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Previously diagnosed influenza infections and the risk of developing epilepsy

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SUMMARY

Several epidemiological studies suggest a possible involvement of viral infection in the development of epilepsy. While recent research from *in vitro* studies increasingly supports the role of herpes simplex virus type 1 (HSV-1) in the pathogenesis of epilepsy, little is known about the role of other viral infections such as influenza. Using data from the Clinical Practice Research Datalink (CPRD), we conducted a matched case-control analysis to assess the association between GP-diagnosed influenza infections and the risk of developing an incident diagnosis of epilepsy. During the study period 11 244 incident epilepsy cases and 44 976 matched control patients were identified. Prior exposure to influenza was reported in 7·5% of epilepsy cases and 6·7% of controls [adjusted odds ratio (aOR) 1·12, 95% confidence interval (CI) 1·03–1·22]. Prior history of 'complicated influenza', i.e. influenza associated with a possible super-infection, was associated with a slightly increased epilepsy risk (aOR 1·64, 95% CI 1·10–2·46), particularly if recorded within the 2 months preceding the epilepsy diagnosis (aOR 6·03, 95% CI 1·10–33·2). Our findings suggest that prior influenza exposure does not appear to materially alter the risk of developing epilepsy. By contrast, influenza episodes accompanied by complications were associated with a slightly increased epilepsy risk.

Key words: Case-control, epilepsy, influenza.

INTRODUCTION

Epilepsy is a chronic neurological condition which is characterized by the occurrence of repeated seizures [1]. Globally, it is estimated that there are 50 million people living with epilepsy [1]. In the UK alone, about 600 000 people have a diagnosis of epilepsy or receive anti-epileptic drugs [2]. The main aetiological factors for epilepsy include genetic susceptibility, medical disorders such as stroke and other vascular diseases, dementia, head trauma, certain developmental disorders, and a history of febrile seizures during childhood [3].

In addition to the aetiological factors mentioned above, there is evidence to suggest that viral infections, such as herpes simplex virus (HSV), may play a role in the development of epilepsy [4–8]. Viral

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infections can result in the occurrence of viral encephalitis, which has been reported to increase the risk of developing epilepsy by 16-fold [5]. It has been noted that among survivors of HSV encephalitis (HSE), epilepsy is a major problem [4]. An observational study that assessed the long-term outcome of 42 patients diagnosed with herpes simplex encephalitis found that 24% of the 34 surviving patients had a later diagnosis of epilepsy [9]. More recent *in vitro* studies of the neuropathogenesis of HSV-associated seizures have shown that HSV-1 infection can lead to epileptiform activity and increased seizure susceptibility. This is thought to be through a direct change to the excitability of the hippocampal CA3 neuronal network and neuron loss, and a subsequent increase in synaptic reorganization in the supragranular area [4, 10, 11].

While there is increasing research and understanding into the role of HSV infection and its association with epilepsy, few studies have examined the role of other viral infections such as influenza. A link between influenza and the development of neurological complications is widely recorded [12–14]. Several case series on the development of neurological complications following influenza reported a high frequency of both seizures and encephalopathy [13, 15–18]. The majority of seizures appeared to be febrile, and a growing number of observational studies suggest an association between the occurrence of febrile seizures and the later development of epilepsy [19–22]. In addition, hemiconvulsions and transient periodic lateralized epileptiform discharges, which are associated with epilepsy [23], have been associated with influenza B-associated encephalopathy [24].

While recent studies support the involvement of HSV-1 infection in the development of epilepsy, the role of other viral infections such as influenza remains largely unclear. In these circumstances, further research into whether an association exists between influenza and the risk of epilepsy would be beneficial. Therefore, we set out to conduct a case-control analysis using data from the Clinical Practice Research Datalink (CPRD), to assess whether influenza episodes are associated with an altered risk of developing an incident diagnosis of epilepsy.

METHODS

Data source

The CPRD provides anonymized healthcare information on some 8 million patients in the UK, going back as far as 1987. Information on demographics (age, sex, weight, height), consultations, symptoms, diagnoses, specialist referrals as well as details on prescribed medications and lifestyle factors (e.g. tobacco and alcohol use) are recorded in the CPRD by specially trained General Practitioners (GPs). Read and Multilex codes are used to classify medical diagnoses and drug prescriptions, respectively. Recorded information on diagnoses and drug exposure has been validated and proven to be of high quality [25, 26]. The CPRD has been previously used for studies on influenza [27–30]. The study protocol was reviewed and approved by the Independent Scientific Advisory Committee (ISAC) for Medicines and Healthcare Products Regulatory Agency Database Research.

Study population

Cases were defined as patients aged $\leqslant 90$ years with a first-time recorded Read code for epilepsy, seizures, convulsions or fits (subsequently referred to as 'epilepsy'), followed by at least $\geqslant 2$ repeat prescriptions for an anti-epileptic medication during the period of 1 January 1995 to 30 July 2012. The index date was defined as the date of the first recorded diagnosis of epilepsy. We excluded all cases with <3 years of recorded history, as well as those with a recording for cancer (excluding non-melanoma skin cancers), developmental disorders (i.e. Down syndrome, cerebral palsy), HIV/AIDS, alcoholism or drug abuse prior to the index date.

Four control subjects were randomly identified for each epilepsy case patient, matched to cases on index date, GP practice, year of birth, gender, and number of years of previous recorded history in the database. Control patients were defined as patients with no recorded history of epilepsy, seizures, convulsions, or fits, and no recorded prescription for anti-epileptic medication prior to the index date. The same exclusion criterion was applied to controls as to cases.

Assessment of influenza

Using Read-coded information recorded in the patient record prior to the index date, the number of influenza episodes and the timing of the last influenza episode prior to the index date were assessed. Patients who ever had an influenza or influenza-like illness (ILI) diagnosis recorded prior to the index date were stratified by number of previous recorded infections (1, 2, $\geqslant 3$ episodes) and by timing of previous influenza episodes

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(last recorded episode recorded within 1–59, 60–364, 365–729, or ⩾730 days prior to the index date). If a patient had more than one influenza episode recorded, these were considered two separate influenza episodes if recorded >30 days apart. Of those who ever had influenza recorded by the GP prior to the index date, we further assessed whether any of these previous influenza episodes were followed within 30 days by a recording for a clinical complication, based on a possible bacterial superinfection; these included sepsis, meningitis, encephalitis, or pneumonia. An influenza episode accompanied by such a recording may reflect a more severe influenza, and were referred to as 'influenza with complications'. Bacterial superinfections are noted to be a common cause of influenza-related hospitalization [31].

Assessment of other exposures

The prevalence of various comorbidities and co-medications was assessed for all cases and controls. A patient was coded as having a comorbidity or medication use if there was a code for that diagnosis or drug in the patient record any time prior to the index date. For other covariates including body mass index (BMI ⩽18·4, 18·5–24·9, 25–29·9, ⩾30 kg/m^2), smoking (never, ex-smoker, current, unknown), and alcohol use (never, ex-drinker, current, unknown), information recorded in the patient record closest prior to the index date was used. In addition, the following covariates were assessed to test for potential confounding: asthma, chronic obstructive pulmonary disease (COPD), ischaemic heart disease, heart failure, atrial fibrillation, stroke or transient ischaemic attack (TIA), hypertension, hypercholesterolaemia, diabetes mellitus, receipt of influenza vaccinations, antibiotic medication, systemic corticosteroids, and immunosuppressant drugs.

Statistical analysis

Conditional logistic regression analyses were conducted to explore the association between influenza episodes prior to the index date and the risk of a first-time epilepsy diagnosis. Univariate and multivariate odds ratios (ORs) with 95% confidence intervals (CIs) were assessed for 'ever *vs.* never' exposure to influenza, as well as analyses stratified by frequency and timing of previous infections. Potential confounding factors were assessed and included in the model if there was a ⩾10% change in the univariate estimate of epilepsy risk associated with influenza. In addition, interaction by gender was evaluated. All statistical analyses were conducted using SAS release 9·3 (SAS Institute Inc., USA).

RESULTS

During the study period 11 244 epilepsy cases were identified and matched to 44 976 control patients (49·7% female). Over 67% of cases were aged <60 years at the index date. Characteristics for both cases and controls are shown in Table 1. A substantially increased risk of epilepsy was observed in individuals with a prior history of stroke and dementia (Table 1). The majority (89%) of influenza episodes appeared to be seasonal, i.e. recorded during the period October through to April.

There was no increased risk of developing epilepsy in patients with one or more influenza episodes at any time prior to the index date compared to those with no recorded influenza (OR 1·12, 95% CI 1·03–1·22) after adjusting for smoking status, alcohol use, history of stroke, and prior use of corticosteroids or antibiotics. There was no material effect of timing of last influenza prior to the index date or by number of prior episodes (Table 2). Tests for interaction by gender revealed no evidence of effect modification ($P = 0{\cdot}1311$). Stratification by gender yielded an adjusted OR (aOR) of 1·20 (95% CI 1·06–1·36) for males, and of 1·05 (95% CI 0·93–1·19) for females.

For patients with 'complicated influenza', over 97% had a subsequent diagnosis of pneumonia. An increased risk of developing epilepsy with prior 'complicated influenza' exposure was observed in both the crude (OR 1·75, 95% CI 1·19–2·56) and adjusted (OR 1·64, 95% CI 1·10–2·46) analyses. In Table 3 we present the effects stratified by timing of the last recorded influenza episode. There was a substantially increased risk of epilepsy for those with a recent (within 60 days) 'complicated influenza' compared to patients with no history of influenza (aOR 6·03, 95% CI 1·10–33·2). This finding, however, was based on only three cases and three controls. A significant trend with increasing time since last influenza episode was observed; however numbers in each category were small (Table 3). For most cases with a 'complicated influenza' the last diagnosis was ⩾730 days prior to the index date and there was an increase in risk in these cases (aOR 1·94, 95% CI 1·22–3·11). The majority (97%) of these patients had only one 'complicated influenza' so we could not evaluate the effects of increasing

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Table 1. *Characteristics of epilepsy cases and their matched controls*

	Cases ($n = 11\,244$)	Controls ($n = 44\,976$)	OR (95% CI)
Gender			
Male	5652 (50·3)	22 608 (50·3)	—
Female	5592 (49·7)	22 368 (49·7)	—
Age, years			
0–9	1257 (11·2)	5079 (11·3)	—
10–19	2249 (20·0)	8958 (19·9)	—
20–29	1609 (14·3)	6418 (14·3)	—
30–39	499 (4·4)	1987 (4·4)	—
40–49	1456 (13·0)	5829 (13·0)	—
50–59	486 (4·3)	1933 (4·3)	—
60–69	1150 (10·2)	4637 (10·3)	—
⩾70	2538 (22·6)	10 135 (22·5)	—
Body mass index (kg/m^2)			
⩽18·4	220 (2·0)	631 (1·1)	1·38 (1·17–1·62)
18·5–24·9	2670 (23·8)	10 474 (23·3)	1·00
25–29·9	2077 (18·5)	8654 (19·2)	0·94 (0·88–1·00)
⩾30	1155 (10·3)	4448 (9·9)	1·02 (0·94–1·10)
Unknown	5122 (45·6)	20 769 (46·2)	0·94 (0·87–1·01)
Smoking status			
Non-smoker	3934 (35·0)	16 261 (36·2)	1·00
Current smoker	1765 (15·7)	6199 (13·8)	1·19 (1·12–1·27)
Ex-smoker	1685 (15·0)	6527 (14·5)	1·09 (1·02–1·17)
Unknown	3860 (34·3)	15 989 (35·6)	0·91 (0·84–0·98)
Alcohol use			
Non-drinker	1647 (14·7)	5412 (12·0)	1·00
Current drinker	5114 (45·5)	20 946 (46·6)	0·79 (0·74–0·85)
Former drinker	163 (1·6)	327 (0·7)	1·68 (1·38–2·05)
Unknown	4320 (38·4)	18 291 (40·7)	0·68 (0·63–0·74)
Risk factors			
Diabetes	577 (5·1)	1854 (4·1)	1·28 (1·16–1·41)
Arrhythmia	666 (5·9)	1747 (3·9)	1·63 (1·48–1·80)
Heart failure	258 (2·3)	833 (1·9)	1·27 (1·10–1·48)
Ischaemic heart disease	776 (6·9)	2814 (6·3)	1·13 (1·04–1·24)
Hypertension	2192 (19·5)	7561 (16·8)	1·31 (1·23–1·40)
Stroke	1774 (15·8)	1343 (3·0)	8·61 (7·87–9·42)
Pulmonary embolism	98 (0·9)	240 (0·5)	1·65 (1·30–2·09)
Deep vein thrombosis	158 (1·4)	419 (0·9)	1·52 (1·27–1·84)
Cholesterol	783 (7·0)	2744 (6·1)	1·19 (1·08–1·30)
Dementia	409 (3·6)	261 (0·6)	8·21 (6·88–9·80)
Prior medication use			
Systemic corticosteroids	1882 (16·7)	6559 (14·6)	1·20 (1·13–1·27)
Immunosuppressant	106 (0·9)	267 (0·6)	1·60 (1·28–2·01)
Antibiotics	9556 (85·0)	37 271 (82·9)	1·23 (1·15–1·31)

OR, Odds ratio; CI, confidence interval.

number of such episodes. A direct comparison between 'complicated influenza' and 'influenza' yielded an aOR of 2·08 (95% CI 0·81–5·34).

DISCUSSION

There have been reports of neurological effects associated with influenza infections, and an increase in seizures and epilepsy reported in both children and adults following the 2009 influenza A(H1N1) pandemic [14, 32]. The exact biological mechanism by which severe influenza may lead to epilepsy, however, is uncertain. Research has shown that viral infections can induce neuronal inflammation and pro-inflammatory cytokine release, leading to an influx of pro-inflammatory mediators into the CNS

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Table 2. *Unadjusted and adjusted odds ratios for the association between epilepsy and previous influenza episodes*

	Cases (n = 11 244)	Controls (n = 44 976)	Unadjusted OR (95% CI)	Adjusted† OR (95% CI)
Influenza‡				
Never	10 404 (92·5)	41 957 (93·3)	1·0	1·0
Ever	840 (7·5)	3019 (6·7)	1·13 (1·04–1·23)	1·12 (1·03–1·22)*
Number of influenza episodes				
0	10 404 (92·5)	41 957 (93·3)	1·0	1·0
1	731 (6·5)	2619 (5·8)	1·14 (1·04–1·24)	1·13 (1·03–1·24)*
2	92 (0·8)	316 (0·7)	1·19 (0·94–1·51)	1·10 (0·86–1·41)
⩾3	17 (0·2)	84 (0·2)	0·82 (0·47–1·43)	0·79 (0·43–1·44)
P_{trend}				0·0420
Timing of last influenza episode, days				
0	10 404 (92·5)	41 957 (93·3)	1·0	1·0
1–59	16 (0·1)	62 (0·1)	1·13 (0·72–1·78)	1·17 (0·65–2·01)
60–364	79 (0·7)	237 (0·5)	1·36 (1·04–1·78)	1·30 (0·98–1·73)
365–729	88 (0·8)	301 (0·7)	1·19 (0·94–1·52)	1·15 (0·89–1·48)
⩾730	657 (5·8)	2419 (5·4)	1·11 (1·01–1·21)	1·10 (0·99–1·21)
P_{trend}				0·0242

OR, Odds ratio; CI, confidence interval.
† Adjusted for smoking status (non, current, ex, unknown), alcohol use (non, current, ex, unknown), history of stroke, prior use of systemic corticosteroids, prior use of antibiotics (all recorded prior to index date).
‡ Prior to index date.
* <0·05 significance.

Table 3. *Unadjusted and adjusted odds ratios for the association between epilepsy and previous 'complicated influenza' episodes*

	Cases (n = 10 442)	Controls (n = 42 044)	Unadjusted OR (95% CI)	Adjusted† OR (95% CI)
Complicated influenza followed by clinical complications				
Never	10 404 (99·6)	41 957 (99·8)	1·0	1·0
⩾1	38 (0·4)	87 (0·2)	1·75 (1·19–2·56)	1·64 (1·10–2·46)*
Last complicated influenza episode, days‡				
0	10 404 (99·6)	41 957 (99·8)	1·0	1·0
1–59	3 (0·03)	3 (0·01)	4·00 (0·81–19·82)	6·03 (1·10–33·20)*
60–364	3 (0·03)	11 (0·03)	1·09 (0·30–3·91)	0·77 (0·20–2·98)
365–729	4 (0·04)	15 (0·04)	1·07 (0·35–3·21)	0·74 (0·22–2·43)
⩾730	28 (0·3)	58 (0·14)	1·93 (1·23–3·03)	1·94 (1·22–3·11)*
P_{trend}				0·0127

OR, Odds ratio; CI, confidence interval.
† Adjusted for smoking status (non, current, ex, unknown), alcohol use (non, current, ex, unknown), history of stroke, prior use of systemic corticosteroids, prior use of antibiotics (all recorded prior to index date).
‡ Prior to index date.
* <0·05 significance.

[33, 34]. It has been suggested that neuroinflammation can create the conditions for a faster than normal rate of neuronal degeneration, with frequent, sustained, or severe periods of non-symptomatic virus driven neuroinflammation, heightening an individual's proclivity to subsequent brain dysfunctions as they grow older [34]. A study by Jurgens *et al.*, which examined the impact of influenza on the hippocampus and on cognition, found evidence to suggest that peripheral influenza infection may induce neuroinflammation, increase microglial reactivity, and alter the morphology of the hippocampal region [35]. Experimental studies

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indicate glial cells and pro-inflammatory mediators play an important role in the pathophysiology of epilepsy [33, 36–38], with the activation of microglial cells resulting in a decrease in the seizure threshold and increased neuronal stimulation through the release of pro-inflammatory molecules [34].

The present large nested case-control study provides little evidence for an association between influenza exposure and epilepsy, with a reported overall OR close to 1 (aOR 1·12, 95% CI 1·03–1·22). Nor was there an association with increased frequency of influenza episodes or timing of influenza. By contrast, any history of 'complicated influenza' episodes followed by additional bacterial infections (i.e. mainly pneumonia) yielded an increased risk of developing epilepsy (aOR 1·64, 95% CI 1·10–2·46), which was particularly pronounced if the infection occurred within 2 months of the epilepsy diagnosis (aOR 6·03, 95% CI 1·10–33·2), and which was elevated for a considerable period of time after the influenza exposure (aOR 1·94, 95% CI 1·22–3·11) for an infection $\geqslant$730 days prior to the index date. However, it is important to note that the numbers in these analyses were small, and we cannot fully rule out the possibility of chance despite the statistical significance of the findings. In addition, we cannot rule out the possible presence of some residual confounding. Consequently, the results should be interpreted with caution. Moreover, the majority of 'complicated influenza' cases included individuals with a subsequent diagnosis of pneumonia. Aspiration pneumonia as a result of the inhalation of food particles during seizures has been reported as a possible complication in epileptic patients [39]. It is thus possible that this observed increase in risk may be a result of pneumonia in patients with undiagnosed epilepsy, which then lead to an epilepsy diagnosis after an episode of aspiration pneumonia. Although, a significant increase in epilepsy risk following 'complicated influenza' was also seen $\geqslant$2 years after an influenza episode, where this notion of reverse causality seems to be unlikely. Even though an observational study like the current one cannot prove causality, this finding may reflect a causal association between 'complicated influenza' and epilepsy, as it has been shown that pandemic 2009 influenza A (H1N1)-associated pneumonia did result in increased influenza viral concentrations, reduced viral clearance and up-regulated plasma pro-inflammatory cytokine responses [40].

This large case-control study utilized data from the CPRD, one of the largest and best-validated databases available, to examine the association between influenza infection and epilepsy risk. As it has been documented that a misdiagnosis of epilepsy can occur in about 20–30% of patients [2], we sought to avoid possible misclassification of epilepsy cases by applying a strict outcome definition and included only those patients who had, in addition to the epilepsy diagnosis, at least two repeat prescriptions for an anti-epileptic medication. An additional strength of this study is the ability to account for a variety of potential confounders including antibiotic use, corticosteroid and immunosuppressant use, and a prior history of stroke. All patients included in this study had at least 3 years of data prior to their index date.

It is also important to highlight potential limitations of the study. First, GP-diagnosed influenza is identified mainly through clinical diagnosis and is generally not supported by a viral test. Therefore, we cannot rule out the possibility that some recorded influenza diagnoses were not a consequence of the influenza virus, but rather as a result of an alternative infectious agent causing an 'influenza-like' illness. Furthermore, as influenza may be managed or treated at home without GP involvement, it is likely that some influenza episodes were not recorded by the GP. However, a study published in 2000 by our group found that the rate of recorded influenza infections over a 6-year period was closely similar to those derived from the UK sentinel system, the gold standard for UK influenza assessment at the time [27]. Additionally, 89% of all last-recorded influenza episodes were seasonal occurring between October and April. Hence, the possible misclassification of influenza episodes is likely to be limited. The clinical complications used to define 'complicated influenza' were based on possible bacterial superinfections (i.e. a subsequent diagnosis of sepsis, pneumonia, meningitis or encephalitis), without laboratory results to confirm a bacterial presence. Even though such complications may also be viral, it has been reported that secondary bacterial infections during and shortly after influenza virus infection recovery are a more common cause of pneumonia [31]. A further limitation is that the diagnosis of influenza and of epilepsy might not be recorded on the same day that the diagnosis was made, so that the analysis of the timing of the last-recorded influenza infection and the occurrence of epilepsy might not be highly accurate. Thus, it is possible that the few cases contributing to the substantially increased epilepsy risk for patients with a complicated influenza within 60 days before the

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index date may have been febrile seizures. However, it is unlikely that the observed increase in epilepsy risk associated with 'complicated influenza' for those who developed epilepsy $\geqslant 2$ years after the last-recorded influenza episode is a result of misdiagnosed influenza-associated febrile seizures. Furthermore, over 68% of epilepsy cases were reported in adult patients in whom febrile seizures are less likely to occur than in children.

In conclusion, this large case-control study found little evidence for an association between influenza exposure and epilepsy risk overall. However, we observed an increased risk of epilepsy in individuals with a history of 'complicated influenza', which was still present 2 years following exposure.

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DECLARATION OF INTEREST

None.

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