The wave called delirium, from onset to consequences
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Chapter 3

The trajectory of CRP levels in elderly hip fracture patients with postoperative delirium

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ABSTRACT

Background: Many important precipitating risk factors for delirium such as infection and surgery are accompanied by an inflammatory response. Inflammatory mediators themselves can affect neuronal and synaptic function thereby inducing delirium in susceptible individuals. Less is known about the time course of these inflammatory markers and their role in the development and outcomes of delirium.

Methods: A prospective cohort study of elderly patients undergoing hip fracture surgery. Baseline characteristics were assessed preoperatively. During hospital admission presence of delirium was assessed daily according to CAM criteria. This study compared C-reactive protein (CRP) levels across time (baseline, postoperative day 1 until postoperative day 5) between people with and without postoperative delirium.

Results: 41 out of 121 patients developed postoperative delirium after hip surgery. Longitudinal analysis using the Generalised Estimating Equations method (GEE) identified that a higher CRP level was associated with postoperative delirium. CRP levels were higher from postoperative day 2 through postoperative day 5 in patients with postoperative delirium. No significant differences in CRP levels (baseline, postoperative day 1 through 5) were found between patients with short (1-2 days) and more prolonged delirium group (≥3 days). Also no significant correlation was found between the highest CRP level and pre-fracture cognitive or illness severity.

Conclusion: The findings in this study suggest that delirium is associated with an increased inflammatory response. The results suggest that CRP is not an early diagnostic marker of delirium, however that this marker does increase after the appearance of delirium and remains elevated throughout the delirium episode.
INTRODUCTION

Many important precipitating risk factors for delirium such as infection and surgery are accompanied by an inflammatory response. Peripherally produced inflammatory mediators can activate microglia cells in the brain which release a range of inflammatory mediators that can affect neuronal and synaptic function thereby inducing delirium in susceptible individuals.\textsuperscript{1,2}

Cognitive impairment and advanced age are well known predisposing risk factors for delirium.\textsuperscript{3} Aging and neurodegenerative disease are accompanied by impaired immune function resulting in an increased neuro-inflammatory state under normal conditions\textsuperscript{1} which can develop into an exaggerated inflammatory response in reaction to systemic inflammation.\textsuperscript{4} This pro-inflammatory state may explain why older and cognitively impaired individuals are particularly susceptible to delirium in the presence of precipitating factors that elicit an inflammatory response.

Cross-sectional studies have linked delirium to elevated levels of proinflammatory cytokines or C-reactive protein (CRP).\textsuperscript{5-7} However, not all studies found an association between delirium and (preoperative) levels of CRP which is induced by cytokines such as interleukin 6 (IL-6).\textsuperscript{8,9} In keeping with the senescence of the immune system, it can be hypothesised that patients with delirium show a different trajectory of CRP levels over time. These differences may also underpin the inconsistent findings of cross-sectional studies. Studies in orthopaedic surgery patients have found an association between delirium and increased levels of CRP.\textsuperscript{10-12}

The aim of the present study was to examine the time course of CRP levels over multiple days, in elderly hip fracture patients with and without postoperative delirium. Secondly, we examined the association between CRP and delirium severity, cognitive impairment, illness severity and delirium duration.

METHOD

Objectives and study design

To describe the time course of CRP levels over multiple days in patients with and without postoperative delirium. CRP was determined at baseline and from postoperative day 1 through 5. Potential risk factors for delirium were assessed preoperatively. Presence of delirium was assessed daily from time of admission until the fifth postoperative day. The time course of CRP levels and baseline risk factors were compared across patients who did or did not develop delirium postoperatively.

Delirium was diagnosed according to the criteria of the Confusion Assessment Method (CAM) criteria which consists of an acute onset and fluctuating course of symptoms, inattention, and either disorganized thinking and/or altered level of consciousness.\textsuperscript{13} The CAM algorithm was rated daily on the basis of an interview with the patient, brief cognitive assessment with the MMSE and the expanded digit span test, discussion with treating
hospital staff, and screening of medical and nursing records for signs of delirium. The CAM remains the most widely used screening test, has good psychometrics, has been validated in several languages and replicated in multiple settings. A diagnosis of delirium was always confirmed by a psychiatrist or geriatrician.

Baseline assessments were completed within 12 hours of admission and before surgery. This consisted of patient and proxy interviews, assessment of delirium, and inspection of all available medical records. We documented the following demographic variables: age, gender, educational level and living situation. To assess mental status we used the Mini Mental State Examination (MMSE) as a measure of baseline cognitive functioning on a scale of 0 (poor) to 30 (good) with scores lower than 24 indicating cognitive impairment. The 16 item Informant Questionnaire on Cognitive Decline in the Elderly Short-Form (IQCODE-N) was used as an estimate of pre-fracture cognitive decline and was scored by a close relative or caregiver on a scale of 16 (improvement) to 70 (decline). A score higher than 57 (i.e. mean item score of 3.6) indicates cognitive decline. Depressive symptoms were assessed with the Geriatric Depression Scale 15 (GDS-15) a 15 item self-rating scale for depression with higher scores indicating depression. Burden of illness included the number and type of medical co-morbidities and medications before hospital admission. We also reviewed the medical record to document the American Society of Anesthesiologists (ASA) physical status classification system (range of 1 (normal health patient) to 5 (moribund patient)) and the Acute Physiology Age and Chronic Health Examination (APACHE II) score (range of 0 (no acute health problems) to 70 (severe acute health problems)). Functional status comprised pre-fracture living arrangement, visual acuity, activities of daily living (ADL) and instrumental activities of daily living (IADL). Visual acuity was assessed with the standardized Snellen test for visual impairment and visual impairment was defined as binocular near vision, after correction, worse than 20/70. Pre-fracture ADL functioning was determined with the Barthel Index (BI) which is scored by a close relative or caregiver on a scale from 0 (dependence) to 20 (independence). IADL was also assessed by a close relative or caregiver on the Lawton IADL scale with a range of 8 (no disability) to 31 (severe disability).

For determination of concentrations of CRP blood samples were drawn into plain tubes (Vacutainer SST, Becton Dickinson, Plymouth, UK). Blood samples were centrifuged at 2500g within 4 hours after collection in order to separate serum from the cellular fraction. CRP concentrations were assayed with C-reactive Protein Reagent (Beckman Coulter Inc, Fullerton, California, USA) on a Synchron DxC 800 analyzer (Beckman Coulter Inc, Fullerton, California, USA). Normal reference values were assessed as CRP <5 mg/L.

Also, we compared the CRP levels of incident delirium cases experiencing short delirium episodes (1 or 2 days) with patients who experienced more prolonged delirium (≥3 days). The primary outcome was duration of delirium. The highly fluctuating nature of delirium makes reliably defining recovery difficult, such that a standard definition
The trajectory of CRP levels in elderly hip fracture patients with postoperative delirium

is lacking. We followed a conservative approach to define recovery of delirium as two subsequent days without delirium according to the Confusion Assessment Method (CAM). Duration of delirium was the number of days from the first delirium day until recovery (2 consecutive days of no delirium according to CAM criteria). A recent review of treatment for delirium which considered available evidence for defining ‘recovery’ concluded that because of the fluctuating course of delirium, recovery is best defined conservatively and in the manner used herein. Patients with no data available on the two days after the last delirious day could not be allocated to one of the duration groups. In this instance we could not define the exact count of delirious days according to the definition used for recovery. A single day without delirium but followed by further delirium was considered part of the delirium episode.

Finally, we examine the association between CRP levels and delirium severity pre-fracture cognitive decline and illness severity. Delirium severity was measured using the Revised Delirium Rating Scale 98 (DRS-R98), a 16-item rating scale comprised of thirteen severity items and 3 diagnostic items. The item-scores range of 0 (no severity) to 3 (maximum severity). Possible total severity scores range of 0 (no severity) to 39 (maximum severity). The IQCODE-N was used as an estimate of pre-fracture cognitive decline and the Acute Physiology Age and Chronic Health Examination (APACHE II) was used as a measure of illness severity.

Statistical analysis
Statistical calculations were performed using SPSS for Windows, version 14 (SPSS; Inc. Chicago, Il). Categorical variables were analysed using Chi-Square or Fisher Exact tests. Continuous variables were tested with Mann-Whitney-U tests or t-tests depending on the sample size and distribution and skewness of the data. The assumption of a normal distribution of data was tested with the Kolmogrov-Smirnov test. We used Generalized Estimating Equations model analyses to examine the association between delirium and CRP. The GEE method takes into account the fact that observations within a subject are correlated and estimates the population average across time. We controlled for the effect of age, gender, treatment (taurine or placebo), IQCODE-N, Barthel Index and APACHE-II score in the initial model. Thereafter, we dropped non-significant variables in order to find the most parsimonious model. We also examined each day separately with a Mann-Whitney analysis for the association between delirium and CRP, and to give a graphic representation of the longitudinal trajectory of the CRP and level in each group (delirium and non-delirium). Linear mixed models were used to examine the association between DRS-R98 severity scores and CRP levels, also in two separate analyses. We controlled for the same variables as in the GEE, and sought the most parsimonious model. The association between the highest CRP and IQCODE-N and APACHE-II scores were investigated with the Pearson product-moment correlation.
RESULTS
A flowchart of the patient selection process is shown in Figure 1. A total of 121 were available for analysis, 41/121 (34%) patients developed postoperative delirium. Characteristics of the patients who developed delirium postoperatively and patients who did not are described in Table 1. Patients who developed postoperative delirium had more evidence of prefracture cognitive decline (IQCODE-N continous, \(P<.001\); dichotomous, \(P<.001\)) and cognitive impairment at baseline (MMSE, continous, \(P=.01\); dichotomous, \(P=.01\)) compared to patients who did not.

Figure 1. Flow Diagram of the Study.

The Generalized Estimating Equations model with data on CRP levels (baseline, and postoperative day 1 through postoperative day 5) was performed with postoperative delirium as a dependent variable, in the initial model we controlled for gender, age, ADL functioning, pre-existing cognitive impairment, physical status and treatment (placebo or taurine). The final most parsimonious GEE model is shown in Table 2 (637 observations, 114 patients included). Delirium was associated with a higher CRP level.

The trajectory of the CRP levels is shown in Figure 2. Compared with non-delirious controls patients that developed delirium after surgery had significantly higher CRP levels from postoperative day 2 through postoperative day 5 (Table 3). Median levels and interquartile range (IQR) of CRP for the delirium and no-delirium group are also shown in Table 3.
Mixed model analysis with data across days (baseline, postoperative day 1 through 5) found that a higher DRS-R98 severity scores were associated with a higher CRP levels. In the final model pre-existing cognitive impairment and ADL functioning also remained associated with the DRS-R98 severity score (Table 4). We also repeated the model in the delirious sample only, CRP and DRS-R98 severity score remained associated.

No significant differences in CRP levels (baseline, postoperative day 1 through 5) were found between the short (1-2 days) and more prolonged delirium group (≥3 days) on each examined day.
Also, no significant correlation was found between the highest CRP level and pre-fracture cognitive decline \((n=38, r=.20, P=.23)\) or illness severity \((n=39, r=-.09, P=.60)\).

**Figure 2.** Trajectory of CRP Levels between Patients with and without Postoperative Delirium.

![Graph showing CRP levels over time for patients with and without postoperative delirium.]

**Table 2.** Generalised Equation Estimation (GEE) model CRP level and Postoperative Delirium.

<table>
<thead>
<tr>
<th></th>
<th>(\beta)</th>
<th>SE</th>
<th>df</th>
<th>Wald (x^2)</th>
<th>95% CI</th>
<th>(P)-value</th>
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<td>IQCODE-N score</td>
<td>-1.6</td>
<td>0.5</td>
<td>1</td>
<td>-0.7</td>
<td>-2.5 – -0.7</td>
<td>&lt;.001</td>
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<tr>
<td>CRP level</td>
<td>-2.0E-7</td>
<td>9.5E-8</td>
<td>1</td>
<td>4.3</td>
<td>-3.8E-7 – -1.1E-8</td>
<td>.04</td>
</tr>
<tr>
<td>Intercept</td>
<td>6.4</td>
<td>1.6</td>
<td>1</td>
<td>15.3</td>
<td>3.2 – 9.6</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

SE=Standard Error  
CI=Confidence Interval  
E with a minus sign signals the number of places the decimal point has to be moved to the left.  
IQCODE- =Informant Questionnaire on Cognitive Decline in the Elderly – Short Form, range 16 (cognitive improvement) to 80 (severe cognitive decline), mean score.
Table 3. Median and IQR of CRP within the Postoperative Delirium Group and Control Group.

<table>
<thead>
<tr>
<th>Postoperative Delirium</th>
<th>CRP baseline</th>
<th>CRP Day 1</th>
<th>CRP Day 2</th>
<th>CRP Day 3</th>
<th>CRP Day 4</th>
<th>CRP Day 5</th>
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<tr>
<td>Yes</td>
<td>41</td>
<td>39</td>
<td>40</td>
<td>36</td>
<td>37</td>
<td>34</td>
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<tr>
<td>Median</td>
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<td>94.0</td>
<td>178.5</td>
<td>170</td>
<td>133</td>
<td>85</td>
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<tr>
<td>Percentiles</td>
<td>25</td>
<td>2</td>
<td>61</td>
<td>150</td>
<td>136</td>
<td>90</td>
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<tr>
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<td>4</td>
<td>94</td>
<td>179</td>
<td>170</td>
<td>133</td>
<td>85</td>
</tr>
<tr>
<td>75</td>
<td>11</td>
<td>148</td>
<td>231</td>
<td>212</td>
<td>189</td>
<td>120</td>
</tr>
<tr>
<td>No</td>
<td>77</td>
<td>76</td>
<td>73</td>
<td>71</td>
<td>71</td>
<td>69</td>
</tr>
<tr>
<td>Median</td>
<td>3</td>
<td>80.5</td>
<td>141</td>
<td>133</td>
<td>102</td>
<td>62</td>
</tr>
<tr>
<td>Percentiles</td>
<td>25</td>
<td>1</td>
<td>48</td>
<td>86</td>
<td>85</td>
<td>60</td>
</tr>
<tr>
<td>50</td>
<td>3</td>
<td>81</td>
<td>141</td>
<td>133</td>
<td>102</td>
<td>62</td>
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<tr>
<td>75</td>
<td>7.5</td>
<td>145</td>
<td>191</td>
<td>185</td>
<td>141</td>
<td>93</td>
</tr>
</tbody>
</table>

Yes vs. No  \(P\)-value .33 .42 .001 .01 .02 .01

Days=postoperative days

Table 4. Linear Mixed Model CRP level and DRS-R98 severity score.

<table>
<thead>
<tr>
<th></th>
<th>Estimate</th>
<th>SE</th>
<th>df</th>
<th>t</th>
<th>95% CI</th>
<th>(P)-value</th>
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<tbody>
<tr>
<td>IQCODE-N score</td>
<td>4.1</td>
<td>0.8</td>
<td>171</td>
<td>5.4</td>
<td>2.6 – 5.7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CRP level</td>
<td>0.02</td>
<td>0.003</td>
<td>587</td>
<td>6.6</td>
<td>0.01 – 0.02</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>BI score</td>
<td>-0.4</td>
<td>0.1</td>
<td>169</td>
<td>-3.5</td>
<td>-0.6 – -0.2</td>
<td>.001</td>
</tr>
<tr>
<td>Intercept</td>
<td>-2.4</td>
<td>4.1</td>
<td>170</td>
<td>-0.6</td>
<td>-10.5 – 5.7</td>
<td>0.6</td>
</tr>
</tbody>
</table>

SE=Standard Error
CI=Confidence Interval
\(E\) with a minus sign signals the number of places the decimal point has to be moved to the left.
IQCODE-N=Informant Questionnaire on Cognitive Decline in the Elderly - Short Form, range 16 (cognitive improvement) to 80 (severe cognitive decline), mean score.
BI=Barthel Index, range 0 (severe disability) to 20 (no disability).

DISCUSSION
This study examined the time course of CRP levels over multiple days and the association between postoperative delirium and CRP in an elderly hip surgery population. In addition, the association between CRP levels and delirium severity, cognitive impairment, illness severity and delirium duration were investigated. We found that postoperative delirium and delirium severity was associated with higher CRP levels. CRP levels increased on postoperative day 2 and also remained higher in postoperative delirium patients. No significant differences in CRP levels were found between short and more prolonged
delirium, nor between the highest CRP level and pre-fracture cognitive decline or illness severity.

The main finding of this study is an increased level of inflammatory markers after surgery with a higher level of these markers associated with postoperative delirium. This finding is consistent with other studies that identified an association between an increased level of CRP and delirium in hip surgery patients.\textsuperscript{10-12} One study examined CRP levels in elderly patients undergoing elective arthroplasty.\textsuperscript{11} They used a cut-off score of 5 ng/mL or greater for CRP, and measured the CRP level preoperatively and on the first postoperative day. No significant difference was found in the proportion of patients with this level of CRP in the group with and without postoperative delirium. This is consistent with our finding that CRP levels were higher starting from postoperative day 2 in patients who developed postoperative delirium. However, Cerejeira et al. found that patients who developed postoperative delirium had a greater production of CRP and proinflammatory to anti-inflammatory ratio after surgery.\textsuperscript{11} Another study conducted multiple measurements of the level of CRP postoperatively, although not on a daily basis.\textsuperscript{10} These authors described higher levels of CRP both 24 hours and 2-3 days after surgery in elderly patients who had undergone hip joint surgery. Also, those who developed delirium had higher APACHE II scores compared to those who did not develop delirium. However, comparison of CRP levels between both groups were only performed with univariate analysis. A third study also found an association between CRP levels and delirium in elderly hip fracture patients.\textsuperscript{12} Postoperatively, CRP levels were higher in patients with an impaired mental status (MMSE score ≤23) compared to cognitively normal patients. A separate comparison of CRP levels between the delirium group and patients with no complications showed that CRP kinetics curves were higher for those patients who developed delirium. However, it remains unclear which information was used for the CAM algorithm and also if the delirium assessments were conducted concurrently with the sampling of CRP levels. The findings in the present study are consistent with these studies, CRP levels increase after surgery and remained at a higher level compared to the preoperative level for an extended time. In contrast to previous research we used daily CRP and delirium assessments and also multivariate, longitudinal analysis to control for important factors such as physical and mental status.

In our study we did not find a difference in preoperative CRP levels between patients who developed delirium or not after surgery. Most other studies, with a single exception,\textsuperscript{7} did not find a difference in CRP levels before surgery between patients who did and did not develop delirium thereafter.\textsuperscript{9,12,26}

Previous studies have suggested that anesthetic technique and other perioperative factors are not associated with postoperative delirium in orthopaedic patients.\textsuperscript{11,27} The present findings suggest that the stress response associated with the surgical procedure may increase the risk of delirium. Surgical trauma has been associated with the activation
The trajectory of CRP levels in elderly hip fracture patients with postoperative delirium

of the peripheral innate immune system, cytokine release and impairment of cognitive function. Several animal studies have shown that activation of the immune system, such as the stress response to surgery, results in an exaggerated inflammatory response in the hippocampus in aged organisms, which is followed by performance deficits in hippocampal-mediated cognitive tests in aged, rather than younger, animal compared to younger animals. It has also been suggested that systemic inflammation activates vascular endothelial cells and perivascular cells in the human brain. A postmortem study in human brain tissue found that systemic inflammation was associated with higher intensity of CRP in the vasculature. The level of CRP in patients who developed delirium remained higher during the following days compared to control patients in our study. Prolonged increase of CRP levels may be associated with cognitive impairment, which in turn may reflect cerebral vascular damage and white matter pathology. In the aged organism, which is more vulnerable to impaired cognitive function after a peripheral immune challenge, this neuroinflammatory response can also be more persistent. It has been suggested that CRP might serve as a marker to assist early diagnosis of delirium, assuming that levels of CRP might already increase in the prodromal phase. A study with elderly hip joint surgery patients stated that CRP levels within 24 hours after surgery and within 48-72 hours after surgery showed statistically significant differences in the delirium group. However compared to the non delirium group they found no difference in CRP level before surgery, at this time no patients were delirious since they excluded preoperative delirium. It is also difficult to disentangle the relevance of CRP levels to the prodromal phase and full delirium, since all were in the same group for analysis. Moreover, the level of CRP was not measured on the same day of assessment as the K-DRS-98 in all subjects. Our study results suggest that CRP is not an early marker for diagnosis of delirium. We found no differences in preoperative levels between the delirium and the non-delirium group. The difference in levels of CRP was evident from postoperative day 2 and onwards. Since the majority of our patients developed delirium on the first postoperative day this is not supportive of CRP as an early marker for diagnosis of delirium. Conversely, cytokine levels might be considered as a possible early marker. It has been shown that IL-6 levels are already higher directly after surgery and also 24 hours after surgery in patients with postoperative confusion compared to patients without postoperative confusion. Moreover, IL-6 is known to induce the expression of CRP, which suggests that a change in cytokine levels precede a change in the level of CRP.

The current study was conducted in a relatively homogeneous patient population. A strength of this study is the inclusion of longitudinal systematic assessments of both presence of delirium and CRP levels. In contrast to other studies we found that the level of CRP was not an early diagnostic marker of delirium, but increased and remained at a higher level after delirium emerged. We were able to control for important factors such as the cognitive and physical status while investigating the association between CRP and
postoperative delirium. We used standardized and validated instruments with systematic, simultaneous measurements of CRP level and delirium. The limitations are that the study population is not a pure observational cohort. Taurine was administered to a part of the sample. However, we controlled for treatment allocation in multivariate analysis, and found no association between treatment and CRP levels.

To conclude, the findings in this study suggest that delirium is associated with an increased inflammatory response. The level of CRP does not seem to be an early diagnostic marker for delirium, but rather is elevated soon after the emergence of delirium. This work, along with other recent studies, raises the possibility that inflammatory mechanisms may underpin the long-term negative consequences of delirium, including persistent cognitive impairment.
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REFERENCES


