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Extrinsic allergic alveolitis: incidence and mortality in the general population

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Summary

Background: Extrinsic allergic alveolitis (EAA) is an important clinical entity, but its incidence and significance in the general population are uncertain.
Aim: To estimate the incidence of EAA, and resulting mortality, in the UK.
Design: General-population-based cohort study in a UK primary care database (THIN).
Methods: THIN patients with an incident diagnosis of EAA were compared with a general population cohort whose members were 4:1 matched with EAA patients by age, sex and GP practice. Follow-up started at the first diagnosis of EAA (and at the same date in the matched controls) and ended at death or end of follow-up, whichever came first. Poisson, logistic, and Cox proportional hazard regression models were used; mortality rate, odd ratios, and hazard ratios were calculated.
Results: We identified 271 incident cases of EAA (mean age at diagnosis 57 years, 51% male). Between 1991 and 2003, the incident rate for EAA was stable at ~0.9 cases per 100 000 person-years. In comparison to the 1084 general population controls, patients with EAA were less likely to smoke (odds ratio 0.56, 95%CI 0.39–0.81), but had a marked increase in the risk of death (hazard ratio 2.98, 95%CI 2.05–4.33).
Discussion: The incidence of EAA in the UK population appears to be stable overtime, and suggests about 600 new cases of EAA each year. People with EAA are less likely to smoke than the general population, but have a markedly increased mortality rate.

Introduction

Extrinsic allergic alveolitis (EAA) is widely recognized as an important clinical problem by respiratory physicians, but there are few data available on how common it is in the general population, and how its incidence varies with age and gender.[1,2] EAA is usually reversible if exposure to the responsible antigen is avoided, but some patients may develop lung fibrosis, which can cause premature death.[3] The extent to which EAA causes premature mortality in the general population is not known, however. We used data from a computerized longitudinal primary-care dataset to quantify the incidence of EAA in the UK general population, and to compare the survival of patients with EAA to that of a matched cohort from the general population.

Methods

The study data are taken from The Health Improvement Network (THIN), a computerized

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longitudinal primary-care database that includes all the data gathered during routine general practice consultations, such as prescriptions and medical diagnoses, and all communications from secondary care, such as hospital letters.[4] At the time of our study, the dataset included data up to the end of November 2004 from 255 general practices based in all areas of the UK. The mean number of people actively contributing data to THIN for each year in the study was just over 1.5 million.

Initially, we identified all people in THIN with a recorded diagnosis of EAA. In THIN, medical diagnoses are coded using the READ coding system, and our list of EAA diagnoses included any READ code for allergic alveolitis, hypersensitivity pneumonitis, Farmers' lung, or Bird-fancier's lung. For each patient, we defined a start date for their data record (the later of: date of registration with the primary care centre or date of centre computerization), and a stop date (the earlier of: death or date of last data collection). We wanted to study people with EAA from the onset of their disease, and thus we attempted to include only newly occurring cases (incident cases), by excluding patients whose first diagnosis was recorded less than 1 year after their start date. We then extracted information on date of first diagnosis, age at diagnosis, sex, smoking habit and time of death (in those who had died) for this cohort. For display and analysis purposes, age at diagnosis was grouped in 10 years categories over the age of 45 years. In addition we grouped the most recent smoking status of each subject as follows: never/non-smoker, ex-smoker and current smoker.

To calculate the annual incidence of EAA, we used the number of new cases of EAA diagnosed each year as our numerator and the mid-year total THIN population for each year as our denominator. We excluded the years before 1991, because over 1987–1990, the number of practices contributing data to THIN increased rapidly, and so the number of people in the denominator changed quickly. We also excluded the year 2004, because we did not have a complete year of follow-up for these patients. We calculated crude incidence rates for EAA, stratified by age, gender and year of diagnosis (grouped as 1991–1995, 1996–1999 and 2000–2003) and then used Poisson regression to estimate incidence rate ratios and 95%CIs.

For our survival analyses, we used data for all incidence cases of EAA, including those diagnosed before 1991 and after 2003. In order to provide a general population comparison cohort, for each EAA patient we identified four people without EAA, matched by gender, primary care centre and age (within 3 years). In addition, controls had to be actively contributing data to THIN at the time that their matched case was first diagnosed with EAA. The follow-up period for this analysis was from the first date of diagnosis of EAA (or match date for controls), to the date of death, or last data collection. We used Cox regression to estimate hazard ratios and 95%CIs, and explored the potential confounding effects of age, sex and smoking habit. We used Stata 9 and SPSS 11.5 statistical software for our analyses, and checked the proportional hazards assumption for our final models using the diagnostic section with Stata.

The study protocol was reviewed and approved by the Nottingham Ethics Committee.

Results

We identified 319 patients with a diagnosis of EAA; 271 were incident cases as defined by our criteria, and all were included in the survival analysis, along with a general population comparison cohort ($n = 1084$) (Table 1). Mean age at incident EAA diagnosis was 57 years (SD 15) and 139 (51%) were male. A subgroup of 226 incident cases of EAA had their first diagnosis recorded between 1991 and 2003, and these patients were included in the incidence analysis. Their demographic details were similar to those of the whole cohort of incident patients.

The overall incidence of EAA between 1991 and 2003 was 0.9 per 100 000 person-years (95%CI 0.8–1.1). Incidence rates were similar in men and women and in different calendar periods, but increased progressively with age up to the age of 75 years (Table 2). Sex ratios remained unchanged across the age groups.

Compared to their matched general population controls, people with a diagnosis of EAA were less likely to be current smokers (OR 0.56, 95%CI 0.39–0.81), but were equally likely to be ex-smokers (OR 1.04, 95%CI 0.76–1.43).

A total of 45 EAA patients died during follow-up, vs. 86 controls. The crude mortality rates for the EAA and control cohorts were 30.7 and 14.1 per 1000 person years respectively. Five-year survival was 82% for EAA patients vs. 93% for controls. Over the whole study period, people with a diagnosis of EAA were twice as likely to die, compared to their controls (Figure 1) (Log rank = 18.72; $p < 0.0001$) (HR 2.17, 95%CI 1.52–3.12). After allowing for the effects of age, sex and smoking habit, the difference in survival between the two cohorts was even greater (HR 2.97, 95%CI 2.04–4.31) (Table 3).

Table 1 General characteristics of study cohorts

	EAA patients	General population	Total
Sex			
Men	139 (51%)	556 (51%)	695 (51%)
Women	132 (49%)	528 (49%)	660 (49%)
Total	271 (100%)	1084 (100%)	1355 (100%)
Age groups (years)[a]			
<45	58 (21%)	232 (21%)	290 (21%)
45–54	54 (20%)	216 (20%)	270 (20%)
55–64	74 (27%)	296 (27%)	370 (27%)
65–74	60 (22%)	240 (22%)	300 (22%)
>85	25 (9%)	100 (9%)	125 (9%)
Total	271 (100%)	1084 (100%)	1355 (100%)
Smoking			
Never/non-smoker	97 (36%)	343 (32%)	440 (32%)
Ex-smoker	111 (41%)	366 (34%)	477 (35%)
Current smoker	50 (18%)	262 (24%)	312 (23%)
Missing	13 (5%)	113 (10%)	126 (9%)
Total	271 (100%)	1084 (100%)	1355 (100%)

[a]Age at index date (start of study follow-up).

Table 2 Crude incidence rates and Poisson regression modelling for EAA

	n	Person-years	Incidence[a] (95%CI)	Rate ratio[b] (95%CI)
Gender				
Male	114	11 765 858	0.97 (0.81–1.16)	1.00
Female	112	12 048 394	0.93 (0.77–1.12)	0.92 (0.70–1.19)
Age group (years)				
<45	50	14 175 445	0.35 (0.27–0.47)	1.00
45–54	43	3 076 644	1.40 (1.04–1.89)	3.97 (2.64–5.96)
55–64	62	2 695 036	2.30 (1.79–2.95)	6.52 (4.49–9.46)
65–74	49	2 017 265	2.43 (1.84–3.21)	6.93 (4.67–10.27)
>75	22	1 849 862	1.42 (0.92–2.20)	3.41 (2.06–5.65)
Calendar period				
1991–1995	68	7 296 401	0.93 (0.74–1.18)	1.00
1996–1999	70	7 894 782	0.89 (0.70–1.12)	0.95 (0.68–1.33)
2000–2003	88	8 623 069	1.02 (0.83–1.26)	1.09 (0.80–1.50)

[a]Incidence rate per 100 000. [b]Derived from Poisson regression mutually adjusted for the other two variable in the table.

Discussion

In this large, general-population-based cohort of EAA patients, the overall incidence rate was approximately 1 per 100 000 UK population, suggesting that each year in the UK there will be ~600 new cases of EAA. The incidence of EAA appears stable since the early 1990s, and rates are only slightly higher in men than in women. However, all-cause mortality was three times higher in EAA patients, compared to the general population, demonstrating that although EAA is often a reversible condition, some patients suffer progressive disease resulting in premature death.

Strengths and weaknesses

The main potential weakness of our study is the validity of the diagnosis of EAA, as we have not tested this directly. The validity of a number of diagnoses, including death, has been assessed in UK primary care datasets and consistently found to be high.[5] We have previously assessed the validity of a diagnosis of another interstitial lung

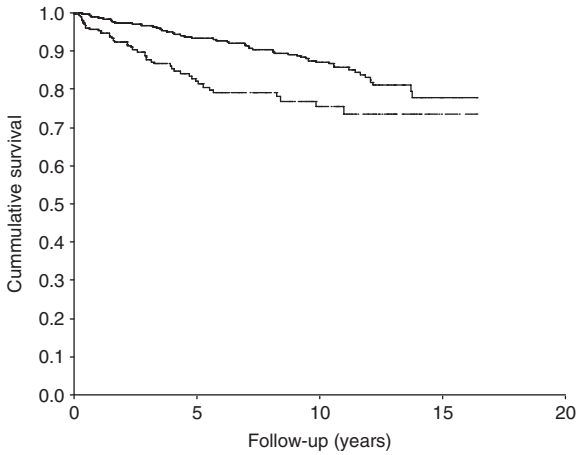

Figure 1. Kaplan Meier curve comparing survival in EAA (dashed line) and general population (solid line) cohorts.

Table 3 Hazard ratios for all-cause mortality (Cox proportional hazard regression)

Cohort	Deaths	Hazard ratio (95%CI)
Unadjusted		
General population	86	1.00
EAA	45	2.17 (1.52–3.12)
Adjusted for age and sex		
General population	86	1.00
EAA	45	2.52 (1.76–3.63)
Adjusted for age, sex and smoking		
General population	86	1.00
EAA	45	2.98 (2.05–4.33)
Adjusted for age, sex and smoking, restricted to the first year of follow-up		
General population	12	1.00
EAA	11	4.66 (1.98–10.94)
Adjusted for age, sex and smoking, restricted to follow-up between the 1st and 5th years		
General population	39	1.00
EAA	26	3.85 (2.29–6.47)
Adjusted for age, sex and smoking, restricted to follow-up beyond the 5th year		
General population	35	1.00
EAA	8	1.43 (0.65–3.15)

disease, cryptogenic fibrosing alveolitis, in a computerized general practice database and found this to be high.[6] It also seems unlikely to us that general practitioners will enter a diagnosis of EAA in their computer system unless this has been verified by a secondary referral, so we expect that the recorded diagnoses have a high specificity. Probably, some cases of EAA go unrecognized, and thus the sensitivity of a recorded diagnosis of EAA may not be as high as the specificity. This potential under-recognition of EAA may also mean that we have under-estimated the true incidence of EAA, and perhaps only included the more severe cases; if so, we may also have over-estimated the increased mortality associated with EAA. Despite these potential problems, this is the best current estimate of the incidence and significance of EAA as currently recognized in the UK.

Consistency with other studies

We have been unable to find any other general-population-based cohort study of EAA incidence to compare our results with. Previous studies have focused on the risk of developing clinical disease amongst subsets of the population with high levels of exposure to particular antigens.[7] For example, the incidence of EAA among Swedish farmers is ~20 per 100 000 person-years, some 20 times higher than our general UK population rate.[8] We found similar incidence rates in men and women, which did not vary by age (data not presented), questioning the extent to which EAA is an occupational disease. Our finding that people with EAA are less likely to be current smokers than the general population has been reported before, but our results should be less subject to recall or selection bias, and our study have a sufficient sample size to give an accurate estimate of the effect.[9,10] Whether cigarette smoking might protect against the development of EAA, and if so, by what mechanism, is unclear, but it suggests that nicotine replacement therapy might be worth trying in difficult cases of EAA. Increased mortality in patients with EAA who develop lung fibrosis has also been reported before, but again, our study puts this finding into a general population context.

Summary

EAA is not a rare condition and most hospital centres with catchment areas of about half a million people can expect to see about five new cases of EAA each year. The diagnosis is associated with a marked increase in mortality, highlighting the need to avoid disease progression and the development of lung fibrosis.

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