ORIGINAL ARTICLE

Epilepsy and associated mortality in patients with multiple sclerosis

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Background and purpose: We aimed to determine the prevalence of epilepsy in patients with multiple sclerosis (MS) at diagnosis, the risk of developing epilepsy after the diagnosis of MS and the relative risk of mortality associated with epilepsy.

Methods: We used the UK Clinical Practice Research Data-link to identify 2526 patients with incident MS and 9980 age-, sex- and index year-matched non-MS controls from 1997 to 2006. Logistic regression was used to estimate odds ratios [95% confidence interval (CI)] for epilepsy and Cox regression was used to estimate hazard ratios (HRs) (95% CI) for epilepsy and mortality.

Results: Patients with incident MS were on average 45 years old and 70.9% were female. At diagnosis, the prevalence of epilepsy in patients with MS was 1.30% compared with 0.57% in non-MS controls. At diagnosis, MS was associated with an adjusted odds ratio (95% CI) of 2.11 (1.36–3.27) for pre-existing epilepsy. Among epilepsy-free patients, the cumulative probabilities of developing epilepsy, first recorded within 10 years of the index date, were 2.77% for patients with MS and 0.90% for controls. MS was associated with an adjusted HR (95% CI) of 6.01 (2.94–12.29) for epilepsy. Among patients with MS, epilepsy was associated with an HR (95% CI) of 2.23 (1.02–4.84) for all-cause mortality.

Conclusions: This population-based study found an increased prevalence of epilepsy in patients with MS at diagnosis when compared with non-MS controls and the risk of developing epilepsy was also higher following the MS diagnosis. Patients with MS with epilepsy had a higher risk of mortality compared with those without.

Introduction

Multiple sclerosis (MS) is a female-predominant central nervous system inflammatory demyelinating disease that is associated with multiple comorbidities and increased mortality [1,2]. Epilepsy is one of the comorbidities in patients with MS that is more common than in the general population [1,3,4], which may lead to lost years of life [5]. However, Finnish and Canadian studies did not document the association between epilepsy and increased mortality in patients with MS [1,4].

Epileptic seizures involve excessive and hypersynchronous cortical brain network electrical activity, and therefore cortical and subcortical lesions in MS potentially contribute to an increased risk of epilepsy in MS [6,7]. The pathogenesis has not been clarified. Previous studies found an earlier disease onset of MS in patients with epilepsy compared with those without epilepsy [8]. However, it is not completely conclusive

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as to how epilepsy modifies the clinical course of MS [9]. It is also possible that epilepsy has an effect on brain atrophy that is additive to that of MS and thus contributes to a more rapid progression [8].

We hypothesized that patients with MS had a higher risk of epilepsy at and after diagnosis and that epilepsy in patients with MS increased mortality. Using data representative of the UK general population from the Clinical Practice Research Data-link (CPRD), we estimated the prevalence of epilepsy at the time of the MS diagnosis compared with matched controls in a primary care setting. We further followed patients with incident MS and their matched controls after initial MS diagnosis to compare their subsequent risks of developing epilepsy. Furthermore, we compared mortality in patients with MS with and without epilepsy.

Methods

The study was approved by the Independent Scientific Advisory Committee for the Medicines and Healthcare products Regulatory Agency Database Research (protocol 14-070).

Data source

The CPRD is a primary care database in the UK that contains prospectively collected medical records of research standards from around 16.5 million individuals registered in over 701 general practices [10]. The validity of the diagnoses recorded in the database is high, with confirmation of diagnoses in a median of 89% for 183 different conditions [11].

Study population

Our source population comprised all participants who contributed data to the CPRD between 1 January 1997 and 31 December 2006. We used Read codes (Table S1) to identify patients with MS, which have been used [2] and validated [12] previously. Patients with incident MS were participants with no evidence of MS prior to the time of diagnosis (assigned as the index date) and with at least a 3-year continuous registration prior to the index date [12,13]. The case definition was based on physician diagnosis using Read codes. Hernán *et al.* [12] reported that 91.8% of patients with a MS diagnosis in the CPRD were confirmed or possible cases of MS after a thorough chart review.

Selection of controls

Matched controls were selected from people who had an active registration in 1997–2006 and had no MS diagnosis. For each patient with MS, four randomly selected controls were matched by year of birth (±2 years), sex, general practice and year of first continuous registration (±2 years) (Fig. 1). The same index date was assigned to matched controls. As with patients with MS, there must have been 3 years of continuous registration prior to the index date.

Study period

We defined two periods to assess epilepsy: (i) the 10 years prior to diagnosis and (ii) from diagnosis to the earliest date of occurrence of the diagnosis of epilepsy, death, transfer out, last data collection time for practice or end of study (30 June 2016), whichever came first (Fig. S1).

Definition of epilepsy

We developed the Read code lists of epilepsy (Table S2) based on the opinions of two senior neurologists and a general practitioner. We were unable to validate epilepsy diagnosis in this study. However, epilepsy is an established paid-for-performance indicator for general practices in the UK to improve quality of care [14] and decrease mortality [15]. We performed sensitivity analyses by using an alternative case definition based on Read codes plus a prescription of antiepileptic drugs (AEDs).

We performed two sensitivity analyses. One included AEDs that were used by >1% of patients with epilepsy in the UK according to a previous CPRD study. The included AEDs were valproate, carbamazepine, lamotrigine, phenytoin, levetiracetam, phenobarbital, clobazam, topiramate, gabapentin, clonazepam, primidone and pregabalin [16]. The other included the aforementioned AEDs except for gabapentin and pregabalin, as both are more often prescribed for pain than for epilepsy.

Mortality

Mortality was based on the recording in the main database. The CPRD has an algorithm to identify death and date of death of participants. We have previously validated the recorded death in the CPRD main database [17]. The recording of death and death date in the CPRD is generally consistent with the national death registration.

Covariates

Covariates included general characteristics [age, sex, body mass index (BMI)], lifestyle factors (smoking status

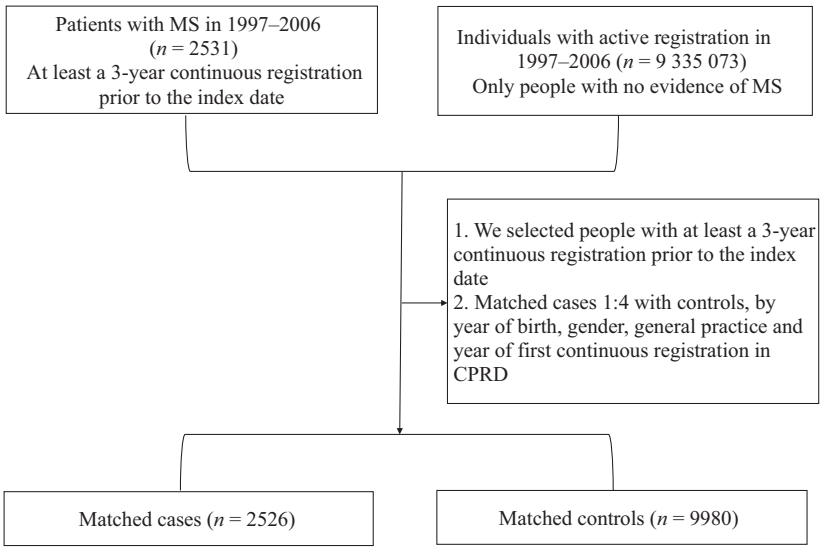

Figure 1 Flowchart of eligible patients with multiple sclerosis (MS) and matched controls. The study comprised patients with incident MS each with four matched non-MS controls who were continuously registered for at least 3 years before the date that MS was first recorded during 1997–2006. CPRD, Clinical Practice Research Data-link.

and alcohol consumption) and Charlson comorbidity index, which were derived from 17 diagnostic categories (Table S3) [18,19]. BMI, smoking and alcohol consumption have been recognized as potentially modifiable factors affecting MS risk [20–22] and possibly epilepsy [23–25]. The definition of these categories was based on physician diagnoses recorded as a list of Read codes [18,26].

Statistical analysis

The prevalence of epilepsy at index date was calculated by dividing the number of people diagnosed with epilepsy before the index date (numerator) by the number of patients with incident MS or non-MS controls (denominators). Odds ratios (ORs) and 95% confidence interval (CI) were used to estimate the association between MS and epilepsy at index date using conditional logistic regression adjusting for age, sex, index year, BMI category, smoking status, alcohol consumption and Charlson comorbidity index. Missing data for BMI, smoking and alcohol status were coded as 'unknown'. Kaplan–Meier plots were used to estimate the probability of epilepsy in people with incident MS and those without MS at and following diagnosis. The log-rank test was used to compare the probability of epilepsy between patients with MS and controls. Only people at risk for epilepsy (not having epilepsy at index date) were considered to estimate the hazard ratios (HRs) for developing epilepsy. HRs and 95% CI were calculated for incident epilepsy using a Cox proportional hazards model. The HRs were adjusted for age, sex, index year, BMI categories, smoking status, alcohol consumption and Charlson comorbidity index.

To examine the effect of epilepsy on death among patients with MS, we limited the analyses to those with MS. Patients with MS were followed from the index date. We considered epilepsy as a time-varying factor. Those with epilepsy at or prior to diagnosis and those without epilepsy through follow-up were followed from the diagnosis to the censor date (the earliest date of occurrence of death, transfer out, last data collection time for the practice or end of study, i.e. 30 June 2016). Patients with MS who developed epilepsy after the diagnosis of MS had their follow-up divided into two parts: non-epilepsy exposure and epilepsy exposure. Non-epilepsy exposure period was defined as from MS diagnosis to the censor date. Epilepsy exposure period was defined as from the first date when epilepsy was diagnosed to the censor date. All statistical analyses were performed using SAS statistical software, version 9.3 (Marlow, Buckinghamshire, UK).

Results

We identified 2526 patients with incident MS from 1997 to 2006 with a mean age of 45.0 ± 12.4 years (70.9% female). The median observation period (interquartile range) was 12 (7–21) and 10 (5–13) years before and after the index date, respectively. They were matched to 9980 controls with similar age and sex structure and observation periods before and after their index dates (Table 1).

Retrospective observation

On the index date, 33 patients with MS (21 females) already had an epilepsy diagnosis, equivalent to a prevalence of epilepsy of 1.30% (95% CI, 0.90%–1.83%). We also identified 57 controls with epilepsy (38 females), with a significantly lower prevalence of

0.57% (95% CI, 0.43%–0.74%; $P < 0.0001$). In a logistic regression model adjusting for age, index year, BMI, smoking, alcohol consumption and Charlson comorbidity index, MS was associated with an OR of 2.11 (95% CI, 1.36–3.27) for epilepsy.

Follow-up data after the index date

Figure 2 compares the cumulative probability of first recorded epilepsy between patients with MS and matched controls who were epilepsy-free at index date (log-rank test, $P < 0.001$). The cumulative probabilities of first recorded epilepsy at 1, 5 and 10 years from index date were 1.46%, 2.07% and 2.77% in patients with incident MS and 0.65%, 0.78% and 0.90% in controls.

Next, we investigated the relative risk of incident epilepsy diagnosis in patients with MS compared with non-MS controls. Using Cox proportional hazard model adjusting for age, index year, BMI, smoking, alcohol consumption and Charlson comorbidity index, MS was associated with an HR (95% CI) of 6.01 (2.94–12.29) for epilepsy (Table 2).

Mortality

We limited the analysis to patients with MS to examine the association between epilepsy and all-cause mortality. After controlling for BMI group, Charlson comorbidity, smoking and alcohol use, epilepsy was associated with an HR of 2.23 (95% CI, 1.02–4.84) for all-cause mortality in patients with MS.

Sensitivity analysis

Using the alternative case definition of epilepsy (a diagnosis plus a prescription of AEDs), we identified 31 patients with MS who already had epilepsy, equivalent to a prevalence of epilepsy of 1.23% (95% CI, 0.84%–1.74%) and 44 controls who already had epilepsy, with a significantly lower prevalence of 0.44% (95% CI, 0.32%–0.59%; $P < 0.0001$). Using a logistic regression model, MS was associated with an adjusted OR (95% CI) of 2.40 (1.37–4.22). Among those without epilepsy at baseline, 31 patients with MS and 20 controls developed epilepsy after the index date. Using Cox proportional hazard model, MS was associated with an adjusted HR of 6.79 (95% CI, 3.78–12.18).

In the second set of sensitivity tests using the case definition of epilepsy with a diagnosis plus a prescription of AEDs excluding gabapentin and pregabalin, we identified 28 patients with MS who already had epilepsy, equivalent to a prevalence of epilepsy of 1.11% (95% CI, 0.74%–1.60%) and 43 controls who already had epilepsy, with a significantly lower

Table 1 Characteristics of patients with incident multiple sclerosis (MS) and matched non-MS controls

Characteristic	Incident MS (n = 2526)	Non-MS controls (n = 9980)	Adjusted[a] OR (95% CI)
Age (years) (±SD)	45.04 ± 12.37	45.17 ± 12.43	
Female gender	1790 (70.9)	7070 (70.8)	
Median observation (years) (IQR)			
Prior to index date	12 (7–21)	12 (7–20)	
After index date	10 (5–13)	10 (6–13)	
BMI (kg/m^2)			
<25.0	1052 (41.65)	3621 (36.28)	Reference
25.0–29.9	685 (27.12)	2670 (26.75)	0.88 (0.79–0.98)*
≥30	469 (18.57)	1871 (18.75)	0.86 (0.76–0.97)*
Unknown	320 (12.67)	1818 (18.22)	0.57 (0.49–0.66)*
Smoking			
Non-smoker	720 (28.5)	2953 (29.59)	Reference
Current smoker	554 (21.93)	1542 (15.45)	1.53 (1.34–1.75)*
Ex-smoker	878 (34.76)	3261 (32.68)	1.09 (0.97–1.24)
Unknown	374 (14.81)	2224 (22.28)	0.62 (0.54–0.72)*
Alcohol consumption (units/week)			
Never/ex-drinker	333 (13.18)	1085 (10.87)	Reference
Current 1–9	1245 (49.29)	4523 (45.32)	0.90 (0.78–1.03)
Current ≥10	344 (13.62)	1321 (13.24)	0.83 (0.68–1.01)
Unknown	604 (23.91)	3051 (30.57)	0.59 (0.50–0.70)*
Charlson comorbidity index			
0	1952 (77.28)	8303 (83.2)	Reference
1–2	501 (19.83)	1518 (15.21)	1.42 (1.27–1.60)*
≥3	73 (2.89)	159 (1.59)	1.99 (1.49–2.66)*

BMI, body mass index; CI, confidence interval; IQR, interquartile range; OR, odds ratio. Data are given as n (%) unless stated otherwise. *$P < 0.05$. [a]Adjusted for age, sex and index year.

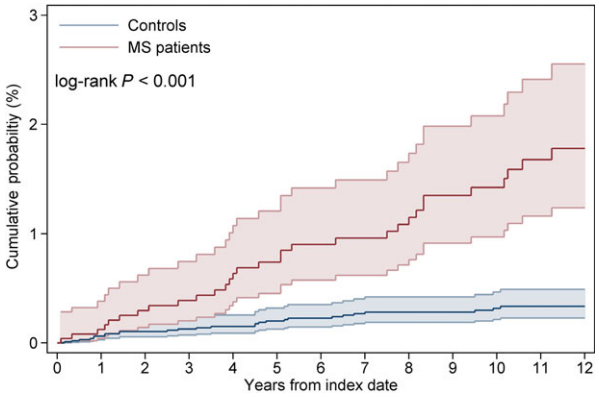

Figure 2 Cumulative probability of first recorded epilepsy in patients with multiple sclerosis (MS) (red) and non-MS controls (blue). Cumulative probability of first recorded epilepsy is higher in patients with incident MS than in matched controls (log-rank test, $P < 0.001$).

Table 2 Cox proportional hazard models examining relative risks of the first recorded epilepsy in patients with incident multiple sclerosis (MS) compared with matched controls

Variable	Crude HR (95% CI)	Adjusted[a] HR (95% CI)
MS	4.53 (2.66–7.72)*	6.01 (2.94–12.29)*
BMI (kg/m^2)		
<25.0	Reference	Reference
25.0–29.9	2.31 (1.20–4.46)*	4.83 (1.90–12.27)*
≥30	1.24 (0.53–2.91)	1.73 (0.56–5.30)
Unknown	0.65 (0.19–2.21)	2.49 (0.50–12.53)
Smoking		
Non-smoker	Reference	Reference
Current smoker	0.53 (0.24–1.17)	0.58 (0.20–1.64)
Ex-smoker	0.76 (0.31–1.83)	0.76 (0.21–2.73)
Unknown	0.25 (0.09–0.70)*	0.10 (0.02–0.51)*
Alcohol consumption (units/week)		
Never/ ex-drinker	Reference	Reference
Current 1–9	0.92 (0.38–2.26)	0.58 (0.16–2.08)
Current ≥10	1.17 (0.52–2.65)	0.79 (0.24–2.59)
Unknown	0.52 (0.19–1.38)	1.39 (0.54–3.56)
Charlson comorbidity index		
0	Reference	Reference
1–2	2.20 (1.04–4.65)*	3.69 (1.31–10.44)*
≥3	3.97 (1.13–13.88)*	3.66 (1.00–13.36)

BMI, body mass index; CI, confidence interval; HR, hazard ratio. Data are given as n (%) unless stated otherwise. *$P < 0.05$. [a]Adjusted by age, sex, registered general practitioner and index year.

prevalence of 0.43% (95% CI, 0.31%–0.58%; $P < 0.0001$). MS was associated with an adjusted OR (95% CI) of 2.37 (1.33–4.24). Among those without epilepsy at baseline, 31 patients with MS and 16 controls developed epilepsy after the index date. Using Cox proportional hazard model, MS was associated with an adjusted HR of 8.64 (95% CI, 4.63–16.09).

Discussion

This population-based study found that approximately one in 80 patients with incident MS already had epilepsy at diagnosis, which is twice as many as for controls. After 10 years of follow-up, 2.77% of epilepsy-free patients with MS at diagnosis were diagnosed with epilepsy. MS was associated with a sixfold risk of epilepsy. Furthermore, our results documented a twofold increase in the risk of mortality in patients with MS with epilepsy compared with those without. Overall, epilepsy is not uncommon in patients with MS and is a poor prognostic factor for death.

A recent systematic review summarized data from 24 studies and estimated that the prevalence of seizure disorders in patients with MS ranged from 0.89% to 8.06% with a high heterogeneity among studies [27]. Several studies reported a comparison of epilepsy risk in patients with MS and controls. In general, the risk ratio between MS and controls ranged from 1 to 16 [27–29]. Allen *et al.* [30] found that patients with MS have a three- to fourfold higher risk of hospital admissions for epilepsy than other patients without MS. The current study found that patients with incident MS have a sixfold risk for epilepsy, which may not need admission, compared with controls using the CPRD.

Several studies estimated the incidence of epilepsy in patients with MS. For example, the cumulative incidence of epilepsy in the Swedish MS register has an increasing trend after MS diagnosis compared with controls [3]. The current study utilized data from the CPRD, which is representative of the primary care population in the UK, to ensure a minimum selection bias. In addition to sex and age, we further matched by factors such as the comorbidity index and lifestyle factors, which are relevant to both MS and epilepsy [18,20–26]. In addition, our design considered the timing of both MS diagnosis and epilepsy onset. We found that patients with MS already had a higher risk of epilepsy at the time of diagnosis and the risk was also higher after the diagnosis. Our findings support that the concurrence of MS and epilepsy is not a chance association, but rather that epilepsy is an integral part of MS.

The pathogenesis of epilepsy in MS remains elusive. Thompson *et al.* [31] reported seven patients with MS with acute seizures whose magnetic resonance imaging data revealed new evolving or enhancing lesions involving the cortex or subcortical areas. Acute seizures may remit as the oedema associated with the lesion resolves, whereas recurrence of seizures may be due to the damaged cerebral structures becoming epileptogenic [31]. The hypothesis that epilepsy is

associated with focal cortical and subcortical lesions in MS is further supported by recent magnetic resonance imaging studies [32–34]. Patients with MS with epilepsy had a higher load of cortical or subcortical lesions than 26 matched patients with MS without epilepsy [32–34]. A previous study also showed that patients with MS with epilepsy have a higher disability score than those without epilepsy after the same disease duration [35], which suggests the effect of MS severity on the development of epilepsy. The mechanism whereby some of the MS lesions become epileptogenic is unknown. A recent histopathological study showed decreased immunostaining of Kir4.1 proteins in acute demyelinating and chronic active demyelinated lesions of the subcortical regions in MS [36]. The Kir4.1 proteins are part of potassium channels present on oligodendrocytes and loss of function of these channels increases seizure susceptibility [37].

The long-term prognosis of patients with MS with epilepsy compared with those without epilepsy was not known previously. The patients with relapsing-remitting MS with epilepsy had a more pronounced cognitive decline and a higher disability over 3 years than those without [34]. Among the whole MS population, disease duration and disability score were associated with epilepsy [3]. Gasparini *et al.* [35] conducted a systematic review and revealed that the age at onset is younger and disability score tends to be higher in patients with MS with epilepsy than those without. This study further found an association between epilepsy and increased mortality in patients with MS.

There are several limitations to this study. First, we could not classify the disease subtypes and severity of MS because this information was not routinely recorded. The life expectancy in patients with MS is related to MS itself and is correlated with disease disability severity and duration [38]. Patients with MS with epilepsy tend to have a higher disability than those without epilepsy [35]. In addition, the severity of epilepsy (e.g. status epilepticus) can contribute to early death, but this was not considered separately because of the low number of cases. In this study, we used the mortality outcome as a surrogate to evaluate the effect of epilepsy on the clinical course of MS. Secondly, misclassification bias may occur as the identification of patients with MS was based on physician diagnosis, rather than according to accepted criteria. However, the diagnosis of MS in the CPRD has been investigated and validated previously [12]. Similarly, there may have been some misclassification of epilepsy. However, we performed a sensitivity analysis for those with epilepsy diagnosis and found similar results. Thirdly, the models did not adjust for all potential risk factors for epilepsy, such as previous head injuries or history of epilepsy in childhood. However, part of these risk factors was accounted for by the Charlson comorbidity index, as it incorporated 17 different categories of illnesses. In addition, with such a large effect size of 4, it is unlikely that any or all of these potential sources of bias explain our findings thoroughly. Furthermore, limited evidence suggests that some disease-modifying treatments and symptomatic treatments may increase the risk of developing epilepsy [39]. We did not examine the use of disease-modifying treatments in this cohort because disease-modifying treatments are given in secondary care and data on their use are not linked in the current dataset.

Conclusion

A fraction of patients with MS (approximately 1%) in the UK already have epilepsy at diagnosis. In epilepsy-free patients, the risk of incident epilepsy was also higher after diagnosis, affecting almost a further 3% by 10 years. Patients with MS with comorbid epilepsy had a higher risk for mortality than those without epilepsy.

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Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Observation of epilepsy in a patient with incident multiple sclerosis.
Table S1. Read codes for multiple sclerosis
Table S2. Read codes for epilepsies
Table S3. The 17 comorbid disease categories and assigned weight in Charlson's comorbid index. An individual's combined comorbidity score is calculated by summing the weights

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