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Preoperative cerebrospinal fluid β-Amyloid/Tau ratio and postoperative delirium

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Abstract

Objective: The neuropathogenesis of postoperative delirium remains unknown. Low cerebrospinal fluid (CSF) β-amyloid protein (Aβ) and high CSF Tau levels are associated with Alzheimer's disease. We, therefore, assessed whether lower preoperative CSF Aβ/Tau ratio was associated with higher incidence and greater severity of postoperative delirium. **Methods**: One hundred and fifty-three participants (71 ± 5 years, 53% men) who had total hip/knee replacement under spinal anesthesia were enrolled. CSF was obtained during initiation of spinal anesthesia. The incidence and severity of postoperative delirium were determined by Confusion Assessment Method (CAM) and Memorial Delirium Assessment Scale (MDAS) on postoperative day 1 and 2. Aβ40, Aβ42, and Tau levels in the CSF were measured by enzyme-linked immunosorbent assay. The relationships among these variables were determined, adjusting for age and gender. **Results**: Participants in the lowest quartile of preoperative CSF Aβ40/Tau and Aβ42/Tau ratio had higher incidence (32% vs. 17%, $P = 0.0482$) and greater symptom severity of postoperative delirium (Aβ40/Tau ratio: 4 vs. 3, $P = 0.034$; Aβ42/Tau ratio: 4 vs. 3, $P = 0.062$, the median of the highest MDAS score) as compared to the combination of the rest of the quartiles. The preoperative CSF Aβ40/Tau or Aβ42/Tau ratio was inversely associated with MDAS score (Aβ40/Tau ratio: -0.12 ± 0.05, $P = 0.014$, adj. -0.12 ± 0.05, $P = 0.018$; Aβ42/Tau ratio: -0.65 ± 0.26, $P = 0.013$, adj. -0.62 ± 0.27, $P = 0.022$). **Interpretation**: Lower CSF Aβ/Tau ratio could be associated with postoperative delirium, pending confirmation of our preliminary results in further studies. These findings suggest potential roles of Aβ and/or Tau in postoperative delirium neuropathogenesis.

Introduction

Postoperative delirium[1] is one of the most common postoperative complications in elderly patients.[2] It has been shown that postoperative delirium has independent adverse effects on short and long-term mortality and morbidity, including poor functional recovery, postoperative cognitive dysfunction, deterioration in quality of life, and increased costs[3–6] (reviewed in refs. 7, 8). However, at the present time, postoperative delirium is a clinical phenomenon, and its neuropathogenesis remains unknown. This gap in knowledge has become a barrier that limits further studies, including the development of potential interventions for postoperative delirium.

β-Amyloid protein (Aβ), including Aβ40 and Aβ42, is the key component of senile plaques in Alzheimer's disease (AD) patients. Tau is the major protein component of intraneuronal neurofibrillary tangles. Both Aβ and Tau are hallmark features of AD neuropathogenesis (reviewed in ref. 9).

Lower levels of cerebrospinal fluid (CSF) Aβ42 have been found to be associated with higher brain amyloid amounts,[10–13] and appear in AD patients as compared to normal controls.[14,15] Higher levels of CSF Tau are associated with elevated brain Tau levels,[13,16] and with the progression of AD.[17–19] Therefore, higher CSF Tau to Aβ42 ratio[20] or lower CSF Aβ42 to Tau ratio[21] can distinguish AD patients from healthy controls and predict the development of AD (reviewed in ref. 22). In addition to Aβ42, Aβ40 has been shown to induce neurotoxicity[23–25] and is associated with cognitive dysfunction and dementia.[26–28] Moreover, we recently published a study that reported that both CSF Aβ40/Tau ratio and Aβ42/Tau ratio were associated with postoperative cognitive changes, although each ratio was associated with changes in different cognitive domains.[29] We, therefore, used the CSF Aβ/Tau ratio, not the mathematically different but scientifically equivalent CSF Tau/Aβ ratio, in the studies, and assessed whether human CSF Aβ40/Tau or Aβ42/Tau ratio would be associated with postoperative delirium.

Therefore, we performed a prospective investigation in patients who had elective total hip/knee replacement under spinal anesthesia to assess whether there were associations between preoperative human CSF Aβ40/Tau or Aβ42/Tau ratio and the incidence and severity of postoperative delirium. The current proof of concept study was performed in 153 participants. The primary hypothesis in this study was that lower preoperative CSF Aβ42/Tau ratio would be associated with greater severity of post operative delirium. Our secondary hypotheses were that preoperative CSF Aβ40/Tau ratio would be also associated with postoperative delirium severity, and that both CSF Aβ42/Tau ratio and Aβ40/Tau ratio would be associated with the incidence of postoperative delirium. We chose the severity of postoperative delirium in the current research because there have been no studies to determine the association between the human CSF biomarkers and the severity of postoperative delirium. Moreover, given our anticipated relatively small sample size, using the continuous outcome of delirium severity maximizes statistical power, which is appropriate for this hypothesis generating study. The outcomes from this study mainly served to establish a system and to generate a concept that Aβ and/or Tau might contribute to the neuropathogenesis of postoperative delirium, which would promote more studies to further investigate the neuropathogenesis of post operative delirium.

Methods

Study enrollment

The protocol was approved by the Institutional Review Board of Partners Human Research Committee, Boston, MA, United States of America. A total of 354 adults who were scheduled to have elective total hip or knee replacement surgery at the Massachusetts General Hospital were asked to participate in this study (see Fig. 1, the flow diagram). The inclusion criteria included: (1) 63 years old or older; (2) proficient in English, and (3) candidates for spinal anesthesia. Individuals who met these criteria were further screened in an initial interview. After reviewing participant medical records, individuals excluded from participation were those identified as having: (1) past medical history of neurological and psychiatric diseases including AD, other forms of dementia, stroke, or psychosis; (2) severe visual or hearing impairment; and (3) unwillingness to comply with the protocol or procedures. Consent was obtained by study coordinators in the Pre-Admissions Testing Area at Massachusetts General Hospital when the participants came to the hospital for preoperative evaluation. A total of 244 participants were enrolled in the study from September 2011 to May 2013, though 91 were excluded due to dropping out preoperatively or changing their mind about spinal anesthesia, bringing the total number of participants to 153. There have been no major changes in the surgery or anesthesia practice since the start of our studies in 2011. We calculated that a sample size of 150 participants would be sufficient to determine a correlation >0.20 between Aβ/Tau ratio and Memorial Delirium Assessment Scale (MDAS) score (which measures the severity of delirium[30]) with 80% power and 5% type I error. The power calculation

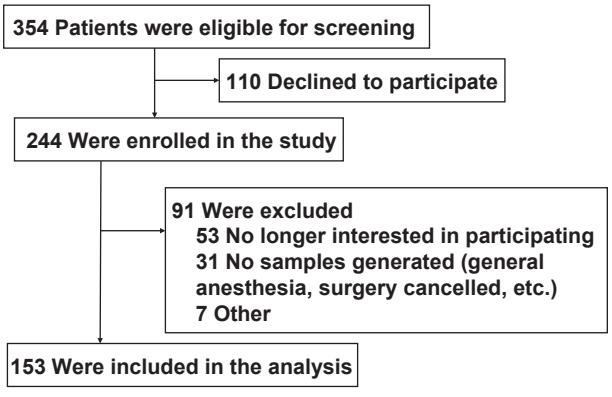

Figure 1. Flow diagram. The flow diagram shows that 354 participants were initially screened for the studies and finally 153 participants were included in the data analysis.

was performed in the design phase of the study and was based on our primary hypothesis that lower preoperative Aβ42/Tau ratio was associated with greater severity of postoperative delirium. We powered our study to be able to detect a correlation of greater than 0.20 based on the best estimation from our previous studies examining the association between the preoperative CSF Aβ40/Tau ratio with the postoperative Brief Visuospatial Memory Test Total Recall score, and between the preoperative CSF Aβ42/Tau ratio with the postoperative Hopkins Verbal Learning Test Retention score.[29]

Anesthesia, CSF sample collection, and measurement of β-Amyloid and Tau

All of the participants had spinal anesthesia for the scheduled surgery. One milliliter of CSF was collected from a spinal needle by anesthesiologists during the spinal anesthesia before the administration of the local anesthetic. The CSF was collected in an Eppendorf tube and was immediately placed in ice. The CSF was then stored in a −80°C degree freezer until the time of measurement when the samples were thawed. Levels of Aβ (including Aβ40 and Aβ42) and total Tau in the CSF were measured by using Enzyme-linked immunosorbent assay (ELISA) kits (Aβ40: Cat. # 292-62301; Aβ42: Cat. # 296-64401, Wako, Richmond, VA; Tau: Cat. # KHB0041, Invitrogen, San Francisco, CA) as described in our previous studies.[29] The assay to measure the CSF Aβ level was performed in triplicate. The assay to measure the levels of CSF Tau was performed in duplicate because we did not have a sufficient volume of CSF. The average level of CSF Aβ40, Aβ42, and Tau was obtained and used for the data analysis. All of the CSF samples in this study were analyzed using the same methods by one person (Y. D.); therefore, the relative differences in the values between the participants were consistent.

Surgery

All of the participants had total hip or total knee replacement under spinal anesthesia by one surgeon to avoid potential confounding factors owing to varying surgery skills or different surgical practices. All of the participants had standardized perioperative care, including spinal anesthesia, sedation, and postoperative pain control. The spinal anesthesia included the administration of 0.5% bupivacaine into the spinal space (mean dose: 3.24 ± 0.63 mL). Most patients received versed (midazolam, intravenous administration, mean dose: 2.38 ± 0.88 mg) before the surgery and propofol (intravenous administration, mean dose: 279.89 ± 162.1 mg) during the surgery for sedation. We did not measure the depth of sedation in the current studies. The postoperative pain control included a standard postoperative pain management, for example, morphine for patient-controlled analgesia (1 mg of morphine per injection and the interval time of injection was 6 minutes with a total of 10 mg of morphine per hour). There were no major complications among the participants during the immediate postoperative period.

Postoperative interviews

Trained clinical research assistants (C. S. and S. W.) interviewed the patients on the first and second day post surgery. The assessment of delirium was performed once per day between 8:00 AM to 10:00 AM. Patient notes were not reviewed for episodes of delirium which could occur outside the time of assessment. The clinical research assistants who performed the delirium assessments in this study had good training and went through quality control procedures. We used state-of-the-art delirium detection methods, which tend to report a higher incidence of delirium. The interview included the Confusion Assessment Method (CAM) and MDAS. CAM is a diagnostic algorithm used to determine the presence or absence of delirium.[30,31] The CAM algorithm consists of four clinical criteria: (1) acute onset and fluctuating course, (2) inattention, (3) disorganized thinking, and (4) altered level of consciousness. For delirium to be defined, both the first and the second criteria have to be present, plus either the third and/or the fourth criterion. MDAS was used to determine the severity of delirium[30,32] by quantifying the symptoms related to delirium based on 10 features, including reduced level of consciousness/awareness, disorientation, short-term memory impairment, impaired digit span, reduced ability to maintain and shift attention, disorganized thinking, perceptual disturbance, delusions, decreased or increased psychomotor activity, and sleep–wake cycle disturbance. Each of the features is scored from 0 (best) to 3 (worst symptom) with a maximal score of 30 for all of the features. Given that MDAS can evaluate the features of delirium described in CAM and can be administrated by trained nonclinical interviewers, we chose to use the MDAS rather than the Delirium Rating Scale (DRS).[33] The highest MDAS score from the post operative day 1 and day 2 was presented in the studies. MDAS scores were evaluated for all patients, regardless of whether they met CAM criteria on that day.

Statistical analysis

The data were presented as median and interquartile range (25–75% percentile) for Aβ40/Tau or Aβ42/Tau ratio, and mean ± standard deviation (SD) for other

measurements. Postoperative delirium incidence was presented as a percentage. We used Mann–Whitney test to determine the difference in Aβ40/Tau or Aβ42/Tau ratio between the participants with and without postoperative delirium. Chi-square test was used to compare the postoperative delirium incidence between the participants in the first (lowest) quartile of Aβ40/Tau or Aβ42/Tau ratio and the combination of the participants in the second, third, and fourth (highest) quartile of Aβ40/Tau or Aβ42/Tau ratio. Finally, we applied simple linear regression to determine the association between the Aβ40/Tau or Aβ42/Tau ratio and MDAS scores, and multiple linear regression to determine the association after the adjustment of age and gender. The regression coefficient ± standard error (SE) was used to illustrate the association between Aβ40/Tau or Aβ42/Tau ratio and MDAS score. *P*-values less than 0.05 were considered statistically significant. We used SAS (SAS institute Inc., Cary, NC) software (version 9.2) and Prism 6 software (La Jolla, CA) to analyze the data.

Results

Characteristics of participants

Three hundred and fifty-four eligible participants were screened, among them 244 participants provided informed consent for the study. Ninety-one participants were subsequently excluded from the study owing to various reasons (see Fig. 1, the flow diagram), yielding 153 participants who were included in the final data analysis. The age, gender, and education of the 91 patients who were excluded were comparable to those of the 153 participants who were finally included in the data analysis. The demographic and clinical data of the participants are presented in Table 1. Thirty-one participants (20%) were defined as having postoperative delirium by using CAM. The median of the highest MDAS score of all participants (regardless of delirium status) over the first two postoperative days was 3 (2–5) (median and 25–75% percentile). The median of the highest MDAS score of participants with postoperative delirium was 7 (5–10), which was higher than that of the participants without postoperative delirium (3 [2–4] [$P < 0.0001$]). Because we have previously demonstrated that MDAS scores have prognostic significance even in patients without delirium,[30] we analyzed the MDAS scores in the entire population, not just in those with delirium.

We did not include patients with dementia, stroke, or psychosis in the studies because we believed we would not be able to recruit enough participants with dementia, stroke, or psychosis in the studies to determine the contribution of these variables to postoperative cognitive delirium. The primary goal of the current studies was to assess a concept that Aβ and/or Tau may contribute to the neuropathogenesis of delirium, rather than validating Aβ and Tau as a biomarker for delirium. Therefore, preoperative cognitive function (e.g., Mini-Mental State

Table 1. Characteristics of the participants.

	(*N* = 153)
Age (years)	
Mean ± SD	71 ± 5
64–69	73 (48%)
70–75	43 (28%)
76–80	37 (24%)
Male sex – no. (%)	80 (52%)
Race or ethnic group, no. (%)	
White	151 (98.7%)
Black	1 (0.65%)
Hispanic	0
Asian Indian	0
Others or unknown	1 (0.65%)
Education, no. (%)	
Graduate of College or Postgraduate School	110 (72%)
Some College/Vocational/Technical Program	17 (11%)
High School Graduate/GED	19 (12%)
Less than high school graduation	4 (3%)
Unknown	3 (2%)
Height (cm) mean ± SD	170 ± 10
Body weight (kg) mean ± SD	85 ± 17
BMI (kg/m^2) mean ± SD	29 ± 5
ASA class	
I	1
II	119
III	27
Unknown	6
Length of anesthesia (min)	125 ± 18
Length of surgery (min)	81 ± 16
Total hip arthroplasty/replacement	72 (46%)
Total knee arthroplasty/replacement	83 (54%)
Estimated blood loss (mL) mean ± SD	162 ± 93
Aβ40 (median and 25–75% percentile)	4820 (3800–6411) pg/mL
Aβ42 (median and 25–75% percentile)	570 (370–768) pg/mL
Tau (median and 25–75% percentile)	380 (303–519) pg/mL
Aβ40/Tau ratio (median and 25–75% percentile)	12.6 (9.2–16.1)
Aβ42/Tau ratio (median and 25–75% percentile)	1.4 (0.9–2.1)

The length of anesthesia was defined from the time anesthesiologists started the spinal anesthesia in the participants to the time when the participants were sent to the post-anesthesia care unit. The length of surgery was defined from the time of initial incision to the time of the closure of the skin. The values of Aβ40, Aβ42, Tau, Aβ40/Tau ratio and Aβ42/Tau ratio in the CSF of all 153 participants were obtained using ELISA methods (see text for details). ASA, American Society of Anesthesiologists; GED, general educational development; cm, centimeter; min, minute; kg, kilogram; mL, milliliter, SD, standard deviation; Aβ, β-amyloid; CSF, cerebrospinal fluid.

Examination [MMSE]) was not determined in the current studies.

The distribution of postoperative delirium incidence in quartiles of preoperative CSF Aβ40/Tau or CSF Aβ42/Tau ratio

The intra-assay coefficient of variations of CSF Aβ40, Aβ42, and Tau were 21.8%, 18.7%, and 6.8%, respectively. The interparticipant coefficient variations of CSF Aβ40, Aβ42, and Tau were 35.5%, 45.7%, and 50.4%, respectively. There was no significant difference among the values of CSF Aβ40 ($F = 0.028$, $P = 0.963$, N.S., one-way analysis of variance [ANOVA]), Aβ42 ($F = 1.600$, $P = 0.215$, N.S., one-way ANOVA), and Tau ($P = 0.789$, N.S., Student's *t*-test) obtained in different measurements.

The average ratio of preoperative CSF Aβ40/Tau and Aβ42/Tau from the participants were 12.6 (9.2–16.1) and 1.4 (0.9–2.1) (median and 25–75% percentile), respectively. We then compared these ratios in the participants with postoperative delirium and those without it. Mann–Whitney test showed that the preoperative CSF Aβ40/Tau (12.2 [8.1–14.8]) or Aβ42/Tau ratio (1.3 [0.7–1.9]) in the participants who developed postoperative delirium was not significantly different from those who did not develop postoperative delirium (Aβ40/Tau: 12.6 [9.6–16.1], $P = 0.241$; or Aβ42/Tau ratio: 1.4 [1.0–2.1], $P = 0.192$).

However, the relationship between preoperative CSF Aβ40/Tau or CSF Aβ42/Tau ratio and postoperative delirium incidence may not be linear (e.g., a threshold effect), we, therefore, divided the participants into quartiles according to the levels of preoperative CSF Aβ40/Tau or CSF Aβ42/Tau ratio. We compared the incidence of postoperative delirium among these quartiles and found that more postoperative delirium occurred in the lowest quartile of CSF Aβ40/Tau (32%) or CSF Aβ42/Tau ratio (32%) than in the rest of three quartiles of the Aβ40/Tau ratio (second: 11%, third: 21% and fourth: 18%) or the Aβ42/Tau ratio (second: 8%, third: 24%, and fourth: 18%). Therefore, we dichotomized the preoperative Aβ/Tau ratio and compared the postoperative delirium incidence between the participants in the first quartile and the participants in the combination of the second, third, and fourth quartiles. We found a significantly higher incidence of delirium in participants with CSF Aβ40/Tau ratio in the lowest quartile versus all others (32% vs. 17%, $P = 0.0482$) and in participants with CSF Aβ42/Tau ratio in the lowest quartile versus all others (32% vs. 17%, $P = 0.0482$) (Fig. 2).

The distribution of postoperative delirium severity in quartiles of preoperative CSF Aβ40/Tau or CSF Aβ42/Tau ratio

Next, we asked whether the preoperative CSF Aβ40/Tau or CSF Aβ42/Tau ratio could also be associated with the postoperative delirium severity. We, therefore, compared the MDAS score, the measurement of delirium severity, between the participants in the first quartile and the participants in the combination of the second, third, and fourth quartiles. We found that the median of the highest MDAS score (4, 2–5) of the participants in the first quartile of CSF Aβ40/Tau ratio was significantly higher than that of the participants in the combination of the second,

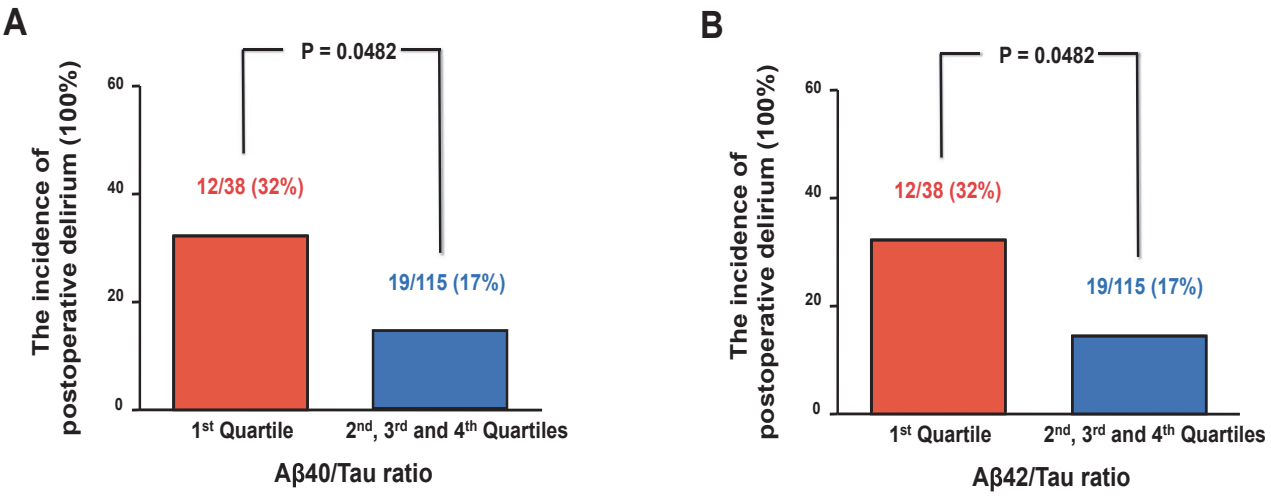

Figure 2. The postoperative delirium incidence in the first quartile and the combination of the other three quartiles of CSF Aβ40/Tau or Aβ42/Tau ratio. Chi-square test shows that there is a significant difference in the postoperative delirium incidence between the first quartile (red bar) and the combination of the second, third, and fourth quartiles (blue bar) of CSF Aβ40/Tau (A) or Aβ42/Tau ratio (B).

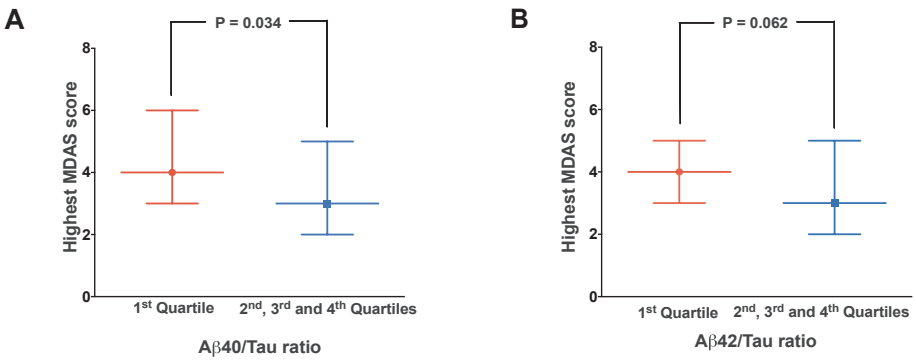

Figure 3. The postoperative delirium severity in the first quartile and the combination of the other three quartiles of CSF Aβ40/Tau or Aβ42/Tau ratio. (A) Mann–Whitney test suggests that there is a significant difference in the highest MDAS score between the first quartile (red bar) and the combination of the second, third, and fourth quartiles (blue bar) of CSF Aβ40/Tau. (B) Mann–Whitney test suggests that there is a borderline difference in the highest MDAS score between the first quartile (red bar) and the combination of the second, third, and fourth quartiles (blue bar) of CSF Aβ42/Tau ratio.

third, and fourth quartiles of CSF Aβ40/Tau ratio (3, 2–5, $P = 0.034$, Fig. 3A). The median of the highest MDAS score (4, 2–6) of the participants in the first quartile of CSF Aβ42/Tau ratio were borderline higher than that of the participants in the combination of the second, third, and fourth quartiles of CSF Aβ42/Tau ratio (3, 2–5, $P = 0.062$, Fig. 3B).

Preoperative CSF Aβ40/Tau or CSF Aβ42/Tau ratio and postoperative delirium severity

Finally, we determined the linear association between the preoperative CSF Aβ40/Tau or CSF Aβ42/Tau ratio and the MDAS score post surgery. Using an unadjusted simple linear regression, we found that the preoperative CSF Aβ40/Tau or Aβ42/Tau ratio was significantly correlated (negatively) with the highest MDAS score (Aβ40/Tau -0.12 ± 0.05, $P = 0.014$; Aβ42/Tau: -0.65 ± 0.26, $P = 0.013$) (Table 2). Thus, as CSF Aβ/Tau goes down, the MDAS scores go up, as would be expected given the previous association of low CSF Aβ40/Tau ratio with the postoperative delirium incidence. Multiple linear regression, after adjusting for age and gender, showed that the preoperative CSF Aβ40/Tau (-0.12 ± 0.05, $P = 0.018$) or Aβ42/Tau (-0.62 ± 0.27, $P = 0.022$) ratio remained significantly correlated (negatively) with the highest MDAS score (Table 2). Age did not contribute to the association between Aβ40/Tau ratio ($P = 0.631$) or Aβ42/Tau ratio ($P = 0.757$) and the highest MDAS score; gender also did not contribute to the association between Aβ40/Tau ratio ($P = 0.439$) or Aβ42/Tau ratio ($P = 0.679$) and the highest MDAS score. We did not include evaluation of other peri-operative variables (e.g., postoperative pain medication) in the analysis. As opposed to age and gender, these postoperative variables are highly complicated and require sophisticated adjustment. For instance, nearly all patients are exposed to postoperative opioids, therefore, meaningful adjustment for postoperative pain medication requires consideration of exposures to individual opioid agents, the dose of exposure, and the time and duration of exposure. This study was not sufficiently large enough to adjust for such complex variables. We will take these factors into account in future larger scale studies.

Table 2. Correlation between MDAS score and the CSFAβ40/Tau or Aβ42/Tau ratio.

Highest MDAS score	Un-adjusted		Adjusted by age and gender	
	Regression coefficient ± SE	*P*	Regression coefficient ± SE	*P*
Aβ40/Tau ratio	−0.12 ± 0.05	0.014	−0.12 ± 0.05	0.018
Aβ42/Tau ratio	−0.65 ± 0.26	0.013	−0.62 ± 0.27	0.022

The left panel of the table illustrates the results of the regression coefficients for CSF Aβ40/Tau or Aβ42/Tau ratio with highest MDAS score in a simple linear regression. The right panel of the table shows the regression coefficients in multiple linear regressions including adjustment of age and gender. MDAS, Memorial Delirium Assessment Scale; CSF, cerebrospinal fluid; SE, standard error.

Discussion

We assessed the association between preoperative CSF Aβ40/Tau or CSF Aβ42/Tau ratio and the incidence and severity of postoperative delirium in this prospective study of 153 older adults who had total hip and knee replacement under spinal anesthesia. Aβ40, Aβ42, and Tau have been reported to contribute to neurotoxicity, cognitive dysfunction, dementia, and postoperative cognitive changes[14,15,17–19,23–29] (reviewed in ref. 9), and dementia is a risk factor of delirium.[4,34] Therefore, we chose Aβ40, Aβ42, and Tau in the studies to determine whether these proteins may also contribute to postoperative delirium.

We found that the patients in the lowest quartile of CSF Aβ40/Tau and CSF Aβ42/Tau ratios (consistent with the AD biomarker) had the highest incidence of delirium (Fig. 2) and more severe symptoms of delirium represented by higher MDAS scores (Fig. 3). We also found that lower CSF Aβ40/Tau and CSF Aβ42/Tau ratios were significantly associated with greater postoperative delirium severity represented by a higher MDAS score (Table 2). Collectively, these findings suggest that Aβ and Tau may contribute to the neuropathogenesis of postoperative delirium, pending further studies.

Delirium incidence is a dichotomous outcome; therefore, we did not use linear models to analyze the incidence of postoperative delirium. Preoperative CSF Aβ/Tau ratio was not significantly associated with the postoperative delirium incidence, but was associated with the severity of postoperative delirium. We believe this difference is explained primarily by issues of statistical power. It is notable that lower preoperative CSF Aβ/Tau ratio is associated with both higher incidence and greater symptom severity of postoperative delirium, which is demonstrated in Figures 2, 3, respectively.

The postoperative delirium incidence depends on type of surgery, varying from 12% (otolaryngological surgery) up to 50% (major abdominal surgery) (reviewed in ref. 7). The postoperative delirium incidence in the patients who have total joint replacement has been reported to be from 3.6% to 41%[35–39] (reviewed in ref. 40). The incidence of postoperative delirium after total joint replacement in all ages of patients is 9–15% (reviewed in ref. 40), and this incidence of postoperative delirium will be higher in older adults. The variation in the postoperative delirium incidence could be due to the influence of perioperative factors, including sedation levels,[41] cognitive status, history of central nervous system disease, and postoperative pain levels.[42] Therefore, the postoperative delirium incidence (20%) in this study was consistent with the incidence reported in other studies of total knee and hip replacement, demonstrating validity to our delirium assessment methods.

In a prospective cohort study in older adults with hip fracture, Witlox et al. found that CSF Aβ42, Tau, and phosphorylated Tau were not associated with postoperative delirium.[43] However, the studies by Witlox et al. did not assess the association of preoperative CSF Aβ/Tau *ratio* with the postoperative delirium.[43] In the current studies, we did not find the association between preoperative CSF Aβ40, Aβ42, or Tau with the incidence or severity of postoperative delirium either (data not shown). However, we investigated the association between the preoperative CSF Aβ40/Tau or Aβ42/Tau ratio and the incidence and severity of postoperative delirium, and we found an inverse association. Also of note, the subject population in the studies by Witlox et al. (patients who had surgical repair for acute hip fracture) was different from the participants in the current studies (patients who had elective total hip or total knee replacement). Taken together, the cohort and the variables measured were different between the studies by Witlox et al. and our current studies, which might explain the different findings and conclusions.

Lower levels of CSF Aβ42 and higher levels of CSF Tau are associated with the progression of AD.[14,15,17–19] Therefore, CSF Tau/Aβ42 ratio has been used for the diagnosis of AD dementia and prediction of its progress. The higher the CSF Tau/Aβ42 ratio[20] or the lower CSF Aβ42 to Tau ratio,[21] the worse the cognitive function in AD patients (reviewed in ref. 22). Consistently, the current findings showed that the lower preoperative CSF Aβ40/Tau or Aβ42/Tau ratio might also predict postoperative delirium and suggested that more severe postoperative delirium symptoms may occur. Dementia is known as the most consistent risk factor of delirium.[4,34] Taken together, these findings suggest that some AD neuropathogenesis, for example, accumulation of Aβ in the brain, could also be part of the neuropathogenesis of postoperative delirium. The future studies to further test this hypothesis are warranted.

Moreover, low CSF Aβ level represents high brain Aβ amounts, owing to the sequestration of Aβ into brain amyloid plaques,[16,44] and CSF Tau levels represent brain Tau levels.[16,44] Therefore, the findings that a lower CSF Aβ/Tau ratio is associated with higher incidence and greater severity of postoperative delirium also suggest that elevated brain Aβ levels may be associated with postoperative delirium. This hypothesis is supported by the fact that age is a risk factor of delirium,[3] and aging is associated with elevated levels of Aβ[45] in the brain. Further studies are needed to test this hypothesis by determining whether the amount of amyloid in the brain is associated with the incidence and severity of postoperative delirium, for example, by using positron emission tomographic imaging (PET) for amyloid.[46]

We previously demonstrated that preoperative CSF Aβ40/Tau or CSF Aβ42/Tau ratio was associated with certain domains of postoperative cognitive change,[29] and this study showed that the preoperative CSF Aβ40/Tau or CSF Aβ42/Tau ratio was associated with the incidence and severity of postoperative delirium symptoms. These results suggest that changes in the levels of Aβ and Tau in CSF and brain may be a common neuropathogenesis underlying both postoperative delirium and postoperative cognitive dysfunction. This hypothesis is further supported by the findings that postoperative delirium is associated with a significant decline in cognitive ability during the first year after cardiac surgery.[4] Collectively, these results would promote further studies to determine the potential association, neuropathologically and behaviorally, among postoperative delirium, postoperative cognitive dysfunction, and dementia.

Postoperative delirium has been suggested to relate to neuroinflammation.[47] However, although all patients may have a surgery-induced increase in proinflammatory cytokines in the blood that can enter the brain through the blood brain barrier[48,49] to induce neuroinflammation, not every patient develops postoperative delirium. Thus, it is plausible that patients who develop postoperative delirium have other changes in the brain that facilitate neuroinflammation. The findings from the current studies that lower CSF Aβ/Tau ratio is associated with higher incidence and greater severity of postoperative delirium symptoms suggest that Aβ or Tau could be one of these changes.

It has been reported that there are large variations in the levels of CSF Aβ and Tau between the different studies,[50] which could be caused by the differences in analytical procedures and the analytical kits. The values of Aβ and Tau in our current studies might also be different from those of the other studies. However, the CSF Aβ and Tau levels in the current studies were measured using the same methods by the same person, who had ample experience with the assays (Y.D.). Therefore, although the absolute values of CSF Aβ and Tau may differ from those reported in other studies, the relative differences in the CSF Aβ and Tau levels between the subjects are consistent. Moreover, the intra-assay coefficient of variations of CSF Aβ40 (21.8%), Aβ42 (18.7%), and Tau (6.8%) were still in the acceptable to good range, and within the range reported elsewhere in the literature (13–36%).[50] Finally, there was no significant difference among the repeated values of CSF Aβ40, Aβ42, and Tau obtained in different measurements of our current studies. Taken together, we believe the results provide strong evidence that the associations between the CSF Aβ/Tau ratio and the postoperative delirium incidence and severity in the current studies are valid.

This study has several limitations. First, the majority of the participants were white and had education beyond high school. It remains unknown whether the association between CSF Aβ/Tau ratio and postoperative delirium would still exist in nonwhite participants with lower education levels. Second, we did not determine the preoperative cognitive function (e.g., MMSE) in this study, therefore, it remains unknown whether the relationship between preoperative CSF Aβ/Tau ratio and postoperative delirium remains significant after adjusting for measured preoperative cognitive function. However, the primary goal of the current studies was not to validate the CSF Tau/Aβ ratio as an independent predictive biomarker for delirium, but rather to assess a concept that Aβ and Tau might contribute to the neuropathogenesis of delirium. Therefore, we did not want to adjust for MMSE because low preoperative cognitive function (measured by MMSE) would be on the causal pathway between Aβ and Tau effects and delirium. However, given we did not perform baseline cognitive function, we could have missed some (milder) cases of dementia. Third, we did not assess whether patients had preoperative delirium. However, the patients all came to hospital by themselves for elective surgery, and they were assessed, including mental function examination, by both nurses and anesthesiologists before surgery. Therefore, the likelihood of participants having preoperative delirium is low. Finally, the spectrum of delirium was mild in this study as the MDAS score was relatively low. The observation could be due to the fact that the population of this study was relatively healthy and, it is possible that MDAS scores might represent mild reversible cognitive impairment. Nevertheless, our findings with delirium severity complement and extend the findings with CAM-defined postoperative delirium.

In conclusion, we have found that the patients who have lower preoperative CSF Aβ40/Tau or Aβ42/Tau ratio, particularly those in the lowest quartile, are more likely to develop postoperative delirium and have more severe symptoms. These findings have established a system and generated a concept for the future studies. If confirmed and extended in future studies, these findings may shed light on the currently undefined neuropathogenesis of postoperative delirium. These studies will hopefully promote the development of more targeted interventions to prevent and treat postoperative delirium, ultimately leading to safer surgery care and better postoperative outcomes for patients.

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Author Contribution

Study concept and design: Marcantonio, Sunder and Burke, and Xie. Acquisition of data: Swain, Ward, and Dong. Analysis and interpretation of data: Marcantonio, Zhang, Escobar, Zheng and Xie. Drafting of the manuscript: Marcantonio and Xie. Critical revision of the manuscript for important intellectual content: Marcantonio and Xie. Obtained funding: Xie. Administrative, technical, and material support: Sunder, Burke, Zhang and Xie. Study supervision: Xie. Zhongcong Xie had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of Interest

None declared.

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