The risk of dementia and death after delirium

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Abstract

Background: delirium is common and is associated with many adverse short-term consequences.

Objectives: to examine the relationship between an episode of delirium and subsequent dementia and death over 3 years.

Design: prospective cohort study.

Setting: patients (n = 203) were aged 65 years or older at baseline and survivors of the index admission.

Methods: Using a standard assessment of cognitive function, we followed 38 inpatients diagnosed with delirium (22 with delirium and dementia, 16 with delirium only) and 148 patients with no delirium or dementia, for a median of 32.5 months. Follow-up was by personal interviews, supplemented by standardized clinical examinations. We calculated the incidence and odds of dementia and the incidence and hazard ratio for death, with adjustment for potential confounders.

Results: The incidence of dementia was 5.6% per year over 3 years for those without delirium and 18.1% per year for those with delirium. The unadjusted relative risk of dementia for those with delirium was 3.23 (95% confidence interval 1.86–5.63). The adjusted relative risk of death also increased (1.80; 1.11–2.92), while the median survival time was significantly shorter in those with (510 days; 433–587) than in those without delirium (1122 days; 922–1322).

Conclusion: delirium appears to be an important marker of risk for dementia and death, even in older people without prior cognitive or functional impairment.

Keywords: delirium, dementia, epidemiology

Introduction

Recent reports have focused attention on cognitive impairment syndromes which fall short of dementia but may be precursors to the dementia syndrome [1, 2]. Delirium, which is a common presentation of illness in elderly people [3–12] particularly those in frail health [11, 13–15] is held by some to increase the risk of dementia [16, 17]. This proposition has, however, received scant formal inquiry [5, 7, 18] and, while individual symptoms of delirium may persist [7, 9, 12], no precise estimate of the relative risk of clinically diagnosed dementia following delirium is available.

We report the relationship between an episode of delirium at presentation to hospital and the incidence over the next 3 years of dementia and death in those who survived the initial hospital admission.

Methods

Between October 1991 and August 1992, we enrolled 247 patients (65+ years) consecutively admitted to the general medicine services of a tertiary-care teaching hospital in a before/after study designed to increase recognition of delirium by medical staff [10]. Twelve patients were readmitted and 32 died in hospital, leaving a cohort of 203 for prospective follow-up (Figure 1).

Follow-up took place between June 1994 and August 1995. Dementia incidence and death were the primary outcomes. We determined vital status in all cases. We recorded data on potential confounders for dementia (age, gender, comorbid illness [19]) and death (age, gender, comorbid illness, frailty, atypical disease presentation [15], delirium severity [20] and living arrangements) at baseline. Premorbid frailty was defined as functional impairment 2 weeks before admission [15], as measured by Granger’s modification of the Barthel index (0 = worst through 100 = best point scale) [21]. We obtained informed consent, or proxy consent for those with cognitive impairment, from all patients who agreed to participate. The
protocol was approved by our institutional research review committee.

**Subjects with delirium at baseline**

We identified 38 subjects with delirium on admission, 22 with delirium and underlying dementia and 16 with delirium only (Figure 1). The criteria of the Diagnostic and Statistical Manual of Mental Disorders, fourth revision (DSM-IV) were used to assess delirium [22]. The criteria were operationalized using clinical judgement (the accepted standard) supplemented by the Mini-Mental State Examination [23], the Delirium Rating Scale [20, 24] and a rating of illness severity [25]. Dementia diagnosis [22] conformed to the Canadian Study of Health and Aging dementia protocol [26].

Twenty of the 22 patients with baseline delirium and dementia had died by follow-up. We collected only proxy informant data on function, institutionalization and vital status for this subgroup. Ten of 16 people diagnosed with ‘delirium–no dementia’ died within 3 years. The Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) [27] was used to evaluate the dementia status of nine (one refusal) decedents. Modification of the IQCODE preamble required symptom presentation for at least 3 months. Preterminal cognitive decline (cognitive impairment for less than 3 months before death) was excluded. We used an IQCODE cut point of 3.38/3.42 (sensitivity = 0.75, specificity = 0.89 [28]) to distinguish the categories dementia and no dementia.

We followed up the six living patients in the ‘delirium–no dementia’ group in two stages. A screening interview, administered in the home by a nurse (S.C.), evaluated cognition (Mini-Mental State Examination, Blessed dementia rating scale [29]) and function (Barthel index, Physical Self-Maintenance Scale [30]). All six patients screened positive for cognitive impairment and were invited for a standardized examination [26] by a geriatrician (K.R. or D.C.) to determine the presence and type of dementia. Data were also collected on comorbidity [19, 25], cognition and dementia severity [31, 32]. Two patients were clinically examined. The four patients who were not examined (one no longer in the area, two who had died between screening and clinical and one who was hospitalized) or their representatives agreed to an IQCODE interview.

**Subjects without delirium at baseline**

One hundred and sixty-five patients did not meet the DSM-IV criteria for delirium at baseline (Figure 1). For the 17 patients with baseline dementia only function, details on institutional care and vital status were obtained at follow-up.

One hundred and forty-eight patients were classified as ‘no delirium–no dementia’ (Figure 1). Sixty patients died by follow-up, and IQCODE interviews were obtained from 51 proxy informants (six refused, three provided incomplete data). Of the 88 patients who were alive, 74 completed a screening interview (13 refused, one provided incomplete data). Thirty-two subjects screened positively for cognitive impairment and 23 of them attended a clinical examination. One of the nine subjects who were not examined refused to provide any further information. The remaining eight (three no longer in the area, three who had died before the examination and two who refused a clinical examination) or their representatives agreed to an IQCODE interview.

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**Figure 1. Follow-up of the cohort and status of data collection.**

<table>
<thead>
<tr>
<th>Enroll ment</th>
<th>N=247</th>
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<td>12 readmissions</td>
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<td>32 died in hospital</td>
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**Enrollment Table**

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<tr>
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<th>No Delirium-No Dementia</th>
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<tr>
<td>n=22</td>
<td>n=16</td>
<td>n=148</td>
<td>n=17</td>
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**Baseline Cohort**

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**Follow-up**

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<table>
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<tbody>
<tr>
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<td>n=10</td>
</tr>
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<td></td>
<td>(?)</td>
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<table>
<thead>
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<th>Died</th>
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<tr>
<td>n=6</td>
<td>n=11</td>
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</table>

<table>
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<th>Died</th>
</tr>
</thead>
<tbody>
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<td>n=17</td>
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</tr>
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</table>

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Analysis

We analysed data using the SPSS 6.1 for Windows software package [33]. To examine prospectively the relationship between delirium and dementia, we calculated unadjusted relative risk and 95% confidence intervals (CIs) from 2×2 tables. Unadjusted and adjusted (age, sex, comorbid illness) odds of dementia were estimated using logistic regression. We constructed Kaplan–Meier survival curves to compare time to death for those with and without delirium at baseline. We tested the significance of differences in survival using the log-rank test. Cox proportional hazards modelling, with backward selection, was used to adjust for the effects of delirium and potential confounders on the risk of death.

Results

Survival

The median follow-up of the cohort was 32.5 months. One hundred and one patients died before follow-up. The mean age at baseline for the whole group (79 years) was similar to that of the subjects who remained alive at follow-up. More survivors were women (62% versus 57% at baseline), lived in nursing homes (29% versus 23%) and were demented (28% versus 19%). Fewer survivors had limitations in activities of daily living (median Barthel index = 93.5, inter-quartile range 73–100) than the baseline cohort (median Barthel index = 90.0, inter-quartile range 50–100), reflecting a healthy survivor effect.

Survival times are shown in Figure 2. Of the 38 patients with delirium, only eight (21%) were alive at follow-up, compared with 94 (57%) of those without delirium. The median survival time was significantly shorter for those with delirium (510 days; 95% CI 433–587) than for those without (1122 days; 95% CI 922–1322; log-rank = 16.40; P = 0.0001). Similarly, the median survival time was 539 days (95% CI 292–786) in those with dementia compared with 1226 days (95% CI 812–1640) in those without dementia at baseline (log-rank = 8.62; P = 0.003). Median survival times were also lower for those who were frail at baseline (735 days; 95% CI 542–942) than those who were not frail (1015; 95% CI 899–1131, log-rank = 11.46; P<0.001).

Table 1 reports hazard ratios using Cox modelling for death after delirium, with adjustment for pre-selected characteristics including comorbid illness (two levels), dementia, frailty, age, sex, marital status and living arrangements. Delirium was associated with a higher hazard ratio for death. Secondary analyses accounting for other atypical disease presentations (falls, acute incontinence, immobility), delirium severity (coded by the Delirium Rating Scale score) and incident dementia did not substantially alter the hazard estimates listed in Table 1.

Delirium and the risk of dementia

Nine (60%) of the 15 patients with follow-up cognitive status and a diagnosis of ‘delirium–no dementia’ at baseline developed dementia. The annual incidence of dementia for individuals with delirium is 18.1%. Of the 148 subjects without delirium or dementia at baseline, data on subsequent cognitive status were ascertained for 124, of whom 23 developed dementia. The incidence of dementia among subjects without cognitive delirium at baseline is 5.6% per year.

The unadjusted relative risk of dementia for those with delirium at baseline is 3.23 (95% CI 1.86–5.63). The risk is significantly increased, and remains so when adjusted for age, sex and comorbid illness (unadjusted odds ratio 6.59, 95% CI 2.13–20.35; adjusted odds ratio 5.97, 95% CI 1.83–19.54; P = 0.003).

Discussion

We investigated the risk of dementia and death after delirium. An episode of delirium increased the risk of dementia over a median 32.5 months in elderly patients, even in those not known to have cognitive impairment at baseline. Delirium was also associated with an increased risk of death, even after adjusting for a number of potential confounders, including comorbid illness and physical frailty.

Our study has important limitations. Data on exposures were gathered only at baseline, so we do not know about any preceding or subsequent delirious episodes. The resulting misallocation results in a conservative bias (i.e. some subjects designated as not having delirium may have had a previous or subsequent episode of delirium). In addition, while vital status could be determined for all patients, we do not have follow-up cognitive data on 25 of the 203 subjects. Importantly, the number of subjects with
delirium who were otherwise apparently well was small \((n = 15)\). In consequence, the resulting estimate for dementia risk may be unstable (for example, the 95% CI was 1.86–5.63), but the risk of dementia is greater than in those without delirium and is unlikely to have occurred by chance. Finally, the IQCODE was used to identify dementia in patients who died or were unavailable for a clinical examination. Although this tool was designed as a retrospective screen for dementia, we believe it is preferable to use the information it provides than to exclude subjects who have died, are unavailable or refuse a clinical examination from the statistical analysis.

Our study advances information from other reports in its use of a detailed examination for dementia at baseline, its stringent protocols for the detection and differential diagnosis of dementia, its longer follow-up and its attempt to ascertain the occurrence of dementia in those who died before the recontact interview. The IQCODE has been validated against autopsy [34], and extensive data support its usefulness in the retrospective diagnosis of dementia [28, 35, 36]. Our risk estimate for death after delirium is similar to that of a previous report [18]. We corroborate studies that prospectively identified cognitive decline post-delirium [18, 37] and extend these findings with clinical confirmation of dementia and an estimate of dementia risk.

The mechanism by which delirium is associated with an increased risk of dementia is not understood. There are two possibilities. Delirium may give rise to brain injury which results in predisposition to (or even initiation of) dementia. This would be consistent with the view of dementia as aberrant brain repair [38]. Alternately, delirium may serve as a marker of a subclinical dementing process [39]. Further work will need to distinguish between severity of insult and severity of delirium to help clarify this.

Almost half (101/203) of the patients died during follow-up, including most (80%, \(n = 30\) of those with delirium, of whom 21 (84%) were in institutional care. Even in previously well patients, the occurrence of delirium is an important marker of poor prognosis. These data confirm earlier reports that delirium is associated with an increased risk of adverse health outcomes, in the short term, even in those who were previously well [7, 8, 11, 18]. Given that delirium is a risk for death independent of the effects of dementia, our study reinforces the idea of delirium as a marker of physical frailty [40].

These data are also of interest in defining a group at high risk for dementia who may benefit from preventive strategies or early treatment.

**Acknowledgements**

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**Table 1. Adjusted hazard ratio of selected characteristics on the occurrence of death at follow-up \((n = 203)\)**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Unadjusted Hazard ratio (95% confidence interval)</th>
<th>Adjusted Hazard ratio (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delirium</td>
<td>2.36 (1.54–3.63)</td>
<td>1.71 (1.02–2.87)</td>
</tr>
<tr>
<td>Comorbid illness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>1.75 (1.05–2.93)</td>
<td>1.84 (1.08–3.12)</td>
</tr>
<tr>
<td>Severe</td>
<td>2.73 (1.64–4.55)</td>
<td>3.11 (1.84–5.28)</td>
</tr>
<tr>
<td>Dementia</td>
<td>1.89 (1.23–2.91)</td>
<td>1.04 (0.63–1.73)</td>
</tr>
<tr>
<td>Frailty</td>
<td>2.17 (1.37–3.43)</td>
<td>1.29 (0.75–2.21)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>1.05 (1.02–1.07)</td>
<td>1.02 (0.99–1.05)</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>1.35 (0.92–2.00)</td>
<td>1.64 (1.06–2.52)</td>
</tr>
<tr>
<td>Not married</td>
<td>1.21 (0.80–1.83)</td>
<td>1.06 (0.66–1.71)</td>
</tr>
<tr>
<td>Institutionalized</td>
<td>2.75 (1.83–4.13)</td>
<td>2.03 (1.25–3.31)</td>
</tr>
</tbody>
</table>

*aAll characteristics were dichotomized as present/absent, except for age.
*bOverall \(\chi^2\) 58.59, \(P < 0.001\).
*c2–3 comorbid illnesses [25] (excluding dementia).
*d4+ comorbid illnesses [25] (excluding dementia).
*e<99 on Barthel index 2 weeks prior to admission.
Dementia and death after delirium

Key points

- Subjects aged 65 or older with delirium at baseline had a greater risk of dementia and death over 3 years than those without.
- Delirium appears to be an important marker of risk for dementia and death, even in older people without prior cognitive or functional impairment.

References

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