Research Letters

Temporal relationship between influenza infections and subsequent first-ever stroke incidence

SIR—an excess of deaths from cardiovascular disease in winter months that might be related to previous acute respiratory infections has been reported [1–3]. Only few studies of reasonable size and length have reported a peak of stroke incidence in the respective winter months in the Northern (December to March) and Southern (July to August) hemisphere [4, 5]. Furthermore, only one large-scale study has reported a significant association between respiratory infection and subsequent stroke [6]. However, this study did not differentiate between stroke subtypes despite different underlying pathomechanisms between ischaemic and haemorrhagic strokes.

A number of studies have failed to demonstrate a protective effect of antibiotics on cardiovascular risk underlining the importance of viruses for respiratory infections, of which influenza represents a major contributor [7, 8]. Additionally, influenza infections are routinely monitored by national surveillance systems in England and Wales. Therefore, we took advantage of an established active national surveillance system monitoring influenza infections in England and Wales (http://www.hpa.org.uk) and compared these infection rates with subtype-specific first-ever stroke data from the South London Stroke Register (SLSR) in order to assess the seasonality of stroke incidence in the SLSR and the temporal relationship between influenza and ischaemic and/or haemorrhagic strokes.

Influenza data
Weekly number of influenza patients in England and Wales by time period was obtained from the Health Protection Agency (HPA) for the period from 1995 to 2004 (http://www.hpa.org.uk). The HPA centre for infectious diseases (CfI) monitors and records influenza cases in England and Wales. Clinical data were obtained from GP’s surgeries which reported the consultations for influenza-like illness and other acute respiratory illness. The clinical cases that were confirmed by NHS and HPA laboratories were reported to the CfI. The virological data that were used in this study were collected by two sentinel schemes: the Respiratory Diseases Department, CfI, collaborative study and the Virus Reference Department & Royal College of General Practitioners, collaborative study (http://www.hpa.org.uk).

Statistical analysis
The seasonal distributions of stroke and influenza cases were separately analysed with the R package surveillance [11]. The algorithm by Farrington et al. was used to identify outbreaks of the two time series with a random error level of \( \alpha = 0.0001 \) [12]. Zero counts of weekly influenza or stroke data were replaced by 0.1 to ensure the convergence of the algorithm. We estimated seasonal trends based on LOESS as suggested by Cleveland and colleagues [13].

We performed a multivariate time series analysis to assess an association between influenza infections and strokes using the established ‘3h-algorithm’. This algorithm is based on a multivariate branching process with immigration and yields robust and valid estimations [14]. We considered different time lags between preceding influenza and stroke from 1 week up to 5 weeks to identify the length of increased hazard after an influenza infection. We used likelihood ratio tests estimating the goodness of fit of different models.

All calculations were carried out with the statistical software package R version 2.6.1 [15].
Ethics

Patients and/or their relatives gave written informed consent to participate in stroke-related studies within the SLSR. The design was approved by the ethics committees of Guy’s and St Thomas’ Hospital Trust, King’s College Hospital, Queens Square, and Westminster Hospital (London); no additional approval was required for this study.

Results

Between 1995 and 2004 a total of 2,874 patients with first-ever stroke were registered in the SLSR. Overall 2,092 (73%) ischaemic and 566 (20%) haemorrhagic strokes were registered throughout the study period. The seasonal trend of first-ever ischaemic strokes showed three peaks, a peak from end December to end January, a peak at the end of April and a peak from mid-September to mid-October (Figure 1). The distribution of haemorrhagic strokes showed only one peak from mid-February to beginning of May (data not shown).

In the respective time period, 21,473 influenza cases were reported to the HTA. Most cases occurred between the end of December and March. Three outbreaks could be identified for influenza by the Farrington algorithm, in 1998, 1999 and 2003. Although slightly more influenza infections could be observed than expected for certain weeks in 2001, 2002 and 2004, these only occurred in few single, not linked weeks (Figure 2). In contrast, no outbreak in ischaemic, haemorrhagic or overall strokes was identified by the Farrington algorithm during the entire observation period (data not shown).

Multivariate analysis of the influenza and ischaemic stroke time series yielded a significant association between influenza and first-ever strokes with a time lag of 1 week and 2 weeks (both $P < 0.001$). For a time lag of more than 2 weeks, no significant association could be observed (e.g. $P = 0.315$ for a time lag of 3 weeks).

We also observed an association between influenza and haemorrhagic strokes for a time lag of 1, 2, 3 and 4 weeks with $P$-values <0.001, while a time lag of 5 or more weeks did not show any association (e.g. $P = 0.401$ for time lag of 5 weeks). Both ischaemic and haemorrhagic strokes showed the best fit for the shortest time lag after influenza infection (1 week) and a decreasing goodness of fit for larger time lags in terms of likelihood ratios.

Discussion

A temporal relationship between influenza infections and strokes was observed. The strength of the relationship was inversely related to the length of the time lag between influenza and stroke pointing to a contemporary increased stroke risk after influenza. This relationship could partly explain the increased number of ischaemic strokes within 2 weeks and the increased number of haemorrhagic strokes within 4 weeks after the seasonal influenza peak. However, the distribution of ischaemic strokes had also an early autumn peak outside the influenza season indicating that preceding influenza might only be a trigger besides various other risk factors contributing to stroke aetiology and possibly responsible for the other peaks outside the influenza season. Additionally, the relationship between influenza and stroke was not specific with regard to different subtypes except with respect to the time element.

We observed a statistical link between preceding influenza infections and strokes that is similar to the only
study reporting respiratory infections related to stroke incidence [6]. However, this study looked at respiratory infections in general, pointing to the nonspecific role of influenza. Additionally, evidence from the literature shows that stroke might be related to other acute infections like urinary tract infections [16]. A review also reported a strong evidence of an association between inflammation and ischaemic stroke, possibly due to atherogenic mechanisms and/or possible plaque ruptures [17].

Additionally, levels of inflammatory markers such as fibrinogen and platelets are known to exhibit a biphasic distribution among the elderly with increasing levels in late winter and a second peak in late summer/early autumn [18, 19], while protein C and antithrombin were lower in winter suggesting an increased risk of atherothrombotic disease [20]. A small subsequent study by the same authors failed to show an association between winter infections and variations in C-reactive protein and fibrinogen levels, however, possibly due to the lack of sample power [21]. Nevertheless, the two fibrinogen peaks might partially coincide with two of the ischaemic stroke peaks in the SLSR occurring in early spring and autumn.

The observed link between influenza and haemorrhagic strokes suggests that other reasons than the possible inflammatory mechanisms for ischaemic strokes may be involved in the aetiology of chronic vascular diseases after acute infections. Reduced endothelial reactivity that has been observed after infections might play a role in the increased haemorrhagic stroke risk after influenza [22]. The longer lasting increased hazard from the time of infection to haemorrhagic stroke with 4 weeks in total compared to ischaemic stroke with 2 weeks in total after influenza further indicates different underlying mechanisms for both diseases. However, our data do not allow the study of potential pathological mechanisms.

While influenza data were obtained for England and Wales, stroke cases were only registered in the SLSR area. Unfortunately, we lacked information on weekly influenza numbers for the SLSR area only. A bias due to varying influenza seasons in the SLSR area compared to the whole area of England and Wales cannot be ruled out, but seems to be unlikely due to (1) the rapid spread of influenza infections and (2) London and Southern England contributing to more than one-third of all registered influenza cases.

Recurrent strokes might also be triggered by influenza. However, this possible association was not assessed since only first-ever strokes were considered due to appropriate sample power.

**Conclusion**

An unadjusted statistical link between influenza infections and first-ever strokes was observed. However, a peak of ischaemic strokes could also be observed in early autumn that is unlikely to be related to influenza. We unfortunately lacked information on additional seasonal factors such as temperature, humidity, weather patterns or RSV infections that should also be considered in future studies. Additionally, other acute infections were also reported to be related to first-ever strokes; general rather than influenza-specific inflammatory responses might be instrumental. Since both ischaemic and haemorrhagic stroke were associated with preceding influenza, exact mechanisms of acute infections and subsequent vascular disease have to be further disentangled.

**Key points**

- Excess of deaths from cardiovascular disease in winter months have been described, but only one study reported a relationship between respiratory infections and total stroke incidence without considering the subtype.
- A seasonal trend for ischaemic strokes with three peaks in winter, early spring and early autumn could be observed, while there was only one long-lasting late winter/early spring peak for haemorrhagic strokes.
- There was a significant increase of ischaemic strokes within 2 weeks after influenza infection and within 4 weeks after infection for haemorrhagic strokes.

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**Conflict of interest**

The authors declare no conflict of interest.

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**References**

The prevalence and characteristic of patients with ‘acopia’

SIR—‘Acopia’ is a pejorative term used in hospitals to describe patients who are unable to cope with activities of daily living. Although the term is not a recognised English word or disease entity, it is becoming increasingly common for older patients to be triaged as ‘acopia’ on admission to the Accident & Emergency (A&E) department.

Australian studies have shown that the term is mainly used to describe either patients with no acute medical problems or who are deemed inappropriate admissions [1, 2]. Older patients identified as being ‘social admissions’ are known to have a significantly higher risk of death or increased dependence [3]. Richardson showed that the presence of a ‘social problem’ was more strongly associated with death or increased dependence than cardiac failure [1].

This study aims to assess the frequency of the usage of the term ‘acopia’ in a district general hospital in the UK and to determine the characteristics of these patients.

**Method**

A retrospective review of patients’ medical records was carried out at a district general hospital from January 2005 to March 2006. Patients who were triaged with ‘acopia’ as their presenting complaint on their A&E ‘front sheet’ were identified via a computer-generated search for the term. The following data were collected from patients’ case notes: age, sex, pre-admission usage of social services, length of stay, admission and discharge diagnosis, medical co-morbidities and discharge destination. Patients who presented within 2 weeks of discharge from the hospital were considered as a failed discharged. Patients who presented to the A&E department monthly for 6 consecutive months were deemed to be frequent attendees.

**Results**

A total of 93 patients were identified as presenting with ‘acopia’ to the A&E department during the study period. The A&E and medical records of 81 patients were retrieved for the study. Twelve patients were excluded from the study as their case notes could not be located. The total number of patients attending A&E during this period was 50,335; 13,411 (26.6%) were aged >65, and 36,924 (73.4%) aged ≤65. The median age of patients presenting with ‘acopia’ was 85 years.