

CLINICAL INVESTIGATION

Association between cerebrospinal fluid biomarkers of neuronal injury or amyloidosis and cognitive decline after major surgery

Mattias Danielson¹, Andreas Wiklund², Fredrik Granath³, Kaj Blennow^{4,5}, Souren Mkrtchian², Bengt Nellgård¹, Jonatan Oras¹, Malin J. Fagerlund², Anna Granström⁶, Anna Schening⁶, Lars S. Rasmussen⁷, Helena E. Harris⁸, Henrik Zetterberg^{4,5,9}, Sven-Erik Ricksten¹ and Lars I. Eriksson^{2,*}

¹Department of Anesthesiology and Intensive Care Medicine, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Sahlgrenska University Hospital, Gothenburg, Sweden, ²Department of Physiology and Pharmacology, Section of Anesthesiology and Intensive Care Medicine, Karolinska Institutet, Stockholm, Sweden, ³Clinical Epidemiology, Department of Medicine, Karolinska Institutet, Stockholm, Sweden, ⁴Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, The Sahlgrenska Academy at the University of Gothenburg, Mölndal, Sweden, ⁵Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden, ⁶Function Perioperative Medicine and Intensive Care, Karolinska University Hospital, Stockholm, Sweden, ⁷Department of Anaesthesia, Centre of Head and Orthopaedics, Rigshospitalet, and Institute of Clinical Medicine University of Copenhagen, Copenhagen, Denmark, ⁸Rheumatology Unit, Center for Molecular Medicine, Department for Medicine Solna, Karolinska Institutet, Stockholm, Sweden and ⁹Department of Neurodegenerative Disease, UCL Institute of Neurology, And UK Dementia Research Institute at UCL, London, UK

*Corresponding author. E-mail: Lars.I.Eriksson@ki.se

Abstract

Background: Postoperative neurocognitive decline is a frequent complication in adult patients undergoing major surgery with increased risk for morbidity and mortality. The mechanisms behind cognitive decline after anaesthesia and surgery are not known. We studied the association between CSF and blood biomarkers of neuronal injury or brain amyloidosis and long-term changes in neurocognitive function.

Methods: In patients undergoing major orthopaedic surgery (knee or hip replacement), blood and CSF samples were obtained before surgery and then at 4, 8, 24, 32, and 48 h after skin incision through an indwelling spinal catheter. CSF and blood concentrations of total tau (T-tau), neurofilament light, neurone-specific enolase and amyloid β (A β 1-42) were measured. Neurocognitive function was assessed using the International Study of Postoperative Cognitive Dysfunction (ISPOCD) test battery 1–2 weeks before surgery, at discharge from the hospital (2–5 days after surgery), and at 3 months after surgery.

Results: CSF and blood concentrations of T-tau, neurone-specific enolase, and A β 1-42 increased after surgery. A similar increase in serum neurofilament light was seen with no overall changes in CSF concentrations. There were no differences between patients having a poor or good late postoperative neurocognitive outcome with respect to these biomarkers of neuronal injury and A β 1-42.

Conclusions: The findings of the present explorative study showed that major orthopaedic surgery causes a release of CSF markers of neural injury and brain amyloidosis, suggesting neuronal damage or stress. We were unable to detect an association between the magnitude of biomarker changes and long-term postoperative neurocognitive dysfunction.

Keywords: amyloidosis; biomarker; cognitive dysfunction; neuronal injury; orthopaedic surgery; postoperative neurocognitive dysfunction; spinal anaesthesia

Received: 26 June 2020 Accepted: 19 September 2020

© 2020 The Authors. Published by Elsevier Ltd on behalf of British Journal of Anaesthesia. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

For Permissions, please email: permissions@elsevier.com

Editor's key points

- Postoperative neurocognitive decline is a frequent complication after major surgery, but the mechanisms involved are not known.
- In this observational study, associations between CSF and blood biomarkers of neuronal injury or brain amyloidosis with long-term changes in neurocognitive function were studied.
- Major orthopaedic surgery led to increased CSF biomarkers of neural injury and brain amyloidosis, consistent with neuronal damage or stress, but these changes did not correlate with long-term postoperative neurocognitive dysfunction.

Higher brain functions related to cognitive processes are impaired by surgery and trauma, and postoperative neurocognitive decline with risk for later dementia is now globally recognised as a major health concern,¹ with the older >60-yr-olds being most vulnerable.^{2–4} Typically, 25–35% of surgical patients display cognitive impairment at 1 week after surgery and 10% of older patients at 3 months. This can impair rehabilitation, return to work, quality of life, and social dependency with increased 1-yr mortality.^{3,5,6}

Concern for adverse postoperative brain outcomes is driven by growing experimental and clinical observations that surgery triggers key neuroinflammatory and neurodegenerative processes related to Alzheimer's disease (AD), and a transient increase in CSF and systemic biomarkers of AD and neuronal injury.^{7–11} Evered and colleagues¹² have shown rapidly increasing plasma concentrations of the two neuronal injury markers total tau (T-tau) and neurofilament light (NFL) after orthopaedic surgery under general anaesthesia, suggesting postoperative CNS neuronal damage.¹² A recent study focusing on cardiac surgery with cardiopulmonary bypass showed even more marked increases in plasma concentrations of T-tau and NFL.¹³ However, there was no follow-up of postoperative cognitive function in those studies, and it is not known if such increases in systemic brain biomarkers are associated with later adverse neurocognitive outcomes.

The primary aim of this secondary analysis of data collected in a prospective descriptive study was to explore temporal changes in CSF and systemic biomarkers of neuronal injury and brain amyloidosis in patients undergoing major orthopaedic surgery. The secondary aim was to explore the association between CNS and systemic biomarkers of neuronal injury and brain amyloidosis and postoperative neurocognitive outcomes at hospital discharge and 3 months after surgery. Systemic and CSF concentrations of T-tau, NFL, neurone-specific enolase (NSE), and amyloid β (A β 1-42) were measured before and during 48 h after start of surgery by an indwelling intrathecal catheter, and cognitive function was assessed by a validated psychometric test battery before surgery, at hospital discharge, and 3 months after surgery. We hypothesised that surgery induces neuronal injury and release of A β 1-42 that is more pronounced in patients developing neurocognitive dysfunction at 3 months after surgery.

Methods**Participants and study design**

This study is a secondary analysis of a prospective observational study (NEUPORT),¹⁴ approved by the Regional Ethics Committee in Stockholm, Sweden (Dnr 2013/2297–31/4 and 2014/834–32) and subsequently registered at www.clinicaltrials.gov; identifier: NCT02759965.

After informed and signed written consent, we included patients undergoing elective total hip or knee replacement surgery. Patients with pre-existing neurological, psychiatric or clinically evident neurovascular disease, recent or ongoing treatment with anti-inflammatory drugs, severe organ failure (e.g. cardiac, renal, or hepatic), coagulopathy, alcohol or drug abuse, poorly controlled diabetes mellitus, or autoimmune disease were excluded. Preoperative screening was performed using Mini Mental State Examination to exclude patients with mild cognitive impairment as defined by a test score of 24 or less.

After placement of an intrathecal catheter, the surgical procedure was performed under spinal anaesthesia supplemented by light sedation (see [Supplementary material](#)). The intrathecal catheter was left in place for 48 h to allow serial CSF sampling. Preoperatively and at 4, 8, 24, 32, and 48 h after skin incision, CSF (5 ml) and blood (20 ml) were collected and subsequently centrifuged, aliquoted, and stored at -80°C for subsequent analysis.

CSF and blood biomarkers

CSF T-tau concentration was determined using a sandwich enzyme-linked immunosorbent assay (ELISA) (INNOTEST hTAU Ag; Fujirebio, Ghent, Belgium) specifically constructed to measure all tau isoforms irrespective of phosphorylation status. CSF NFL concentration was determined using a commercial assay as described by the manufacturer (UmanDiagnostics AB, Umeå, Sweden). CSF and serum NSE were measured using an immunofluorescent assay with time-resolved amplified cryptate emission (TRACE) technology (Kryptor-NSE; BRAHMS, Hennigsdorf, Germany). CSF A β 1-42 was determined using a sandwich enzyme-linked immunosorbent assay constructed to measure A β 1-42 (INNOTEST[®] β -amyloid (1–42) (Fujirebio). Intra-assay coefficients of variation were <10% for all analyses. The CSF cut-offs for AD pathology were <550 pg ml⁻¹ for A β 1-42¹⁵ and 400 pg ml⁻¹ for T-tau. Plasma concentrations of T-tau and A β 1-42 and serum concentration of NFL were measured using single molecule array technology as described by the manufacturer (Quanterix, Billerica, MA, USA) to calculate blood to CSF ratios.

Neurocognitive testing

Neurocognitive function was assessed using the International Study of Postoperative Cognitive Dysfunction (ISPOCD) test battery⁴ 1–2 weeks before surgery, at hospital discharge 2–5 days after surgery and at 3 months after surgery (see [Supplementary material](#)). In brief, the ISPOCD test battery captures cognitive performance within three domains of memory, executive functions, and attention, using four

Table 1 Group characteristics by neurocognitive outcome at 3 months. Values are median (Q1–Q3). Group differences tested by Mann–Whitney U-test and Fischer’s exact test. ASA, American Society of Anesthesiologists; WBC, white blood cell.

Characteristics	Good neurocognitive outcome (n=21)	Poor neurocognitive outcome (n=6)	P-value
Preoperative			
Age, yr	71 (65–76)	68 (65–71)	0.32
Sex, male, n (%)	8 (38)	1 (17)	0.63
Weight, kg	80 (73.5–89)	79 (75–88.5)	0.93
Height, cm	171 (167–179)	166 (163–175)	0.24
BMI, kg m ⁻²	26.7 (24.6–29.4)	27.9 (25.7–31.5)	0.44
Comorbidity			
Hypertension, n	11	4	0.66
Diabetes mellitus, type 1, n	2	0	1
Diabetes mellitus, type 2, n	0	1	0.22
History of myocardial infarction, n	1	0	1
ASA physical status 1/2/3/4, n	7/13/1/0	0/6/0/0	0.197
Blood haemoglobin, g L ⁻¹	138 (128–147)	143 (134–157)	0.41
Serum creatinine, µmol L ⁻¹	71 (62–89)	68 (47–96)	0.63
Preoperative WBC count	6.3 (5.4–7.9)	7.7 (6.5–8.7)	0.22
Intraoperative			
Propofol, mg	170 (80–291)	168 (75–288)	1.0
Fentanyl, n	4	0	0.55
Alfentanil, n	2	0	1.0
Vasopressor, n	12	5	0.36
Intravenous fluids, ml	1200 (950–1350)	925 (750–1560)	0.44
Duration of procedure, min	89 (72–102)	86 (72–101)	0.93
Procedure			
Hip replacement, n	14	5	0.63
Knee replacement, n	7	1	0.63
Bleeding, ml	300 (150–450)	225 (150–550)	1.0
Postoperative (24 h)			
PACU length of stay, min	165 (98–225)	171 (128–579)	0.47
Intravenous fluids, ml	1000 (750–1850)	1575 (260–2500)	0.48
Medication			
Gabapentin, n	6	2	1
Oral opioid, n	20	6	1
Intravenous opioid, n	13	3	0.66
Post-spinal puncture headache, n	0	1	0.22
Blood patch, n	0	1	0.22

different tests that generate seven cognitive variables for analysis. Changes in cognitive performance were calculated for each of seven test variables and corrected for practice effects and variability using data from an age-matched non-surgical control group who underwent serial tests at similar intervals using the same test battery. To quantify the change from preoperative to postoperative test, a z-score calculated for each variable was combined into a composite z-score. Poor neurocognitive outcome was defined a composite z-score ≥ 1.0 at 3 months after surgery, whereas good neurocognitive outcome was defined as a composite z-score < 1.0 at 3 months.

Sleep, pain, and delirium assessment

A 10-point VAS was used to assess quality of sleep and severity of postoperative pain at regular intervals after surgery. Delirium was assessed 24 and 48 h postoperatively using the Confusion Assessment Method for the ICU.¹⁶

Statistical analysis

Postoperative longitudinal changes of the biomarkers of neuronal injury independent of group were analysed by analysis of variance for repeated measurements. Group-time interaction analysis of covariance of neuronal injury markers and blood to CSF ratios was used to compare groups with poor

or good cognitive outcomes at 3 months after surgery using baseline measurements as a covariate. This statistical approach adjusts for baseline differences between groups. Two-way analysis of variance for repeated measurements was used to assess differences between patients with or without cognitive decline at 3 months after surgery with respect to quality of sleep and the severity of postoperative pain (VAS). To study the correlation between CSF and blood concentrations of T-tau and NFL, Pearson correlation coefficients were calculated. Data on preoperative and intraoperative patient characteristics are presented as median and inter-quartile range. Data on CSF and systemic biomarkers are presented as mean (standard deviation [SD]). A P-value < 0.05 was considered significant. A *post hoc* power analysis revealed that the power to detect a 40–50% difference in peak postoperative CSF T-tau between groups was 0.69–0.87 at an SD of 225 pg ml⁻¹. The power to detect a 40–50% difference in peak CSF Aβ1-42 was 0.64–0.82 at an SD of 275 pg ml⁻¹.

Results

A CONSORT diagram is shown in [Supplementary Fig. S1](#). We assessed 156 patients for eligibility, and between September 2014 and March 2016, 34 patients were included at Karolinska University Hospital, Stockholm (n=14) and Sahlgrenska

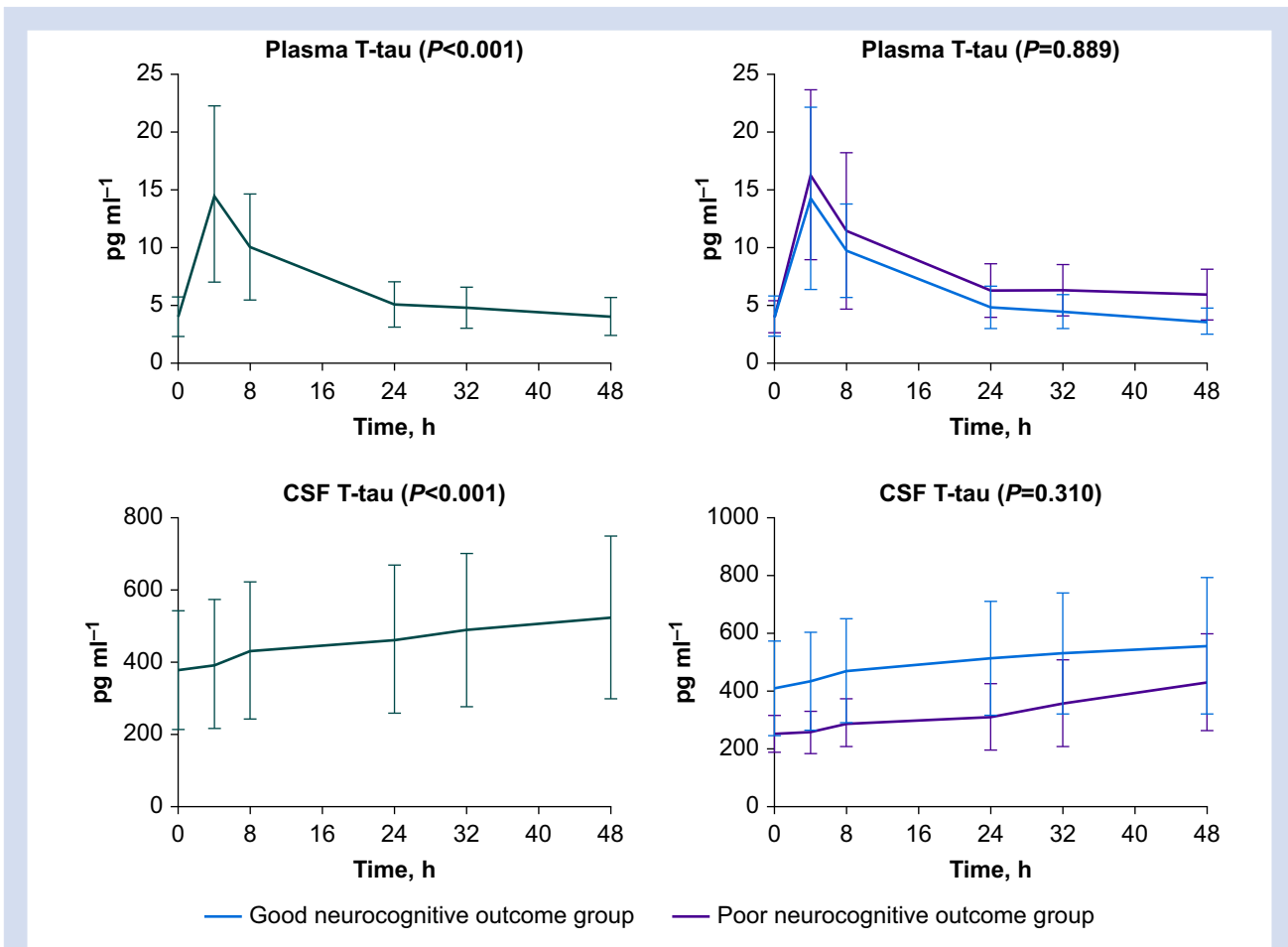


Fig 1. Temporal changes in CSF and plasma T-tau concentrations after major orthopaedic surgery. At baseline before surgery, there was a markedly positive CSF to plasma gradient for T-tau. The concentration of CSF T-tau increased continuously over time ($P < 0.001$). In contrast, there was an early peak increase in the concentration of plasma T-tau (2.5 times baseline, $P < 0.001$) at 4 h after surgery, followed by a rapid decline to baseline at 48 h. There was no difference in temporal change in CSF T-tau after surgery between patients with good vs poor postoperative neurocognitive outcome ($P = 0.310$). The early peak increase in plasma T-tau was seen in both groups with no difference between groups.

University Hospital, Mölndal ($n = 20$), out of which seven patients were not analysed for reasons described in [Supplementary Fig. S1](#). Thus 27 patients were included for analysis. Patient characteristics and comorbidities are presented in [Table 1](#).

Neurocognitive outcomes and perioperative patient characteristics

Data on neurocognitive outcomes within this cohort ([Supplementary Fig. S2](#)) have been published.¹⁴ At hospital discharge, 21 patients (78%) showed a composite z-score ≥ 1.0 , and 13 of these (48%) had a composite z-score > 1.96 . At 3 months after surgery, six of 27 (22%) showed a composite z-score ≥ 1.0 (poor neurocognitive outcome group, $n = 6$), where two of these patients had a composite z-score of > 1.96 . The remaining 21 patients (78%) had a composite z-score < 1.0 (good neurocognitive outcome group, $n = 21$).

There were no differences between patients in the good vs poor neurocognitive outcome groups with respect to patient

characteristic variables, comorbidity burden, ASA physical status, preoperative haemoglobin, serum creatinine, ongoing medication, administration of sedatives, vasoactive drugs, fluid management, intraoperative bleeding, duration and type of procedure, or length of stay in the PACU. The VAS score for assessment of pain and sleep quality did not differ between the two groups. One patient with long-term cognitive decline developed post-spinal headache and was successfully treated with an epidural blood patch. None of the patients developed postoperative delirium.

CSF and blood biomarkers of neural injury and AD after surgery

Before surgery, we found a markedly positive CSF to plasma gradient for T-tau with 85 times higher concentrations in CSF than in plasma. During the 48-h period after surgery, CSF T-tau increased continuously over time by 33% ($P < 0.001$) ([Fig. 1](#)). In contrast, there was a transient increase in plasma T-tau, with a peak at 4 h after surgery (2.5-fold compared with baseline,

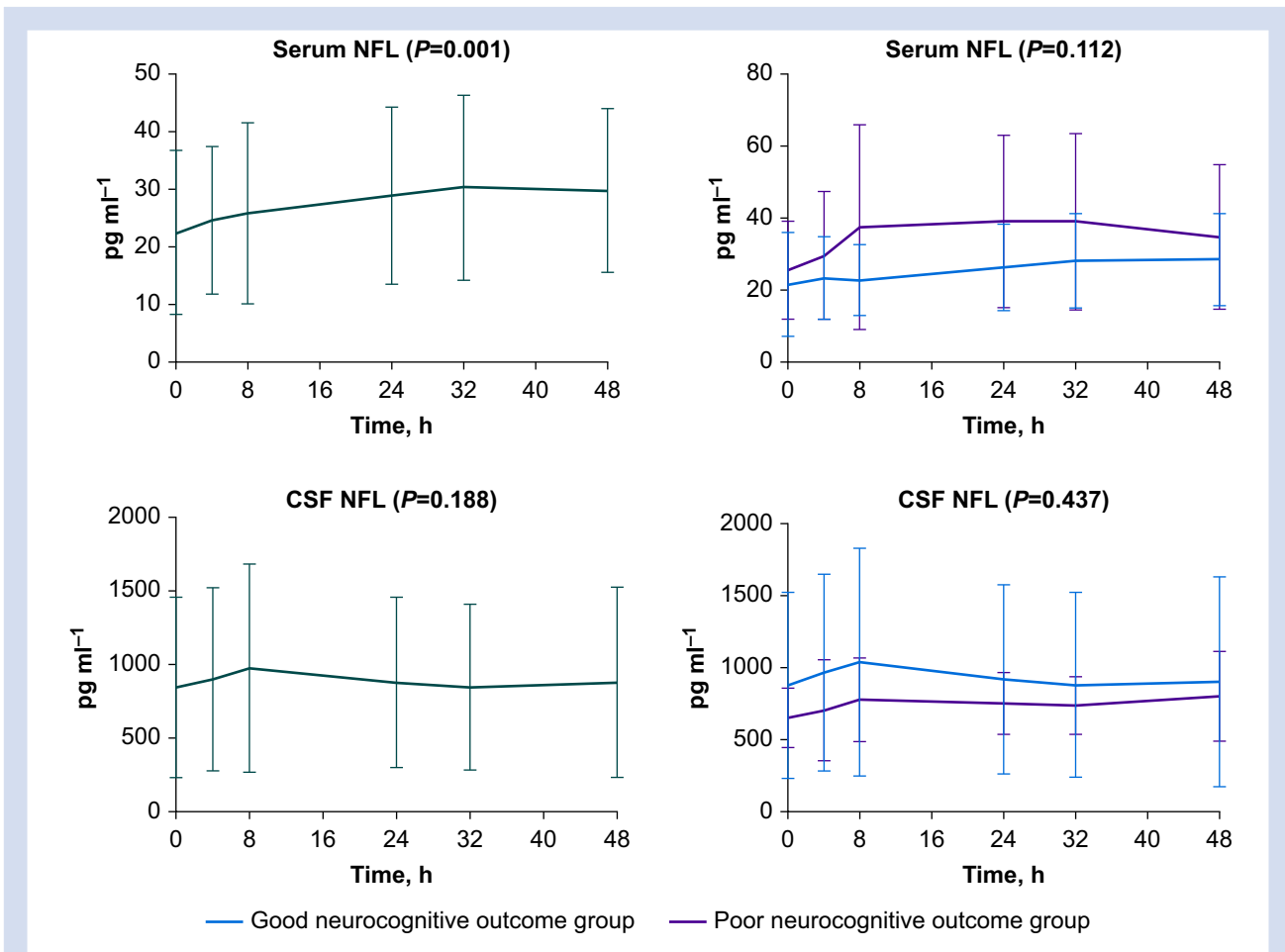


Fig 2. Temporal changes in CSF and serum NFL after major orthopaedic surgery. At baseline before surgery, there was a pronounced CSF to serum gradient for NFL. CSF concentrations of NFL did not change over time ($P=0.188$), whereas there was a gradual increase in serum concentrations of NFL with a maximal increase at 32 and 48 h after surgery ($P<0.001$). There was an initial transient increase in CSF concentrations of NFL in both groups with no difference between groups ($P=0.437$). Serum concentrations of NFL increased in both groups with no difference between patients with good vs poor postoperative neurocognitive outcome ($P=0.112$). NFL, neurofilament light.

$P<0.001$), followed by a rapid decline to baseline at 48 h. There was no correlation between plasma and CSF T-tau ($r=0.015$, $P=0.85$, [Supplementary Fig. S3](#)).

For NFL, we recorded a markedly positive CSF to serum gradient before surgery, with CSF NFL concentrations 30 times higher in CSF compared with serum. Whereas CSF NFL did not change significantly during the 48-h sampling period after surgery ($P=0.19$, [Fig. 2](#)), there was a gradual postoperative increase in serum concentrations of NFL with a maximum 35% increase in the latter part of the sampling period (i.e. at 32–48 h after surgery) ($P=0.001$). There was a poor but significant correlation between serum and CSF NFL ($r=0.26$, $P<0.001$, [Supplementary Fig. S4](#)).

Serum NSE was 50–100% higher in serum compared with CSF, indicating a reverse CSF to serum gradient. Both CSF and serum concentrations of NSE increased over time postoperatively ($P=0.002$ and $P=0.009$, respectively) ([Fig. 3](#)), both with maximum concentrations at 8–32 h after surgery followed by a late decline to baseline at 48 h.

Both CSF and plasma A β 1-42 increased gradually over time after surgery, with maximal concentrations at 48 h ([Fig. 4](#)).

CSF and blood biomarker response to surgery in patients with good vs poor postoperative neurocognitive outcome

There were no differences in temporal changes in CSF T-tau after surgery between patients with good vs poor postoperative neurocognitive outcome ($P=0.31$, [Fig. 1](#)). The early peak increase in plasma T-tau was seen in both groups with no difference between groups ($P=0.89$).

There was an initial transient postoperative increase in CSF concentrations of NFL in both groups with no difference between groups ($P=0.44$). Serum concentrations of NFL increased in both groups with no difference between patients with good vs poor postoperative neurocognitive outcome ($P=0.11$) ([Fig. 2](#)).

Neither CSF ($P=0.12$) nor serum ($P=0.061$) postoperative concentrations of NSE differed between patients with good vs poor postoperative neurocognitive outcome ([Fig. 3](#)).

After surgery, neither CSF ($P=0.057$) nor plasma ($P=0.17$) concentrations of A β 1-42 differed between patients with good vs poor postoperative neurocognitive outcome ([Fig. 4](#)). Preoperative CSF values of A β 1-42 were 616 (321) and 496

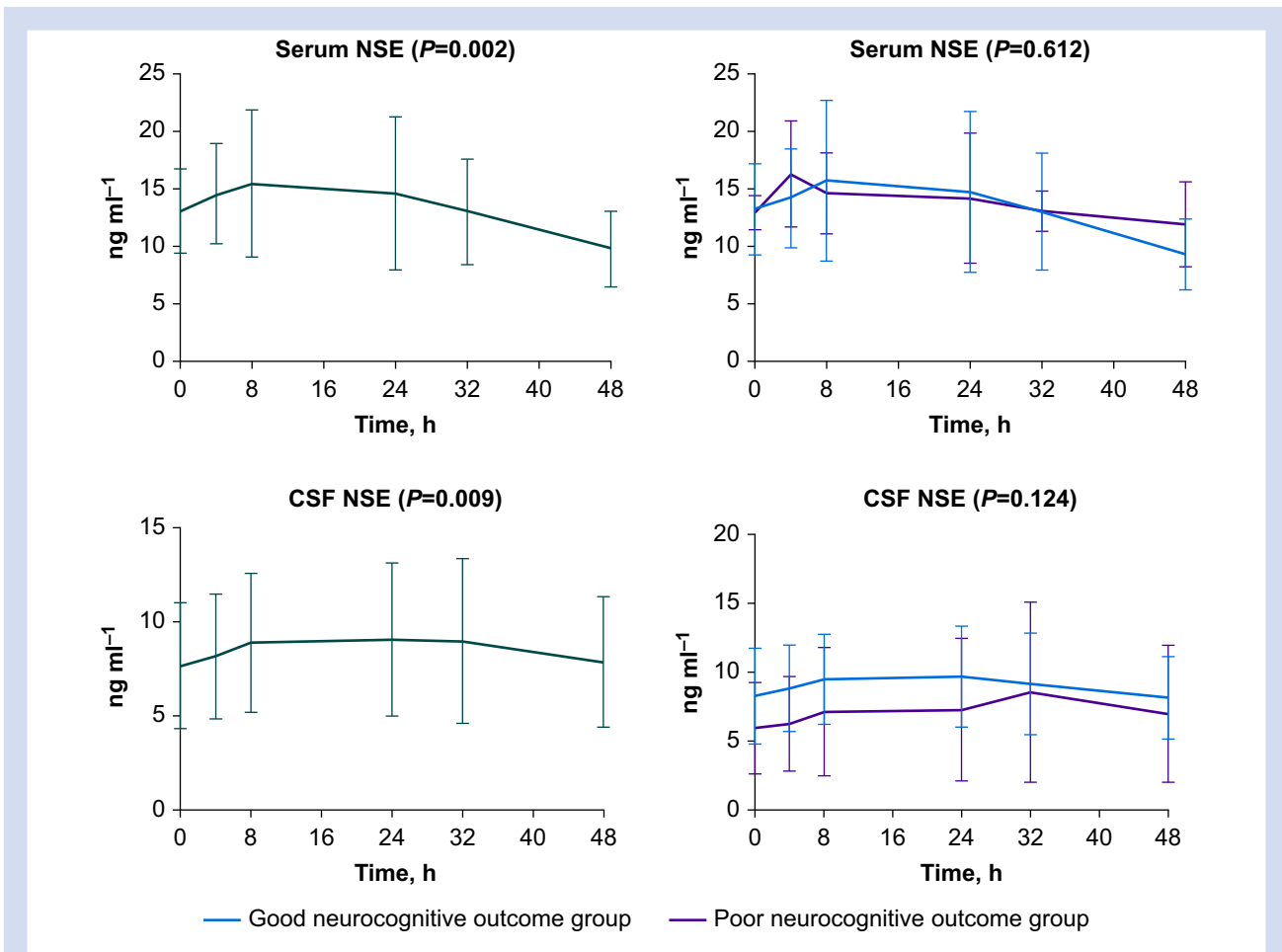


Fig 3. Temporal changes in CSF and serum NSE after major orthopaedic surgery. Serum concentrations of NSE were 50–100% higher in serum compared with CSF, suggesting a negative CSF to serum gradient. Both CSF and serum concentrations of NSE increased over time ($P=0.009$ and $P=0.002$, respectively) both with maximal concentrations at 8–32 h after surgery followed by a slow decline to baseline at 48 h. Neither CSF ($P=0.124$) nor serum ($P=0.612$) concentrations of NSE differed between patients with good vs poor postoperative neurocognitive outcome. NSE, neurone-specific enolase.

(217) pg ml⁻¹, respectively, for patients with good vs poor postoperative neurocognitive outcome ($P=0.40$). Four out of 16 patients (25%) with A β 1-42 concentrations <550 pg ml⁻¹ and 2/11 patients (18%) with A β 1-42 concentrations >550 pg ml⁻¹ had poor neurocognitive outcome ($P=1.0$). Preoperative CSF values of T-tau were 411 (163) and 253 (64) pg ml⁻¹, respectively, for patients with good vs poor postoperative neurocognitive outcome ($P=0.03$).

Blood/CSF ratios were higher in the poor neurocognitive outcome group for T-tau ($P=0.028$), NFL ($P=0.172$), and A β 1-42 ($P=0.038$) (Fig. 5).

Discussion

The main findings were that CSF and systemic concentrations of the two neuronal injury markers, T-tau and NSE, and of the brain amyloidosis marker A β 1-42, increased after major orthopaedic surgery. A similar increase in serum NFL was seen with no overall changes in CSF concentrations after surgery. These findings suggest that major surgery induces neuronal

stress or damage. However, as there were no differences in the release of these neuronal injury or brain amyloidosis biomarkers according to postoperative neurocognitive decline, it is less likely that adverse neurocognitive outcomes after surgery are associated with surgery-induced neuronal injury or brain amyloidosis. We could also show that there was an absent (T-tau) or poor (NFL) correlation between blood and CSF concentrations of these two neuronal injury markers, suggesting that one should be cautious when evaluating surgery-induced neuronal injury that solely relies on blood sampling.

To our knowledge, this is the first report on the association between major surgery and perioperative CSF release of neuronal injury and brain amyloidosis markers and the association of such changes to later neurocognitive outcomes. Evered and colleagues¹² reported serial sampling of plasma T-tau and NFL until 48 h after surgery under general anaesthesia. A maximum increase in NFL was seen 48 h after surgery (67%), whereas a peak increase (257%) was noted in T-tau after 6 h, suggesting transient neuronal injury where the relative impact from surgery or anaesthesia could not be separated.

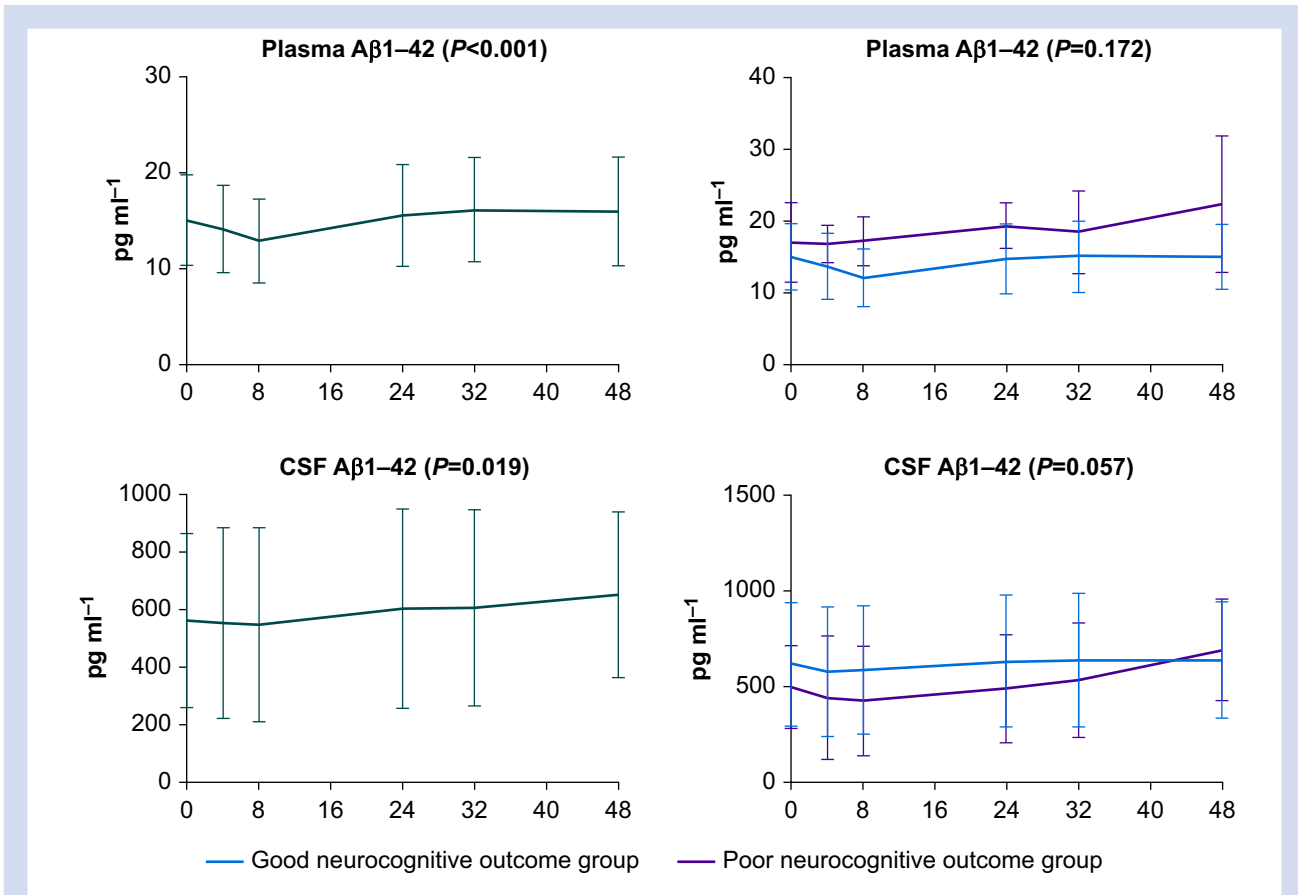


Fig 4. Temporal changes in CSF and plasma Aβ1-42 after major orthopaedic surgery. Both CSF ($P=0.019$) and plasma concentrations ($P<0.001$) of Aβ1-42 increased gradually over time after surgery. Neither CSF ($P=0.057$) nor plasma ($P=0.172$) concentrations of Aβ1-42 differed between patients with good vs poor postoperative neurocognitive outcome. Aβ, amyloid β.

The present study was carried out in patients undergoing surgery under spinal anaesthesia with light sedation. In this setting (without the potential impact of general anaesthesia) we confirm the systemic release patterns for plasma T-tau and NFL as reported by Evered and colleagues,¹² which suggests that the primary impact on the brain is related to the surgical trauma rather than to general anaesthesia.

Tau proteins are a family of six isoforms, with roles in stabilising axonal microtubules. They are released from unmyelinated cortical interneurons after exposure to traumatic or ischaemic brain injury.^{17,18} The temporal change in systemic T-tau concentrations after surgery, with a peak increase in the early part of the 48-h sampling period, corresponds to the relatively short-lasting and early opening of the blood–brain barrier (BBB), previously shown to occur at 4–8 h after surgery,¹⁴ potentially allowing the T-tau complex to distribute rapidly from CSF to blood.

In contrast to T-tau, NFL is released from myelinated subcortical axons in traumatic brain injury¹⁹ and in ischaemic stroke.²⁰ We were unable to detect changes in CSF concentrations of NFL within 48 h after the surgical procedure. Supported by findings after neurosurgical trauma,²¹ we speculate that the failure to capture changes in CSF NFL may be because of a protracted increase in CSF NFL that becomes apparent after the 48-h sampling period. Contrary to CSF NFL, we found

a rapid and gradual increase in serum NFL, more likely associated with surgery-dependent peripheral nerve injury.

In regards to NSE, there was a prominent reverse CSF to serum gradient with serum NSE 65% higher compared with CSF. A similar reverse CSF to serum gradient has also been described in cardiac surgery patients.²² The release pattern of NSE in serum and CSF was almost identical with an initial increase followed by a gradual decline to baseline. We speculate that the initial increase of serum NSE after surgery emanates from extracerebral sources, such as peripheral neurones, erythrocytes (as in haemolysis), platelets, or neuroendocrine cells. This initial increase in serum NSE influences CSF concentrations of NSE, primarily because of the serum-to-CSF concentration gradient and rapid and transient disintegration of the BBB. With respect to brain injury in surgical patients, changes in CSF and serum concentrations of NSE should be regarded with caution, as the CSF concentrations will be affected by serum concentrations as a result of the reverse concentration gradients.

Surgery may induce neuroinflammation,²³ and a distinct neuroinflammatory response has been demonstrated in orthopaedic^{7,9–11,24} and cardiac surgery^{8,22} patients based on increased CSF concentrations of cytokines after surgery, followed by signs of increased BBB permeability.^{8,22} A recent study of postoperative patients using positron emission

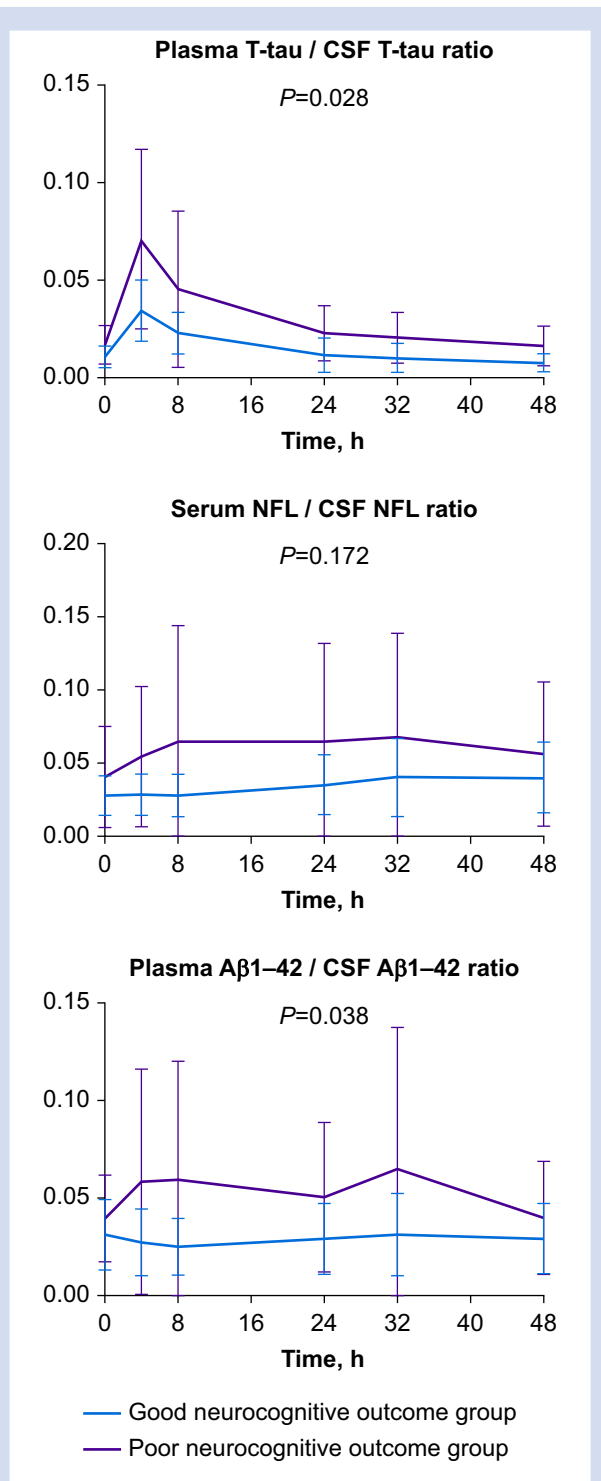


Fig 5. Temporal changes in the blood/CSF ratios of T-tau, NFL, and Aβ1-42 after major orthopaedic surgery. Blood/CSF ratios were higher in the poor compared with the good neurocognitive outcome group after surgery. Aβ, amyloid β; NFL, neurofilament light.

tomography imaging reported marked changes in CNS immune activity together with a reduction in higher cognitive brain functions associated with up-regulation of CNS immune activity.²⁵ Postoperative blood/CSF ratios were greater in the poor neurocognitive outcome group for T-tau, NFL, and Aβ1-42, suggesting a greater perturbation of the BBB in this outcome group.

We recently reported a rapid CSF neuroinflammatory response pattern associated with postoperative neurocognitive outcomes¹⁴ in patients undergoing orthopaedic surgery under regional anaesthesia and light propofol sedation. These findings are in sharp contrast to the lack of association between the release of neurodegenerative and neuronal injury markers and long-term postoperative neurocognitive outcome in the present study. This suggests a greater role for neuroinflammation than neuronal damage in postoperative neurocognitive outcomes.

Data on preoperative and postoperative CSF concentrations of Aβ1-42 are scarce. Tang and colleagues¹⁰ measured CSF concentrations of AD biomarkers up to 48 h postoperatively in patients undergoing minor surgery under general anaesthesia, and found that Aβ1-42 was not affected. In contrast, in cardiac surgery CSF concentrations of Aβ1-42 were elevated early (24 h postoperatively),²⁶ and 1 week after surgery.²⁷ Such an increase in CSF concentrations of Aβ1-42 after major surgery was confirmed in the present study. It has been speculated that the inflammatory response to major surgery may trigger proteolysis and cleavage of the amyloid precursor protein, which would increase concentrations of Aβ1-42.²⁶

Low preoperative CSF concentrations of Aβ1-42 have been shown to predict neurocognitive decline at 3 months, and it has been suggested that patients with CSF-defined AD neuropathology are more prone to develop postoperative neurocognitive decline.^{28,29} In the present study, there was no difference in preoperative CSF concentrations of Aβ1-42 comparing the good vs poor neurocognitive outcome groups. The poor neurocognitive outcome group showed no accumulation of patients with preoperative CSF concentrations of Aβ1-42 <550 pg ml⁻¹. Preoperative CSF concentrations of T-tau were, if anything, higher in the good neurocognitive outcome group. Taken together, our data do not support that pathological preoperative CSF concentrations are associated with late poor neurocognitive outcome.

Anaesthetic regimen was uniform and there were no differences between the two outcome groups with respect to patient characteristics, comorbidity, risk factors, perioperative medication/anaesthetics, procedure duration, postoperative pain scores, pain treatment, and sleep quality, which all could have influenced postoperative cognitive function.

A major limitation of this explorative study is the small sample size. According to our *post hoc* power analysis, the sample size allowed us to detect only a 40–50% difference in peak postoperative CSF markers of neuronal injury and brain amyloidosis between the good and poor neurocognitive outcome groups, at an acceptable power. Another limitation is that the study was conducted before publication of the international nomenclature consensus document.³⁰ The data should therefore be regarded as preliminary, and must be confirmed using the novel nomenclature guideline in a larger patient cohort. Finally, we cannot exclude the possibility that

the spinal catheter may have caused local inflammation that may have affected the release of neuronal injury markers.

Conclusions

Major orthopaedic surgery causes a release of CSF biomarkers of neural injury and brain amyloidosis, consistent with neuronal damage or stress, which we were unable to associate with long-term postoperative neurocognitive dysfunction.

Authors' contributions

Study supervision: LIE, SER

Study design and data analysis: MD, AW, FG, KB, SM, BN, JO, MJF, LS, HZ, SER, LIE

Data collection: MD, AW, BN, JO, MJF, AS, AG, SER, LIE

Drafting of the manuscript: MD, AW, FG, KB, SM, BN, JO, MJF, LS, HZ, SER, LIE

Gave final approval of the submitted version: all authors
Mattias Danielson and Andreas Wiklund contributed equally
Lars I Eriksson and Sven-Erik Ricksten contributed equally

Declarations of interest

HZ has served at advisory boards of Roche Diagnostics, CogRx, Samumed, and Wave, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB, a GU Ventures-based platform company at the University of Gothenburg. KB has served as a consultant or at advisory boards for Abcam, Axon, Biogen, Lilly, MagQu, Novartis, and Roche Diagnostics, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program, all unrelated to the work presented in the present paper. LIE has received lecture fees from MSD Sweden. The other authors have no disclosures to report.

Funding

Swedish State Support for Clinical Research (ALFGBG-721141, ALFGBG-144341, ALFGBG-139671, ALFGBG-75130, ALFGBG-73450, ALFGBG-720931, SLL20140188 and SLL20170127), the Gothenburg Medical Society, the Swedish Research Council (K2016-01122, K2010-61X-14002, K2010-63P-21562-01-4, K2015-02776-3, K2011-61X-20401-05-6, and 2018-02532), the European Research Council (#681712), the Knut and Alice Wallenberg Foundation, the Olav Thon Foundation, Torsten Söderberg Foundation, Frimurarestiftelsen and Hjärnfonden. The funders/sponsors had no role in the design and conduct of the study such as collection, management, analysis, and interpretation of the data, in the preparation, review, or approval of the manuscript or the decision to submit the manuscript for publication.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.bja.2020.09.043>.

References

- Mahanna-Gabrielli E, Schenning KJ, Eriksson LI, et al. State of the clinical science of perioperative brain health: report from the American society of anesthesiologists brain health initiative summit 2018. *Br J Anaesth* 2019; **123**: 464–78
- Paredes S, Cortinez L, Contreras V, Silbert B. Post-operative cognitive dysfunction at 3 months in adults after non-cardiac surgery: a qualitative systematic review. *Acta Anaesthesiol Scand* 2016; **60**: 1043–58
- Monk TG, Weldon BC, Garvan CW, et al. Predictors of cognitive dysfunction after major noncardiac surgery. *Anesthesiology* 2008; **108**: 18–30
- Moller JT, Cluitmans P, Rasmussen LS, et al. Long-term postoperative cognitive dysfunction in the elderly ISPOCD1 study. ISPOCD investigators. International Study of Post-Operative Cognitive Dysfunction. *Lancet* 1998; **351**: 857–61
- Steinmetz J, Christensen KB, Lund T, Lohse N, Rasmussen LS, Group I. Long-term consequences of postoperative cognitive dysfunction. *Anesthesiology* 2009; **110**: 548–55
- Phillips-Bute B, Mathew JP, Blumenthal JA, et al. Association of neurocognitive function and quality of life 1 year after coronary artery bypass graft (CABG) surgery. *Psychosom Med* 2006; **68**: 369–75
- Hirsch J, Vacas S, Terrando N, et al. Perioperative cerebrospinal fluid and plasma inflammatory markers after orthopedic surgery. *J Neuroinflammation* 2016; **13**: 211–21
- Reinsfelt B, Ricksten SE, Zetterberg H, Blennow K, Freden-Lindqvist J, Westerlind A. Cerebrospinal fluid markers of brain injury, inflammation, and blood-brain barrier dysfunction in cardiac surgery. *Ann Thorac Surg* 2012; **94**: 549–55
- Bromander S, Anckarsater R, Kristiansson M, et al. Changes in serum and cerebrospinal fluid cytokines in response to non-neurological surgery: an observational study. *J Neuroinflammation* 2012; **9**: 242–54
- Tang JX, Baranov D, Hammond M, Shaw LM, Eckenhoff MF, Eckenhoff RG. Human Alzheimer and inflammation biomarkers after anesthesia and surgery. *Anesthesiology* 2011; **115**: 727–32
- Buvanendran A, Kroin JS, Berger RA, et al. Upregulation of prostaglandin E2 and interleukins in the central nervous system and peripheral tissue during and after surgery in humans. *Anesthesiology* 2006; **104**: 403–10
- Evered L, Silbert B, Scott DA, Zetterberg H, Blennow K. Association of changes in plasma neurofilament light and tau levels with anesthesia and surgery: results from the CAPACITY and ARCADIAN Studies. *JAMA Neurol* 2018; **75**: 542–7
- Alifler M, Olsson B, Andreasson U, et al. Cardiac surgery is associated with biomarker evidence of neuronal damage. *J Alzheimers Dis* 2020; **74**: 1211–20
- Danielson M, Wiklund A, Granath F, et al. Neuro-inflammatory markers associate with cognitive decline after major surgery: findings of an explorative study. *Ann Neurol* 2020; **87**: 370–82
- Palmqvist S, Insel PS, Stomrud E, et al. Cerebrospinal fluid and plasma biomarker trajectories with increasing amyloid deposition in Alzheimer's disease. *EMBO Mol Med* 2019; **11**: e11170
- Shi Q, Warren L, Saposnik G, Macdermid JC. Confusion assessment method: a systematic review and meta-analysis of diagnostic accuracy. *Neuropsychiatr Dis Treat* 2013; **9**: 1359–70
- Franz G, Beer R, Kampfl A, et al. Amyloid beta 1-42 and tau in cerebrospinal fluid after severe traumatic brain injury. *Neurology* 2003; **60**: 1457–61

18. Ulamek-Kozioł M, Czuczwar SJ, Januszewski S, Pluta R. Proteomic and genomic changes in tau protein, which are associated with Alzheimer's disease after ischemia-reperfusion brain injury. *Int J Mol Sci* 2020; **21**: 892
19. Shahim P, Gren M, Liman V, et al. Serum neurofilament light protein predicts clinical outcome in traumatic brain injury. *Sci Rep* 2016; **6**: 36791
20. Pujol-Calderon F, Portelius E, Zetterberg H, Blennow K, Rosengren LE, Hoglund K. Neurofilament changes in serum and cerebrospinal fluid after acute ischemic stroke. *Neurosci Lett* 2019; **698**: 58–63
21. Bergman J, Dring A, Zetterberg H, et al. Neurofilament light in CSF and serum is a sensitive marker for axonal white matter injury in MS. *Neurol Neuroimmunol Neuroinflamm* 2016; **3**: e271
22. Danielson M, Reinsfelt B, Westerlind A, Zetterberg H, Blennow K, Ricksten SE. Effects of methylprednisolone on blood-brain barrier and cerebral inflammation in cardiac surgery – a randomized trial. *J Neuroinflammation* 2018; **15**: 283
23. Terrando N, Eriksson LI, Ryu JK, et al. Resolving postoperative neuroinflammation and cognitive decline. *Ann Neurol* 2011; **70**: 986–95
24. Anckarsater R, Vasic N, Jideus L, et al. Cerebrospinal fluid protein reactions during non-neurological surgery. *Acta Neurol Scand* 2007; **115**: 254–9
25. Forsberg A, Cervenka S, Jonsson Fagerlund M, et al. The immune response of the human brain to abdominal surgery. *Ann Neurol* 2017; **81**: 572–82
26. Reinsfelt B, Westerlind A, Blennow K, Zetterberg H, Ricksten SE. Open-heart surgery increases cerebrospinal fluid levels of Alzheimer-associated amyloid beta. *Acta Anaesthesiol Scand* 2013; **57**: 82–8
27. Palotas A, Reis HJ, Bogats G, et al. Coronary artery bypass surgery provokes Alzheimer's disease-like changes in the cerebrospinal fluid. *J Alzheimers Dis* 2010; **21**: 1153–64
28. Evered L, Silbert B, Scott DA, Ames D, Maruff P, Blennow K. Cerebrospinal fluid biomarker for alzheimer disease predicts postoperative cognitive dysfunction. *Anesthesiology* 2016; **124**: 353–61
29. Xie Z, Swain CA, Ward SA, et al. Preoperative cerebrospinal fluid beta-amyloid/Tau ratio and postoperative delirium. *Ann Clin Transl Neurol* 2014; **1**: 319–28
30. Evered L, Silbert B, Knopman DS, et al. Recommendations for the nomenclature of cognitive change associated with anaesthesia and surgery-2018. *Br J Anaesth* 2018; **121**: 1005–12

Handling editor: Hugh C Hemmings Jr