Association of delirium post-stroke with early and late mortality

SIR—Delirium is a complex neuropsychiatric condition that occurs commonly post-stroke, with period prevalence estimates ranging from 13 to 48% [1]. Most cases occur early and frequently last at least 4 weeks [2]. Delirium remains understudied post-stroke, with little known about associations with clinical outcome and long-term prognosis. Only two previous prospective studies have reported the 6 month prognosis of delirium post-stroke [3, 4], one of these also reported 12 month data [3]. This is in contrast with other clinical settings where there is robust data linking delirium to adverse clinical outcomes: for example, in acute medical inpatients [5], in orthopaedic patients [6, 7] and in intensive care units [8]. We undertook the current study to test the hypothesis that the development of delirium post-stroke is an independent predictor of both early and late mortality post-stroke.

Methods

Participants

The study sample was recruited over a 7-month period starting October 2005. All consecutive stroke patients admitted to the Stroke Unit at King’s College Hospital NHS Foundation Trust, London were eligible. The hospital admits all stroke patients directly to the Stroke Unit. The inclusion criteria for the study were: (i) an admission diagnosis of cerebral infarction or intracerebral haemorrhage and (ii) a delirium assessment within 4 days of admission. Our exclusion criteria were (i) patients whose symptoms lasted <24 h, (ii) patients who did not speak English and (3) patients with a Glasgow Coma Scale (GCS) score of <8.

Risk factor assessment

Predisposing factors for delirium were considered as covariates for this analysis and these have been outlined in detail previously [2]. Stroke type was defined using the Bamford classification [9]. We recorded pre-stroke cognitive impairment using the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) [10]. We defined pre-stroke cognitive impairment as a score on the IQCODE > 3.

Diagnosis of delirium

Participants were screened for delirium using the Delirium Rating Scale (DRS) [11] and the Confusion Assessment Method (CAM) [12]. All assessments were carried out by the one assessor—a senior Specialist Registrar in Geriatric Medicine who had specific training in the use of both instruments. We recently found that the CAM is equivalent to the DRS when used by a trained non-psychiatrist in the acute stroke setting [13]. In the present study, the first assessment took place within 4 days of admission and weekly thereafter for a maximum of 4 weeks, unless the patient was discharged earlier. For the purpose of this analysis, delirium was defined as present if either the CAM or DRS was positive for delirium.

Follow-up

Patient outcome measures were inpatient mortality, mortality post-discharge up to 1 year and mortality post-discharge from 1 to 2 years. Mortality data post-discharge were collected from primary and secondary records.

Statistical analysis

Data were analysed using SPSS, version 14 (SPSS Inc., Chicago, IL, USA). We first used binary logistic regression to test for associations between independent covariates between delirium and mortality, defining the latter as that occurring during the inpatient stay, post-discharge up to 1 year and post-discharge from 1 to 2 years. Odds ratios for risk factors associated with mortality according to these analyses were then entered into multiple logistic regression analyses to build models for determining independent predictors of mortality. Only predictors that were significant were kept in the final model. The level of significance was set at 0.05.

Ethics approval

Ethics approval for the study was obtained from King’s College Hospital Research Ethics Committee. Written informed consent was obtained from all participants. In those unable to give consent, a next-of-kin gave informed assent.

Results

Sample characteristics

Of 110 patients eligible for the study, 82 were recruited. Baseline characteristics of the group have been outlined previously [2]. Of the 28 patients excluded, consent/assent was not obtained in 13 cases, 6 did not speak English, there was a time delay in recruiting 5 and 4 had a GCS < 8. Of the 82 participants, 51 were male and 31 were female. The mean age of the sample was 66.4 years (range 24–97, SD 15.9 years). Within 1 month of stroke, delirium was detected in 23 participants (28%).
Inpatient mortality

Of the 82 participants, 8(10%) died during the inpatient period. Inpatient mortality was higher in those with delirium (30.4 versus 1.7%, \( P < 0.001 \)). In unadjusted analysis, the following factors were significantly associated with inpatient mortality: delirium, increased age, pre-stroke cognitive impairment, small vessel disease on brain CT, previous stroke or transient ischaemic attack (TIA), atrial fibrillation, lower admission Barthel score, unsafe swallow on admission and total anterior circulation stroke (TACI) on the Bamford Classification (Table 1). In adjusted logistic regression models, age \( (P = 0.03, \text{OR} 1.15, 95\% \text{CI for OR} 1.02–1.31) \) and delirium \( (P = 0.01, \text{OR} 21.45, 95\% \text{CI for OR} 1.83–251.37) \) remained significantly associated with inpatient mortality.

Mortality post-discharge

Post-discharge data were available for 70 of the 74 participants who survived to discharge. Of the four participants with missing data, two had left the country and two were not registered with the family doctor whose details were recorded on admission.

Mortality post-discharge up to 1 year post-stroke

Delirium post-stroke was associated with a higher 1 year mortality post-discharge but did not reach statistical significance (25 versus 7.4%, \( P = 0.07 \)). In unadjusted analyses, the following factors were significantly associated with 1 year mortality: age, poor hearing, pre-stroke cognitive impairment, small vessel disease on brain CT scan and being on more than four medications on admission (Table 2). In adjusted logistic regression models, we found that age \( (P = 0.01, \text{OR} 1.14, 95\% \text{CI} 1.03–1.27) \) and pre-stroke cognitive impairment \( (P = 0.04, \text{OR} 7.08, 95\% \text{CI} 1.08–46.28) \) remained significantly associated.

Mortality post-discharge from 1 to 2 years

Delirium post-stroke was not associated with a higher mortality from 1 to 2 years post-discharge (8.5 versus 10.2%, \( P = 0.85 \)). In unadjusted analyses, age, poor vision and pre-stroke cognitive impairment were significantly associated with mortality. In adjusted logistic regression models, only cognitive impairment \( (P = 0.03, \text{OR} 16.66, 95\% \text{CI for OR} 1.35–204.9) \) independently predicted mortality.

Discussion

In this single-centre, observational study, we found that delirium independently predicts inpatient mortality but not mortality after discharge post-stroke. With regards inpatient mortality, the literature in this area is conflicting. Caeiro et al. [14] found that delirium post-stroke was associated with death or dependency on discharge. However, neither Sheng et al. [3] nor Henon et al. [4] found this. While we did not find that delirium predicted mortality post-discharge, the small number of patients in the study and the fact that follow-up data were not available for four participants in the study means that these results need to be treated with caution and warrant verification in a larger study. Although this is a preliminary study, the results do suggest that a possible association with post-discharge mortality up to 1 year \( (P = 0.07) \) that would require

Table 1. Significant variables on univariate analysis for inpatient mortality

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n = 82)</th>
<th>Inpatient mortality (n = 8)</th>
<th>Inpatient survival (n = 74)</th>
<th>OR</th>
<th>95% CI for OR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delirium (%)</td>
<td>28</td>
<td>87.5</td>
<td>21.6</td>
<td>25.37</td>
<td>2.91</td>
<td>0.003</td>
</tr>
<tr>
<td>Mean age (SD)</td>
<td>66.4 (15.8)</td>
<td>83.9 (8.5)</td>
<td>64.5 (15.3)</td>
<td>1.13</td>
<td>1.04</td>
<td>0.005</td>
</tr>
<tr>
<td>IQCODE &gt; 3 (%)</td>
<td>25.6</td>
<td>75</td>
<td>20.27</td>
<td>0.61</td>
<td>1.94</td>
<td>0.006</td>
</tr>
<tr>
<td>Small vessel disease on brain CT scan (%)</td>
<td>37.8</td>
<td>75</td>
<td>33.78</td>
<td>5.88</td>
<td>1.11</td>
<td>0.04</td>
</tr>
<tr>
<td>History of CVA or TIA (%)</td>
<td>20.7</td>
<td>62.5</td>
<td>16.2</td>
<td>8.61</td>
<td>1.81</td>
<td>0.007</td>
</tr>
<tr>
<td>Atrial fibrillation (%)</td>
<td>25.6</td>
<td>62.5</td>
<td>21.6</td>
<td>6.04</td>
<td>1.3</td>
<td>0.02</td>
</tr>
<tr>
<td>Total number of vascular risk factors (mean ± SD)</td>
<td>22.7 (1.46)</td>
<td>4.14 (1.25)</td>
<td>2.07 (1.34)</td>
<td>2.79</td>
<td>1.48</td>
<td>0.002</td>
</tr>
<tr>
<td>Admission Barthel (mean ± SD)</td>
<td>11.12 (8.11)</td>
<td>1.63 (4.21)</td>
<td>12.15 (7.77)</td>
<td>0.77</td>
<td>0.62</td>
<td>0.09</td>
</tr>
<tr>
<td>Unsafe swallow on admission (%)</td>
<td>26.8</td>
<td>87.5</td>
<td>20.3</td>
<td>27.53</td>
<td>3.14</td>
<td>0.003</td>
</tr>
<tr>
<td>TACI (%)</td>
<td>18.3</td>
<td>62.5</td>
<td>13.5</td>
<td>10.67</td>
<td>2.2</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Table 2. Significant variables on univariate analysis for one year mortality post-discharge

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n = 70)</th>
<th>One year mortality post-stroke (n = 8)</th>
<th>One year survival post-stroke (n = 62)</th>
<th>OR</th>
<th>95% CI for OR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (SD)</td>
<td>65.74 (14.55)</td>
<td>82 (6.63)</td>
<td>63.65 (13.97)</td>
<td>1.13</td>
<td>1.04</td>
<td>0.005</td>
</tr>
<tr>
<td>IQCODE &gt; 3 (%)</td>
<td>21.42</td>
<td>62.5</td>
<td>16.13</td>
<td>7.67</td>
<td>1.57</td>
<td>0.012</td>
</tr>
<tr>
<td>Small vessel disease on brain CT scan (%)</td>
<td>35.71</td>
<td>75</td>
<td>30.64</td>
<td>6.79</td>
<td>1.25</td>
<td>0.026</td>
</tr>
<tr>
<td>Poor hearing (%)</td>
<td>8.57</td>
<td>50</td>
<td>3.23</td>
<td>30</td>
<td>4.16</td>
<td>0.001</td>
</tr>
<tr>
<td>Greater than four medications on admission (%)</td>
<td>28.57</td>
<td>62.5</td>
<td>24.19</td>
<td>5.11</td>
<td>1.09</td>
<td>0.04</td>
</tr>
</tbody>
</table>
a larger study to confirm. Only two previous studies have reported long-term follow-up data relating to delirium post-stroke. Sheng et al. [3] found that delirium predicted 6 and 12 month mortality, whereas Henon et al. [4] did not find increased mortality at 6 months.

There is, therefore, uncertainty about the prognostic implications of delirium post-stroke. This goes against the overall evidence from the medical literature that delirium predicts a poor outcome [15]. There are several possible reasons for this. Methodologically, most delirium studies have suffered because they use different screening tools for delirium, use different definitions for delirium, screen at different time intervals and have short follow-up periods—none of which make it difficult to compare results. In addition, the pathophysiology of delirium remains unclear, so it may be that delirium is a ‘risk marker’ rather than a ‘risk factor’ for poor outcome. For example, recently it has been shown that albumin, IL-6 and IFN-γ are stronger mortality predictors than delirium in medical patients [16].

Age is one of the major risk factors for stroke with good evidence that older patients have a higher mortality post-stroke [17, 18]. We also found that pre-stroke cognitive impairment predicted mortality post-discharge up to 2 years post-stroke. Previous epidemiological studies in stroke also identified cognitive impairment as an independent predictor of both short-term [19] and long-term mortality [20] after a stroke.

There are several limitations of our study. This was a pilot study and the small number of participants mean that a larger study is needed to assess the association between delirium post-stroke and long-term prognosis in more detail. We may have underestimated the baseline incidence of delirium as we excluded six non-English speakers and four patients with a GCS score <8. Long-term follow-up was not available for four patients, none of whom developed delirium post-stroke. We only screened for delirium on a weekly basis so some cases of delirium would have been missed.

In summary, the findings of this study show that delirium, a common complication post-stroke, is an independent predictor of mortality during the initial inpatient stay, but does not seem to influence mortality post-discharge.

**Key points**

- Delirium is a common complication post-stroke.
- It is an independent predictor of inpatient mortality.
- It does not predict mortality post-discharge.

**Conflicts of interest**

None declared.

**References**

Association of adverse drug reactions with drug–drug and drug–disease interactions in frail older outpatients

SIR—The most common type of medication-related adverse events in older adults is Type A (‘augmented’) adverse drug reactions (ADRs) [1–3]. Type A reactions are an exaggeration of the expected pharmacologic effect of a drug. These ADRs are more predictable, dose dependent and potentially preventable than Type B (‘bizarre’) ADRs (i.e. allergic reactions) [3, 4].

The relationship of different elements of suboptimal prescribing to ADRs in older outpatients has not been adequately explored. Recently, Chrischilles et al. [5] examined the association between multiple aspects of potentially inappropriate prescribing (defined by explicit criteria for drugs-to-avoid, drug–disease interactions, drug–drug interactions and therapeutic duplication) with self-reported adverse drug events (ADEs). A recent study used a modified weighting system for the medication appropriateness index (MAI), a validated measure that employs a standardised implicit approach to determining prescribing appropriateness, to examine the association of potentially inappropriate prescribing with self-reported ADEs [6, 7].

Neither of the above studies, however, had a specific focus on Type A ADRs.

Given this background, the objective of this study was to determine whether incorrect dosage, incorrect directions, drug–drug interactions and drug–disease interactions, as measured by the MAI, are associated with the Type A ADRs among frail older veterans transitioning from the hospital to the community.

Methods

Study design and study sample
This retrospective cohort study included a random sample of 400 patients from the Geriatric Evaluation and Management (GEM) Drug Study, which examined the impact of GEM care on drug-related problems in 1,388 older veterans from 11 Veterans Affairs Medical Centers (VAMC) [8]. Details about inclusion and exclusion criteria can be found elsewhere [8]. We further restricted the sample to those 359 patients taking one or more high-risk medications (see Supplementary data available in Age and Aging online; http://www.ageing.oupjournals.org/) [3, 9, 10]. The study was approved by the VAMC Research and Human Subjects Committees at each study site and the Institutional Review Boards of Duke University and the University of Pittsburgh.

Potential drug-related adverse events: data collection, abstracted chart screening and self-report

Detailed information about data collection and screening for potential drug-related adverse events has been previously published [8, 11]. Briefly, a trained research assistant at each site prepared an abstract of each patient's VAMC inpatient and outpatient medical chart. A trained research nurse reviewed the abstracted charts and screened for potential drug-related adverse events using a standardised approach. In addition, at the 12 month closeout a trained research clinical pharmacist queried patients for self-reports of potential drug-related adverse events using previously validated methods [5]. For each potential drug-related adverse event identified by chart review and/or patient interview, a trained clinical pharmacist created a detailed narrative based on reporting information required by the Food and Drug Administration MEDWatch program [12].

Main outcome

The primary outcome measure was any Type A ADR with a causality rating of at least ‘possible’ [8]. Blinded geriatrician and geropharmacist pairs evaluated ADR causality using the narrative and the validated Naranjo ADR causality algorithm [13]. These ADRs were also assessed for type of ADR (i.e. Type A or not) [3, 4]. Any discordances among evaluators regarding the presence or type of ADR were resolved by clinical consensus conference.

Primary independent variables

The primary independent variables were inappropriate dosage, directions, drug–drug and drug–disease interactions. Physician–pharmacist pairs evaluated each patient's medication regimen for these potential problems using the MAI [6]. Any discordances among evaluators were resolved by clinical consensus conference.

Covariates
Several factors may confound any relationship between potentially inappropriate prescribing and ADRs and were