- Response of individual patients to additional exercise was highly variable across older medical patients.
- Additional exercise significantly improved discharge function scores for patients who required assistance or supervision to ambulate at the time of acute hospital admission.
- The Barthel Index has a ceiling effect for measuring the functional ability of older medical patients in the acute hospital setting.
- Identifying the patient subgroup most likely to benefit from an intervention facilitates the effective targeting of healthcare services.

Centre where work was done

Monash University, Department of Physiotherapy, School of Primary Health Care, Faculty of Medicine, Nursing and Health Sciences.

Conflicts of interest

All authors declare that they have no conflict of interest and therefore have nothing to declare.

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C-reactive protein levels predict the incidence of delirium and recovery from it

Introduction

SIR—Delirium (acute confusional state, a sudden onset, fluctuating state of cognitive decrement and disordered consciousness) is a very common condition that complicates the hospital treatment of many older people, particularly in the specialties of medicine, orthopaedics, and general and cardiovascular surgery. It is greatly distressing, life-shortening, and associated with longer hospital stays and residual cognitive impairment [1]. No laboratory test exists to assist in the diagnosis of delirium and thus its diagnosis depended only on clinical observations [2] and is often missed even in specialist centres [3]. The most consistent known risk factor is pre-existing dementia, suggesting that delirium is actually a part of the syndrome of dementia itself [4]. Its mechanism is unknown and, although anticholinergic activity has been given precedence as a basis for specific therapeutics for many years, no randomised controlled trials of cholinergic enhancement have been published. A possible neuroinflammatory basis for delirium is also emerging and low levels of insulin-like growth factor I (IGF-I) have recently been found as a risk factor for incident delirium [5].

The acute phase protein, C-reactive protein (C-RP), which has traditionally been used as a marker of infection, inflammation, and tissue injury [6], may also be implicated in the cause and outcome of delirium. One previous study investigated the kinetics of C-RP in post-operative elderly patients and reported significantly higher levels of C-RP in those with complications (infections, cardiovascular problems, and delirium) [7]. C-RP has also been correlated with poor cognitive performance and accelerated cognitive decline in a number of community studies [8,9]. Some authors have found an increased C-RP concentration in older people [10–12] and have suggested that this represents subclinical illnesses [13]. Two large epidemiological studies (in Rotterdam and Honolulu) found that increased levels of C-RP were associated with all dementias [14, 15]. C-RP appears to predict coronary events and incident stroke independently of atherosclerosis severity or other cardiovascular risk factors [16, 17], and it appears to be an independent predictor of survival after stroke [18].

We therefore tested C-RP as both a predictor of incident delirium and recovery from delirium as part of a preliminary observational study of a series of 94 acutely ill patients aged 70 or older admitted to a medical unit for older people in a university teaching hospital.

Methods

All 94 patients were initially assessed within 3 days of admission with (i) a standard bedside test of cognitive function, the Mini Mental State Examination (MMSE) [19]: the MMSE score was standardized to give a maximum score of 30 if the patients could not complete sections because of serious disability, e.g. visual ((item score/items completed) ×30); (ii) the confusion assessment method (CAM) to determine the presence or absence of delirium [20]; (iii) the Acute Physiological Score of APACHE-II (APS) [21] to measure severity of acute physical illness (arterial pH and oxygen saturation were omitted as arterial blood sampling was not feasible); and (iv) the Katz ADL scale [22] to measure disability. C-RP was measured routinely in all acute admissions on the day of the first 'battery' of assessments, almost always within 1 day. Presence of delirium was determined by CAM every 3 (plus or minus 1) days until the 18th day of hospitalisation and finally on the 28th day of hospitalisation. Incident delirium was defined as occuring when the initial CAM assessment was negative and any subsequent one was positive, and recovery from delirium was identified when a CAM-positive assessment was followed by CAM-negatives until discharge or death.

The study had ethical approval from the Guy's and St Thomas' Research Ethics Committee.

Results

C-RP levels were available for 86 patients. Their mean age was 82.7 (SD 6.6) years and 37 (43%) of them were male. Admission MMSE scores had a mean of 18.1 (SD 8.2), a median of 19 and an interquartile range of 13. Fifty-four (62.8%) subjects remained non-delirious throughout their admission, 26 subjects (30.2%) were cases of prevalent delirium, and 6 subjects (7%) became CAM-positive after their first assessment (incident delirium). Overall, 37.2% had delirium at some point. From among those with delirium at any point, 14 (43.8%) recovered from delirium before death or discharge and 18 (56.3%) did not. In the patients who remained CAM-negative throughout their admission, the mean C-RP was 52.4 mg/l (SD 55.8), in those already CAM-positive at initial assessment (prevalent delirium) it was 64.8 mg/l (SD 54.5), and in those who were negative at first assessment but who later became positive (incident delirium) it was 148.6 mg/l (SD 82.6). Although a significant difference in the levels of C-RP between the three groups (with prevalent delirium, incident delirium, or never had delirium) was evident (Kruskal–Wallis test, chi-square 10.746, DF 2, $p = 0.005$), there was no significant difference in the levels of C-RP between those with delirium and those without delirium at first assessment (Mann–Whitney test, $p = 0.112$). In a binary logistic analysis, including age, sex, initial MMSE, APS scale score, disability score and C-RP, only the C-RP level predicted the incidence of delirium (Wald 5.56, DF 1, $p = 0.018$). For CAM-negative patients at first assessment, a receiver operator characteristics (ROC) curve for initial C-RP level against incident delirium is shown (dashed line) in Figure 1. The likelihood ratio for incident delirium by initial C-RP level in this group is shown in Figure 2 (dashed line, right hand *Y* axis). In a further binary logistic regression,

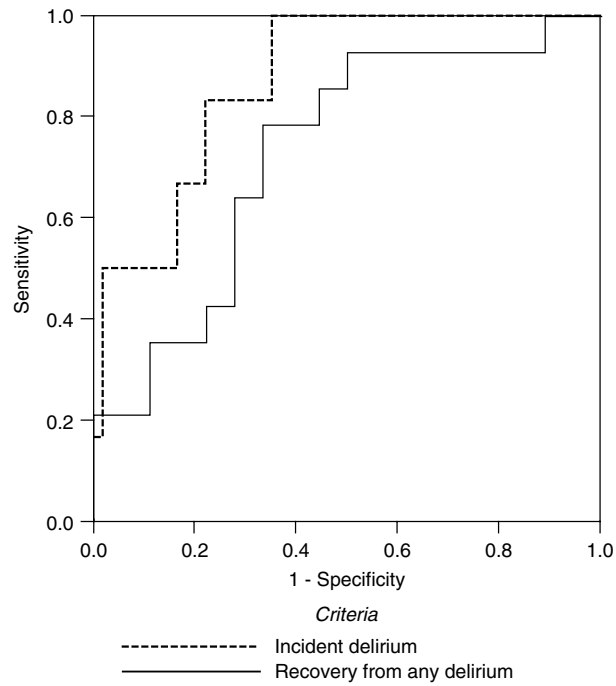

Figure 1. Receiver operator characteristics curves of C-RP with incident delirium (higher C-RP = more incidence) and recovery from incident or prevalent delirium (lower C-RP = more recovery).

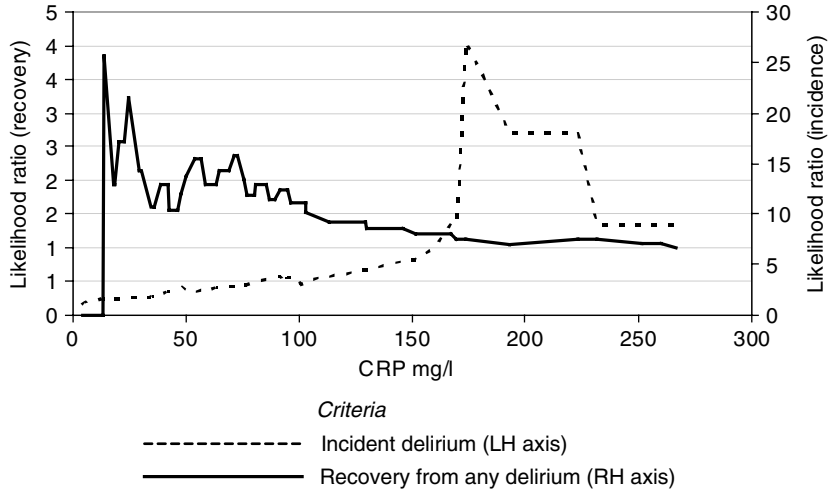

Figure 2. Likelihood ratios for each value of initial C-RP against incident delirium and recovery from delirium.

only a higher (better) initial MMSE score and a low C-RP predicted recovery from the CAM-positive status at any time (Wald statistic 6.49 DF 1$p = 0.011$, Wald statistics 5.67 DF 1$p = 0.017$, respectively). In these patients, an ROC curve against recovery to CAM-negative status is also shown (solid line) in Figure 1. The likelihood ratio for their recovery by initial C-RP level is shown in Figure 2 (solid line, left-hand *Y* axis). The two figures together appear to confirm that the association between C-RP and incident delirium was stronger than that with recovery, at least in this small sample.

Discussion

This is the first report of a possible link between C-RP levels, which is a marker of acute inflammatory response, and delirium in acute medical inpatients. C-RP levels appear to be highly predictive of both incident delirium and recovery even in the small numbers in this study and are independent of our measures of physical illness and disability. C-RP is thought to reflect the intensity of the acute phase response, but we found that the effect was independent of our measures of physical illness and disability, in contrast to that seen in post-operative patients [7]. Evidence has recently emerged of the relationship of C-RP with neuroinflammatory processes; for instance, it is associated in the activation of vascular endothelial cells, a process that may explain the vulnerability of patients with organic brain disease to delirium caused by systemic inflammatory conditions [23]. Considering that C-RP is elevated in inflammation and infection, and its production is under the control of other cytokines [16], it may be that the levels of more specific cytokines are even more closely correlated with such processes and their relationship with delirium. Alternatively, after initiation as a host defence mechanism, C-RP may act as a proinflammatory factor [6] with deleterious effects, as shown in animal studies [24]. Although it could be argued that CAM is quicker than the measurement of C-RP, the fact is that the C-RP measurement is quicker. This may help focus clinical attention on those most at risk of developing delirium and enable the initiation of well-known, evidence-based but expensive preventative measures.

The present study could not determine the mechanisms leading to delirium, and a further study in a new cohort is underway. Given the complex interplay between predisposing and precipitating causes, especially in the presence of multiple conditions that may or may not be relevant, it was not possible to ascertain the illnesses or other factors that were causal in this study. There are always limitations in the applicability of results from small samples to other cohorts of patients; however, in view of the widespread use of C-RP in medical practice, this preliminary finding should be easily replicable. Larger studies in several settings would be needed to determine the best cut-off points for using C-RP as a predictor of delirium incidence and recovery.

Key points

- High levels of C-RP independently predicted the incidence of delirium.
- A higher initial MMSE score and low C-RP predicted the recovery from delirium at any time during hospitalisation for patients with delirium.
- Elevated C-RP should alert clinicians to the possibility of incident delirium.
- C-RP in acute illness merits further investigation as a marker for potential precipitating or perpetuating mechanisms for delirium.

Conflicts of interest

The authors have no conflicts of interest to declare.

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Failure to complete performance-based measures is associated with poor health status and an increased risk of death

Sir—Mobility impairment is common in elderly people, often leads to adverse outcomes [1–4] and is intertwined with frailty [5, 6]. Three types of standardised mobility assessments [self-reported, gait laboratory and performance-based measures (PBMs)] are used, and each has its own advantages and disadvantages, including variable feasibility. PBMs attempt to optimise the practicality of clinical and self reported assessments, and the precision of the gait laboratory [7]. The Timed Up and Go (TUG) [8] and the Functional Reach (FR) [9] are used widely, [10, 11] but often cannot be used for a large proportion on whom the tests are attempted [12]. Such difficulty in undertaking the tests yields missing data, most frequently in those who are ill [13], or frail [14]. We therefore studied infeasibility in PBMs and whether missing data were informative. We compared the characteristics of people from the clinical examination in the Canadian Study of Health and Aging-2 (CSHA-2) who were able to perform both the FR and TUG, with those who could not, and then