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Multiple sclerosis course and clinical outcomes in patients with comorbid asthma: a survey study

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ABSTRACT

Objective: To determine if comorbid asthma is associated with accumulation of multiple sclerosis (MS)-related impairment and disability.

Method: We sent a comprehensive questionnaire to a cohort of patients with MS and examined the association between comorbid asthma and reaching Expanded Disability Status Scale (EDSS) scores 4.0 and 6.0. Multiple Sclerosis Impact Scale (MSIS-29) scores were compared between patients with MS with and without comorbid asthma.

Results: 680 patients participated in our study of whom 88 (12.9%) had comorbid asthma. There was no difference in the prevalence of asthma between our MS cohort and the England general population (OR: 0.89, 95% CI 0.68 to 1.17). We did not observe a significant association between having asthma and the risk of reaching EDSS scores 4.0 and 6.0 (HR: 1.29, 95% CI 0.93 to 1.77, and HR: 1.33, 95% CI 0.93 to 1.89, respectively) after controlling for confounders. Patients with MS with asthma reported higher level of psychological impairments (coefficient: 2.29, 95% CI 0.1 to 4.49).

Conclusions: Asthma is a prevalent condition among patients with MS and it may contribute to the psychological impairment in MS. Although we did not observe significant association between comorbid asthma and physical disability in MS, it seems that the two conditions influence one another.

INTRODUCTION

Several studies report on various aspects of coexisting asthma and multiple sclerosis (MS); however, the results are contradictory. Traditionally, it was argued that the two conditions are mutually exclusive: asthma is mediated by T helper cells 2 (Th2) and MS by Th1 cells. In 2004, an epidemiological study from our centre found an increased prevalence of asthma and all atopy in patients with MS compared with the general population.[1] In contrast, a study by Bergamaschi et al[2] and another by Tremlett and colleagues showed an inverse association

Strengths and limitations of this study

- This is the first study investigating the association between comorbid asthma and the progression of impairment and disability in multiple sclerosis (MS).
- The data used in this study was from a well-established cohort of patients with MS with detailed and robust disability outcomes.
- Our study has a response rate of 54%. A potential selection bias may result from the proportion of non-responders.
- The asthma in our study is self-reported (although this needed to be confirmed by a doctor).

between asthma and MS. However, these studies had lower numbers of study subjects.[3] A systematic review and meta-analysis by Monteiro et al[4] has shown no evidence of an association between asthma and MS. On the other hand, it has been shown that patients with MS in general bear a higher risk of immune-mediated diseases.[5–7] Apart from the speculations on biological plausibility[8] and the underlying mechanisms, the effect of asthma on the clinical course and prognosis of MS has not been well understood.

In this cohort study, we compared the general and clinical characteristics of patients with MS with and without asthma, and investigated the association between comorbid asthma and physical disability and psychological impairment in patients with MS.

METHOD

We analysed data from patients registered in the Nottingham University Hospital MS clinics. These clinics are major catchment and referral centres in East Midlands, UK. The centre and patient population has been described in more detail elsewhere.[9] [10] In 2013, an asthma and smoking questionnaire with questions obtained from Health Survey

BMJ

for England 2010, Respiratory Health (NS)[11] and European Community Respiratory Health Survey II (ECRHS)[12] were sent to 1260 patients with a definite diagnosis of MS. Patients were eligible to participate in the research if they were over 18 years of age and had been diagnosed with clinically definite MS by a neurologist according to the McDonald and/or Poser criteria.[13] [14] Patients were specifically asked if they had any history of asthma and if so, whether this diagnosis had been confirmed by their general practitioner (GP) or any another relevant physician.

OUTCOMES

Through the survey, detailed data regarding any history of asthma, individual smoking status, parental smoking during subjects' childhood and place of living before the age of 5 years were obtained. The level of physical and psychological disability were assessed by the Multiple Sclerosis Impact Scale 29 (MSIS-29), data for which were obtained through the questionnaire.

Data with regard to gender, age, age at the onset of MS, duration of disease modifying treatments (DMTs), initial clinical course of MS (relapse onset vs progressive onset MS), and level of disability due to MS as measured by Expanded Disability Status Scale (EDSS)[15] were obtained from the clinical database held in the Division. The clinical database contained an average of four EDSS scores per patient that were estimated by a neurologist during patients' routine clinic visits.

The study was approved by the National Research Ethics Service East Midlands Ethics Committee Derby-1.

STATISTICAL ANALYSIS

Descriptive statistics were used to categorise the data. Where appropriate, parametric or non-parametric two-sided tests were employed to test the differences between groups, and χ^2 test was used to examine the differences between categorical variables.

Association between asthma and MS

Conditional logistic regression models were used to estimate the likelihood of having asthma in patients with MS compared to the two age and sex matched controls in England's general population.

Risk measurement

We employed Cox proportional hazard regression models to investigate the differences in the risk of reaching two EDSS score milestones: 4.0 (walking more than 500 m unaided but having moderate disability) and 6.0 (can walk 100 m with or without assistance). The HRs were reported as unadjusted and adjusted. Models were adjusted for MS onset age, sex, pack years cigarette smoked, initial clinical course of MS and exposure to DMT. Follow-up time was started at disease onset and ended at the time when EDSS reached the score 4.0 or 6.0 or date of last EDSS (if less than 4 or 6), whichever

occurred first; if none of those, it ended on 31 December 2013.

Median regression models were used to investigate the association between MSIS-29 physical and psychological scales in patients with and without asthma. The models were adjusted for MS onset age, sex, initial clinical course of MS, exposure to DMT and disease duration. Only significant covariates were fitted in the final model.

All statistical analyses were performed with Stata V.13.1 (StataCorp. 2013. *Stata Statistical Software: Release 13*. College Station, Texas, USA: StataCorp LP)

RESULTS

By March 2013, 680 questionnaires had been returned by subjects who met our inclusion criteria, giving a response rate of 54%. Mean age of respondents was 53 (SD±11.33) years with a 2:1 female:male ratio. In the patients with MS group, 57% had relapsing remitting MS (RR MS), 33% secondary progressive MS (SP MS), and 10% primary progressive MS (PP MS). Mean MS duration was 19 (SD±10.4) years and 54% were exposed to at least 1-year of disease modifying treatments (DMTs; table 1).

Characteristics of asthma in patients with MS

In our survey, 12.94% (n=88) of the patients reported a history of asthma, which had been confirmed by their GPs. When age-matched and sex-matched controls without MS (from health survey England 2010) were individually assigned to each MS case, we did not observe any association between occurrence of MS and asthma (OR: 0.89, 95% CI 0.68 to 1.17, p=0.42). Adjustment of the model for smoking status (ever-smoked vs never-smoked) and for parental smoking did not change the risk of developing asthma in patients with MS (OR: 0.92, 95% CI 0.70 to 1.23 p=0.60; detailed analysis not shown).

Median age at the onset of asthma was 14 (range from 2 to 74) years and this onset was 5 years (95% CI 3 to 8, p<0.001) later in people with MS compared with controls without MS. Twenty eight per cent of patients with MS with asthma reported having an attack of asthma in the past 12 months; however, they were 40% less likely to have an attack compared with the controls without MS when controlled for age and sex (OR: 0.60, 95% CI 0.37 to 0.98, p=0.04).

Among patients with MS with asthma, 84% and 86% had their first attack of asthma before MS onset and diagnosis, respectively. Of these patients, 15.2% reported a history of asthma in their fathers and 19.7% in their mothers; 45.8% were receiving treatment for their asthma. Overall, 66.6% received at least 1 year of DMTs (median 2 years) compared with 52% of the whole cohort of patients with MS (χ^2 (1)=6.3, p=0.01).

As per place of residence, 1.1% of patients with MS with asthma lived on a farm, 19.5% lived in a small village, 42.5% lived in a small town, 25.3% lived in a

Table 1 General demographic and clinical characteristics of the cohort

	Total (n=680)	With asthma (n=88)	Without asthma (n=592)
Age (mean (SD))	53 (±11.5)	48 (±11)	53 (±11.2)
Female %	66.67	76	70
Asthma %	12.94	–	–
Smoking %			
Ever-smoked	62	64	62
Regularly smoked	51	48	51
Father smoked	60	55	61
Mother smoked	38	37	38
EDSS (median (IQR))	5.5 (3 to 6.5)	4 (3 to 6.5)	5.5 (3 to 6.5)
MSIS-29 (median (IQR))	85 (60 to 106)	84 (59 to 108)	85 (60 to 106)
Psychological scale	23 (16 to 31)	27 (17 to 34)	23 (16 to 31)
Physical scale	62 (41 to 76)	60 (42 to 77)	62 (41 to 76)
DMT (≥1-year) (%)	53	67	51
MS duration (median (IQR))	17 (11 to 26)	16 (12 to 24)	18 (11 to 27)
Disease course (%)			
Relapsing remitting	57	72	54
Secondary progressive	34	24	35
Primary progressive	9	3	10
Age at the onset of MS (median (IQR))	33 (26 to 41)	30 (23 to 37)	33 (26 to 41)

DMT, disease-modifying treatments; EDSS, expanded disability status scale; MSIS-29, Multiple sclerosis impact scale-29; MS, multiple sclerosis.
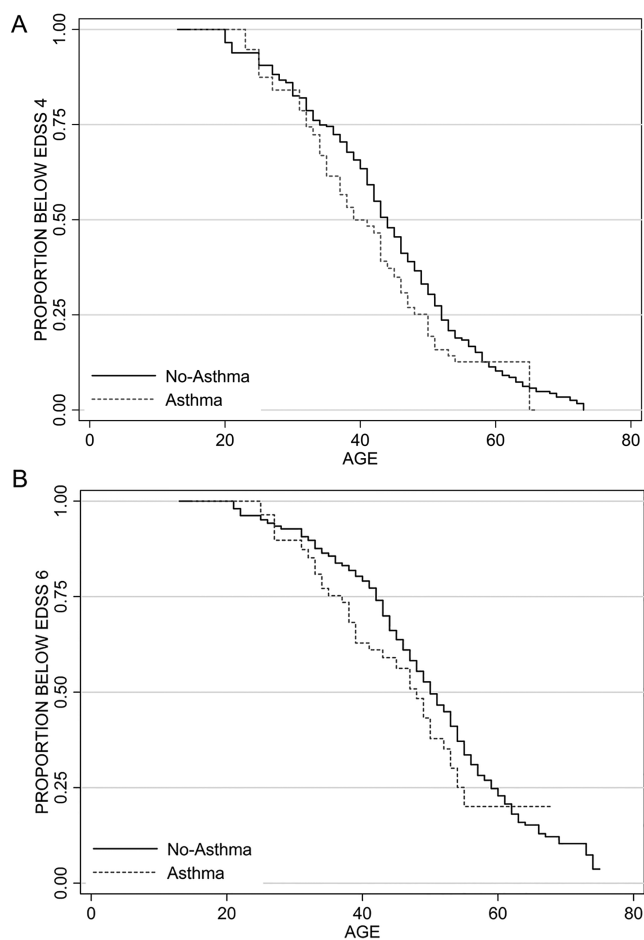
Figure 1 Kaplan–Meier graph showing A, time to expanded disability status scale (EDSS) score 4.0, B, time to EDSS score 6.0 by patients' asthma status.

suburb of a city and 11.5% lived in an inner city when they were under the age of 5 years. For patients with MS without asthma this was 4.5%, 24.9%, 32.1%, 31.5% and 7%, respectively ($\chi^2(4)$=8.37, p=0.08).

PRESENCE OF ASTHMA AND MS DISABILITY
Time to EDSS score milestones 4.0 and 6.0
Data needed to estimate the time to EDSS score 4.0 were available in 85% (n=581) of the patients and time to EDSS score 6.0 in 90% (n=612) of the patients. The proportion of missing data was not significantly different between asthma and non-asthma groups. Total follow-up time was 8347 and 9088 person-years for EDSS 4.0 and for EDSS 6.0, respectively. After controlling for sex, age at the onset of MS, disease initial clinical course, patient's smoking status at the time of disease onset and exposure to DMTs, patients with MS with asthma were not at higher risk of reaching EDSS score 4.0 or 6.0 compared to those without asthma: HRs of 1.29 (95% CI 0.93 to 1.77, p=0.11) and 1.33 (95% CI 0.93 to 1.89, p=0.11), respectively (figure 1A, B).

The unadjusted models showed almost similar results for both EDSS 4.0 and EDSS 6.0. The magnitude was in the same line for both EDSS scores, when the models were adjusted for age, sex, number of pack years of cigarettes (0–1 and more than 1 pack), DMT and MS course (table 2).

The physical and psychological scales (MSIS-29)
We did not observe any significant association between having asthma and overall MSIS-29 score (coefficient: 0.67, 95% CI −10.47 to 11.83, p=0.9) and MSIS-29 physical scale (coefficient: 0.41, 95% CI −7.56 to 8.39,

Table 2 Risk of asthma among the cohort with MS

	Crude HR (95% CI)*	p Value	Adjusted HR (95% CI)†	p Value
Time to EDSS score 4.0 (n=605)				
Asthma				
No	–		–	
Yes	1.27 (0.93 to 1.74)	0.12	1.29 (0.93 to 1.77)	0.11
Gender				
Male	–		–	
Female	0.78 (0.62 to 0.98)	0.03	0.84 (0.66 to 1.08)	0.18
Pack-years smoked from MS onset to EDSS 4.0				
<1	–		–	
>1	1.32 (1.04 to 1.67)	0.02	1.31 (1.03 to 1.67)	0.02
DMT≥1 year				
No	–		–	
Yes	1.25 (1.00 to 1.56)	0.04	1.36 (1.07 to 1.73)	0.01
Disease clinical course at onset				
Relapsing onset	–		–	
Progressive onset	1.85 (1.34 to 2.54)	<0.001	2.29 (1.62 to 3.28)	<0.001
Time to EDSS score 6.0 (n=612)				
Asthma				
No	–		–	
Yes	1.33 (0.93 to 1.88)	0.10	1.33 (0.93 to 1.89)	0.11
Gender				
Male	–		–	
Female	0.74 (0.58 to 0.95)	0.02	0.79 (0.61 to 1.03)	0.09
Pack-years smoked from MS onset to EDSS 6.0				
<1	–		–	
>1	1.19 (0.92 to 1.55)	0.17	1.20 (0.91 to 1.56)	0.18
DMT ≥1 year				
No	–		–	
Yes	1.27 (1.00 to 1.62)	0.04	1.35 (1.03 to 1.76)	0.02
Disease clinical course at onset				
Relapsing onset	–		–	
Progressive onset	1.58 (1.12 to 2.21)	0.008	1.92 (1.32 to 2.78)	0.001

*The univariate cox regression models without any adjustment.
†The model was adjusted for age, sex, pack of cigarette (0 to 1 and more than 1 pack), DMTs and MS course.
DMTs, disease modifying treatments; EDSS, expanded disability status scale; MS, multiple sclerosis.

p=0.91). However, patients with asthma had significantly higher level of psychological impairment as measured by MSIS-29 psychological scale (coefficient: 4.57, 95% CI 1.23 to 7.90, p=0.007; figure 2).

DISCUSSION
Here, we evaluated the association between comorbid asthma and the clinical course of MS. As asthma is a relatively common disease and is increasing in prevalence, affecting almost one in five people in countries, such as UK,[16] it seemed important to evaluate the extent of influence of each condition on the other's clinical course.[17] In the current work, we employed two widely used disability outcomes in MS, EDSS and MSIS-29. We could not find a pronounced association between comorbid asthma and MS physical disability although there was a trend toward a higher psychological impairment in those patients with MS who also had asthma. We found tobacco smoking, male gender and progressive onset to be associated with shorter time

to EDSS score milestones 4.0 and 6.0. These findings are in line with the previously published data.[18] We also found a higher risk of reaching the two disability milestones in those patients who were exposed to DMTs. This paradoxical finding may be related to the effect of the timing of introduction of DMT in the UK on this clinical cohort.

Our finding of the prevalence of asthma in patients with MS is compatible with the results from the meta-analysis by Monteiro *et al*.[4] However, it is different from a previous survey in our centre and the study by Ponsonby *et al*[8] that showed a significantly higher prevalence of asthma in patients with MS;[1] the results from a survey in Wales showed reduced prevalence of asthma in MS cases.[3] The exact reason for this discrepancy needs further investigation. The earlier study in our centre[1] showed a higher proportion of people with asthma and atopy in the MS population compared to this study. There are several possible explanations for this. First, the control population used in the previous work was based on the literature and second, comparisons in the
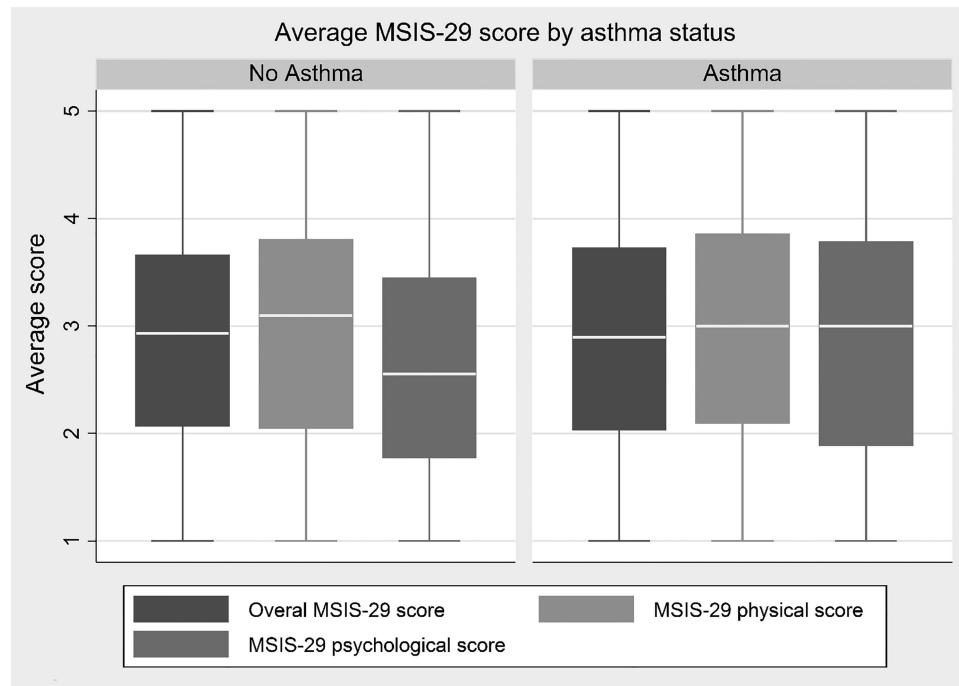
Figure 2 A box and whisker diagram illustrate median and IQR of mean overall Multiple Sclerosis Impact Scale 29 (MSIS-29), Physical MSIS-29 and Psychological scores.

previous work were based on prevalence in the whole group rather than those prevalent in age and sex stratified groups. Another possibility for these different results is that the criteria used in the earlier study were mainly based on current asthma and did not employ the comprehensive questionnaire used in this study. As shown here, when compared to controls without MS, patients with asthma with MS had lower recent attack rates (during the past 12 months) and only 45% were receiving treatment for their asthma. Hence, use of medication for asthma in patients with MS may be lower than controls which may subsequently influence the prevalence rate if prescription of a medication for asthma was used as an identifier for asthma cases. In addition, use of DMTs and steroids in patients with MS should also be considered as these drugs may modify asthma symptoms.[19 20]

Patients with MS are, in general, at higher risk of other immune-mediated disease;[7] however, asthma and rheumatoid arthritis has been reported to be inversely associated with MS.[7 21 3] Most reported risk factors common to both worsening of MS and of asthma are stress, tobacco, having a family member with asthma (6 times higher),[22] MS (2 times higher),[23] and viral infections.[8] Some of these risk factors have probably influenced the risk of MS when the subjects were suffering from asthma.[8]

Conversely, those factors which lower the risk for MS relapses but increase asthma attacks are pregnancy, level of physical activity and age of onset. In general, especially physical activity is lowered in MS and this can

delay the risk of asthma relapses and decrease the asthma diagnosis in patients with MS.

Generally around the age of 20, asthma is reported to be equally distributed between males and females; however, in our study, the sex ratio was constantly in favour of females. This could suggest that female hormones are contributing factors to the increased risk of developing asthma at a higher age.[24]

Strengths of this study include the opportunity to examine both asthma and MS in a well-established cohort of patients with MS with routine clinical follow-ups and detailed information on exposure. We had enough power to report the association between comorbid asthma and the relevant indicators of the course of MS. Further, this study used the self-reported MSIS-29, which is a responsive physical and psychological scale.[25]

Our study has some limitations. First, the asthma in our study is self-reported (although this needed to be confirmed by a doctor) and our analysis is based on only 88 cases of asthma in 680 patients with MS. Hence, our study could not be considered to be definitive. Second, the relatively old age in our cohort (mean age 52), which is typical for MS cohorts, may influence prevalence of asthma as asthma prevalence tends to decrease with age, particularly among smokers who tend to be diagnosed with chronic obstructive pulmonary disease (COPD) rather than asthma.[26 27] In addition, with the response rate of 54%, a potential selection bias may result from the proportion of non-responders among the MS cohort.

There has been extensive speculation regarding the association of autoimmune and allergic diseases. The initial hypothesis of Th1/Th2 dichotomy postulated a deviation of the immune system towards a primarily Th1 (autoimmune) or Th2 (allergic) response, as demonstrated by the tendency towards one or the other type of disease in patient groups.[3] [28] However, the discovery of Th17 and T regulatory (Treg) cells supports a common pathway of disordered reactivity to self or environmental factors, and there is evidence for Th17 and Treg dysregulation in a wide range of autoimmune and allergic disorders, including MS[29] and asthma.[30] [31]

Interestingly, our study shows that while the presence of coexisting asthma has no substantial impact on the clinical features of MS, the coexistence of MS may make asthma milder. In addition, the majority of the patients with MS with asthma (84%) developed asthma before MS onset. This is compatible with the concept that the default immune response is predominantly Th2 (as in asthma) and in our population, most likely to precede the MS-triggering immune response.[32] Such a response would then be disturbed and mitigated when a strong Th1/Th17, that characterises MS, emerges despite the extant Th2 default background.[33] When considering the results of this study, we need to take into account the relatively low number of subjects with coexisting MS and asthma (88 out of 680).

CONCLUSIONS

Asthma is a prevalent condition among patients with MS and it may contribute to the psychological impairment in MS. Although we did not observe a significant association between comorbid asthma and physical disability in MS, it seems that the two conditions influence one another. The shifting toward Th1, a suggested proinflammatory process in MS, may play a role in the lower risk of asthma after MS.

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