order relatives, followed by arthritis (unspecified) 35%, allergies (unspecified) 19%, thyroid disease (unspecified) 17%, Alzheimer disease 12%, Parkinson disease 8%, collagen vascular diseases (unspecified) 3%, demyelinating disease

(unspecified) 4%, and myasthenia gravis <1%. The issue of recall bias and lack of a control group make these data difficult to interpret. However, the alterations in energy metabolism consistently observed in patients with ALS²³ may have overlap with the wider concept of insulin resistance.

The observed number of ALS cases in the thyrotoxicosis cohort was very similar to the expected number, but, as noted above, there was an excess of ALS in the myxoedema cohort. Two large retrospective studies observed that approximately one-fifth of patients with ALS reported a personal or family history of thyroid disease, or had biochemical evidence of such.^{22,24} A case-control study demonstrated a significantly increased incidence of hereditary thyroid disease in the relatives of patients with ALS, with a reported odds ratio for thyroid disease among patients ranging from 1.5 to 2.3 and for another autoimmune disease, pernicious anemia, the ratio was higher at 3.0 to 3.6.²⁵

ALS and some forms of FTD are unified by the presence of cytoplasmic inclusions of the transactive response DNA-binding protein 43 (TDP-43). A case-control study of the prevalence of autoimmune diseases across the phenotypic range of TDP-43-associated FTD revealed significant associations among those with semantic variant primary progressive aphasia, and familial cases linked to *PRGN* mutations. Although small numbers of patients were involved, several of the autoimmune diseases we describe in association with ALS were specifically noted, including diabetes, celiac disease, Sjögren syndrome, systemic lupus erythematosus, thyroid disease, and colitis.²⁶

Finally, multifocal motor neuropathy (MMN) with conduction block is a rare autoimmune disorder that may mimic ALS in its initial presentation, but it does not have similar progression or obvious CNS pathology. However, a case-control study in MMN showed that type 1 diabetes, Hashimoto thyroid disease, and celiac disease were all significantly more prevalent in family members of patients.²⁷ We have previously reported a case of progressive weakness without sensory involvement and striking corticospinal tract MRI changes in the context of celiac disease, which improved with dietary exclusion of gluten.²⁸ The significance of increased premorbid celiac disease in those with ALS, and in family members of patients with MMN remains unclear at present.

Evidence is presented that several preexisting autoimmune disorders are associated with a small increased risk of ALS. The pathogenesis of neurodegenerative disorders more widely seems likely to involve multiple susceptibilities, stochastic events, and environmental triggers. These disease associations raise the possibility of shared genetic or environmental risk factors, or clues to modifiable triggers that might thereby reduce the incidence of ALS.

AUTHOR CONTRIBUTIONS

M.R.T. planned the study and drafted the manuscript. R.G. undertook the analysis and edited the manuscript. S.R. and K.T. edited the manuscript. M.J.G. planned and designed the study and edited the manuscript.

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