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ORIGINAL ARTICLE

Cerebrospinal Fluid Aβ to Tau Ratio and Postoperative Cognitive Change

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Objective: Determination of biomarker and neuropathogenesis of postoperative cognitive change (POCC) or postoperative cognitive dysfunction.

Background: POCC is one of the most common postoperative complications in elderly patients. Whether preoperative cerebrospinal fluid (CSF) β-amyloid protein (Aβ) to tau ratio, an Alzheimer disease biomarker, is a biomarker for risk of POCC remains unknown. We therefore set out to assess the association between preoperative CSF Aβ42 or Aβ40 to tau ratio and POCC.

Methods: Patients who had total hip/knee replacement were enrolled. The CSF was obtained during the administration of spinal anesthesia. Cognitive tests were performed with these participants at 1 week before and at 1 week and 3 to 6 months after the surgery. *Z* scores of the changes from preoperative to postoperative on several key domains of the cognitive battery were determined. We then examined the association between preoperative CSF Aβ42/tau or Aβ40/tau ratio and the outcome measures described earlier, adjusting for age and sex.

Results: Among the 136 participants (mean age = 71 $\pm$ 5 years; 55% men), preoperative CSF Aβ42/tau ratio was associated with postoperative Hopkins Verbal Learning Test Retention [*Z* score = 8.351; age, sex-adjusted (adj.) P = 0.003], and the Benton Judgment of Line Orientation (*Z* score = 1.242; adj. P = 0.007). Aβ40/tau ratio was associated with Brief Visuospatial Memory Test Total Recall (*Z* score = 1.045; adj. P = 0.044).

Conclusions: Preoperative CSF Aβ/tau ratio is associated with postoperative changes in specific cognitive domains. The presence of the Alzheimer's disease biomarker, specifically the Aβ/tau ratio, may identify patients at higher risk for cognitive changes after surgery.

Keywords: Aβ/tau ratio, cognition, surgery [AQ1]

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Postoperative cognitive change (POCC) or postoperative cognitive dysfunction (POCD)[1,2] (reviewed in Silverstein et al[3] and Terrando et al[4]) is one of the most common postoperative complications in older adults who have undergone surgery[5] and is associated with impairments in daily functioning,[6] risk of leaving the labor market prematurely, dependency on social transfer payments,[7] and increased morbidity and mortality.[7–9] However, at the present time, POCC is a clinical phenomenon and its neuropathogenesis remains largely to be determined; moreover, there have been no biomarker(s) that could identify the risk for the development of POCC. This gap in knowledge has become a barrier that prevents further studies and potential intervention of POCC.

β-Amyloid protein (Aβ), including Aβ40 and Aβ2, the key component of senile plaques in patients with Alzheimer disease (AD), and tau, the major protein component of intraneuronal neurofibrillary tangles, are the hallmarks of AD neuropathogenesis (reviewed in Querfurth and LaFerla[10]). Reduction of Aβ40 and Aβ42 levels and elevation of tau levels in cerebrospinal fluid (CSF) have been reported in AD patients[11,12] (reviewed in Holtzman[13]). Moreover, it has been reported that the Aβ42/tau ratio in CSF can better distinguish AD patients from healthy controls of the same age than Aβ42 or tau alone.[12,14] However, whether the Aβ42/tau or Aβ40/tau ratio in CSF is associated with POCC is unknown.

Therefore, we performed a prospective investigation to determine whether preoperative CSF Aβ42/tau ratio or Aβ40/tau ratio is associated with individual components, including verbal learning and visual memory, of a cognitive battery designed to evaluate POCC. We hypothesized that CSF Aβ42/tau or Aβ40/tau ratio will be associated with verbal learning and visual memory. The outcomes from this study may serve 2 purposes: (1) to evaluate preoperative CSF Aβ/tau ratio as a potential biomarker of POCC and (2) to promote more studies to determine the role of Aβ and tau in the neuropathogenesis of POCC.

We used the term "POCC" instead of "POCD" in the article because the studies did not assess the potential association between CSF Aβ40/tau or Aβ42/tau ratio and cognitive function in participants without surgery. Therefore, we were unable to determine the true incidence of POCD because the change scores could be confounded by the learning effects of the participants.

METHODS

Participants

The protocol was approved by the institutional review board of Partners Human Research Committee, Boston, MA. A total of 342 adults scheduled to have elective total hip or knee arthroplasty/replacement surgery at the Massachusetts General Hospital were asked to participate in this study (Fig. 1). Participants were deemed eligible if they were at least 63 years old, spoke proficient English, lived within the greater Boston area, and were candidates for spinal anesthesia. Individuals who met these criteria were further screened during an initial interview that included administration of the Mini-Mental State Examination. Individuals excluded from [F1]

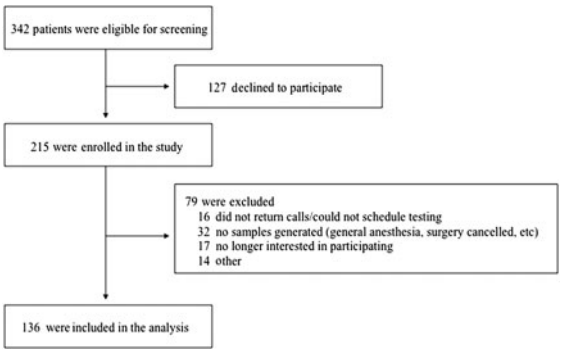

FIGURE 1. Flow diagram. The diagram shows that 342 participants were initially screened for the studies and finally 136 participants were included in the data analysis.

participation were those identified as having the following: (1) existing cognitive impairment as evidenced by Mini-Mental State Examination scores below 24 (of the 30 possible points); (2) a history of neurological and psychiatric diseases including AD, stroke, and psychosis; (3) severe visual or hearing impairment; and (4) unwillingness to comply with the protocol or procedures. Consent was obtained by a study coordinator in the Pre-Admissions Clinic at Massachusetts General Hospital. A total of 136 participants were finally enrolled in the study from 2007 to 2012, and there have been no major changes in the surgery or anesthesia practice since the start of our studies in 2007. We initially targeted a sample size of 100, which would give us 80% power to detect a Pearson correlation coefficient of 0.28 or higher between the measured marker (eg, Aβ42/tau ratio) and cognitive change scores with 5% type 1 error.

Baseline Assessment

Each participant who was enrolled underwent a baseline assessment, which consisted of neuropsychological testing performed 1 week before the scheduled surgery in either a hospital office setting or the participant's home. The cognitive tests included the Hopkins Verbal Learning Test Retention (HVLTRet), Hopkins Verbal Learning Total Recall (HVLTTR), the Brief Visuospatial Memory Test Total Recall (BVMTTR), Brief Visuospatial Memory Test Delayed Recall (BVMTDR), Brief Visuospatial Memory Test Total Learning, Brief Visuospatial Memory Test Retention, the Benton Judgment of Line Orientation (JLO), and Trail Making B (Trails B). These measures are highly sensitive to the types of cognitive impairments[15–17] and are widely used in the field of neuropsychology.[18,19] All neuropsychological tests were administered by the study coordinator (S.M., C.A.S., S.A.P.W., C.G., and K.W.). [AQ5]

Anesthesia, CSF Sample Collection, and Measurement of Aβ and Tau

All participants had spinal anesthesia for the scheduled surgery. One milliliter of CSF was collected by anesthesiologists at the time of spinal anesthesia administration between 7:00 AM and 10:00 AM to avoid confounding influence that resulted from the circadian changes in CSF Aβ levels.[20] Aβ levels (including Aβ40 and Aβ42) in the CSF were measured with enzyme-linked immunosorbent assay (ELISA) kits (Aβ40: cat no. 292-6230; Aβ42: cat no. 296-64401) (Wako, Richmond, VA) as described by Zhang et al[21] with modification. Briefly, the collected CSF was stored in an −80-degree freezer and was thawed before measurement. Human monoclonal antibodies specific to Aβ40 (BA27) or Aβ42 (BC05) were coated on 96-well plates. After blocking with Block Ace, wells were incubated overnight at 4°C with test samples of CSF and then an anti-Aβ (α-Aβ-HR1) conjugated to horseradish peroxidase was added. The plates were developed with 3,3′,5,5′-tetramethylbenzidine reagent, and the well absorbance was measured at 450 nm. The Aβ levels in the test samples were determined by comparison with the signals from unconditioned artificial CSF spiked with known quantities of Aβ40 and Aβ42. The levels of total tau in human CSF were determined with an ELISA kit (cat. no. KHB0041; Invitrogen, San Francisco, CA). Specifically, a monoclonal antibody specific for human tau was coated onto the wells of the provided microtiter strips. Standards of known human tau content, CSF, and control specimens were pipetted into these wells overnight. After washing, a rabbit polyclonal antibody specific for human tau was added. During the second incubation, this antibody bound to the immobilized human tau captured during the first incubation. A substrate solution was added, which was acted upon by the bound enzyme to produce a change in color. The intensity of this colored product was directly proportional to the concentration of human tau present in the CSF. All assays were performed in triplicates, and the average from the triplicates was obtained.

Surgery

All 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. The participants had standardized perioperative care, including preoperative and intraoperative sedation and postoperative pain control. There were no major complications among the participants during the immediate postoperative period.

Postoperative Cognitive Testing

Each participant underwent repeat cognitive testing approximately 1 week postoperatively and then 3 to 6 months postoperatively at the participant's home or a rehabilitation facility. The same neuropsychological test battery that was administered preoperatively (see earlier) was administered by trained study coordinators. Four versions of the test battery (A, B, C, and D) were administered according to a randomized datasheet to reduce participant practice or learning effects.

Statistical Analysis

Postoperative cognitive function was represented by a change score, calculated from the raw score of the postoperative cognitive test result minus the raw score of the preoperative cognitive test result. A *Z* score for each of the change scores was calculated by dividing each individual change score by the total standard deviation of all of the change scores. Negative values of *Z* scores suggest postoperative cognitive decline except for the test of Trails B, which is a timed test where short times are indicative of better performance. Therefore, positive *Z* scores of Trails B suggest postoperative cognitive decline. We then applied Pearson correlation analysis to these scores and calculated Pearson correlation coefficients to analyze the relationship between preoperative CSF Aβ42/tau or Aβ40/tau ratio and *Z* score for each of the cognitive tests. We used linear regression to adjust for age and sex. *P* values less than 0.05 were considered statistically significant. The SAS (SAS Institute Inc, Cary, NC) software (version 9.2) was used for all statistical analyses. [AQ6]

RESULTS

Participant and Surgery Characteristics

Three hundred forty-two eligible participants were screened; among them, 215 participants provided informed consent for the study. Seventy-nine participants were subsequently excluded from the study owing to various reasons (see Fig. 1), yielding 136

participants. The demographic and clinical data of the participants [T1] are presented in Table 1. The average values of Aβ40, Aβ42, and tau from the participants were 9505 ± 3441, 948 ± 641, and 244 ± 153 pg/mL, and the average Aβ40/tau and Aβ42/tau ratios from [T2] the participants were 50 ± 25.3 and 5 ± 4.0, respectively. Table 2 shows the mean cognitive test scores of all participants at baseline, at 1 week, and at 3 to 6 months after the surgery.

Pearson correlation analysis showed that age was negatively associated with preoperative human CSF Aβ42/tau ratio ($R = -0.199$; $P = 0.021$). The JLO was negatively associated with preoperative human CSF Aβ40 ($R = -0.198$; $P = 0.021$) and Aβ42 ($R = -0.183$; $P = 0.034$). Finally, Trails B was negatively associated with preoperative human CSF Aβ42/tau ratio ($R = -0.309$; $P = 0.0003$). The adjusted analyses controlled for age and also for baseline cognitive performance by examining change scores in the various neurocognitive measures.

[AQ7]

TABLE 1. Characteristics of the Participants (N = 136)

Age	
Mean ± SD, yr	71 ± 5
63–69, n (%)	69 (51)
70–75, n (%)	38 (28)
76–82, n (%)	29 (21)
Male sex, n (%)	75 (55)
Race or ethnic group, n	
White	134
Black	1
Hispanic	0
Asian Indian	1
Others or unknown	0
Education, mean ± SD, yr	17 ± 4
Height, mean ± SD, cm	173 ± 10
Body weight, mean ± SD, kg	86 ± 19
ASA class, n	
I	4
II	115
III	17
Length of anesthesia,* mean ± SD, min	126 ± 24
Length of surgery,† mean ± SD, min	83 ± 18
Total hip arthroplasty/replacement, n (%)	76 (56)
Total knee arthroplasty/replacement, n (%)	60 (44)
Estimated blood loss, mean ± SD, mL	194 ± 115

*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 postanesthesia care unit.

†The length of surgery was defined from the time of cutting the skin to the time of the closure of the skin.

ASA indicates American Society of Anesthesiologists.

TABLE 2. The Raw Scores of Cognitive Tests

	Baseline	1 wk	3–6 mo
HVLTRet	73 ± 32.7	72 ± 29.2	84 ± 26.9
HVLTTR	20 ± 4.4	21 ± 5.2	23 ± 5.0
BVMTTR	19 ± 6.2	18 ± 6.9	20 ± 6.2
BVMTDR	8 ± 2.5	7 ± 2.9	8 ± 2.7
JLO	24 ± 6.1	24 ± 6.4	24 ± 5.2
Trails B	87 ± 34.5	92 ± 44.7	80 ± 31.2

The values are average of mean ± SD from the cognitive test of HVLTRet (percentage of the words recalled), HVLTTR (total number of words recalled), BVMTTR (number of shapes recalled), BVMTDR (number of shapes recalled), JLO (number of lines recognized), and Trials B (time in seconds). The higher scores suggest better cognitive function except Trails B. The lower scores of Trails B (shorter completion time) suggest better cognitive function.

Preoperative CSF Aβ42/Tau Ratio and POCC

We assessed the potential correlation between preoperative CSF Aβ42/tau ratio and Z score representing changes in postoperative cognitive function. Unadjusted Pearson correlation analyses showed that the preoperative CSF Aβ42/tau ratio was positively correlated with Z score of postoperative function of HVLTRet at 1 week (7.063, $P = 0.011$) and JLO at 1 week (0.915, $P = 0.024$) and 3 to 6 months (1.139, $P = 0.011$) and negatively correlated with Z score of postoperative Trails B at 1 week (−5.623, $P = 0.019$). Linear regression analysis, after adjusting for age and sex, showed that the preoperative CSF Aβ42/tau ratio was positively associated with postoperative function of HVLTRet at 1 week (8.351, $P = 0.003$), HVLTTR at 3 to 6 months (0.833, $P = 0.046$), and JLO at 1 week (0.954, $P = 0.021$) and at 3 to 6 months (1.242, $P = 0.007$) (Table 3). After adjustment, the preoperative CSF Aβ42/tau ratio was [T3] no longer negatively associated with Trails B at 1 week and was not significantly associated with any other cognitive tests (Table 3). These data suggest that the participants who had a lower preoperative CSF Aβ42/tau ratio (the AD biomarker) performed worse postoperatively on HVLTRet, HVLTTR, and JLO, measures of verbal memory and visuospatial judgment, than those with a higher preoperative CSF Aβ42/tau ratio.

Preoperative CSF Aβ40/Tau Ratio and POCC

Next, we assessed the potential correlation between preoperative CSF Aβ40/tau ratio and Z score representing changes in postoperative cognitive function. Using unadjusted Pearson correlation analyses, we found that the preoperative CSF Aβ40/tau ratio was positively correlated with Z score of postoperative function of BVMTDR (0.413, $P = 0.045$) at 3 to 6 months (Table 4). After [T4] adjusting for age and sex using linear regression, the preoperative CSF Aβ40/tau ratio was still significantly correlated with Z score of postoperative function of both BVMTDR (0.418, $P = 0.046$) and BVMTTR (1.045, $P = 0.044$) at 3 to 6 months (Table 4). The preoperative CSF Aβ40/tau ratio was not significantly associated with changes in other postoperative cognitive functions (Table 4). These data suggest that the participants who had a lower preoperative CSF Aβ40/tau ratio had the worse performance on postoperative function of BVMTTR and BVMTDR, measures of visual memory, than those with a higher preoperative CSF Aβ40/tau ratio.

DISCUSSION

We studied the association of the AD biomarker with changes in cognition after elective surgery and found that the CSF Aβ42/tau ratio is associated with HVLTRet at 1 week and HVLTTR at 3 to 6 months (Table 3). These results are consistent with the findings from the AD research that the CSF Aβ42/tau ratio can be used for the diagnosis of AD and prediction of its progress and that the lower the CSF Aβ42/tau ratio, the worse the cognitive function in AD patients[12] (reviewed in Holtzman[13]).

The CSF Aβ40/tau ratio is not associated with any verbal functions tested in the current studies (Table 4). Instead, the CSF Aβ40/tau ratio is associated with BVMTTR and BVMTDR at 3 to 6 months (after adjustment for age and sex; Table 3). These data suggest that the CSF Aβ40/tau ratio could specifically represent the visual memory domain of POCC. Different from the CSF Aβ42/tau ratio, the CSF Aβ40/tau ratio has not been extensively reported as a biomarker of AD (reviewed in Holtzman[13]). Thus, the future studies are warranted to test a hypothesis that the CSF Aβ40/tau ratio has not been recognized as a biomarker of AD because visual memory tests

TABLE 3. Correlation Between Cognitive Function and the CSF Aβ42/Tau Ratio

	Unadjusted			Adjusted by Age and Sex		
	Estimate (*Z* Score)	**Standard Error (*Z* Score)**	***P***	**Estimate (*Z* Score)**	**Standard Error (*Z* Score)**	***P***
HVLTRet 1 wk	7.063	2.732	0.011	8.351	2.734	0.003
HVLTRet 3–6 mo	2.531	2.824	0.372	3.680	2.828	0.196
HVLTTR 1 wk	0.474	0.398	0.236	0.412	0.408	0.314
HVLTTR 3–6 mo	0.740	0.406	0.071	0.833	0.412	0.046
BVMTTR 1 wk	0.315	0.565	0.579	0.174	0.562	0.758
BVMTTR 3–6 mo	0.152	0.508	0.766	− 0.022	0.515	0.966
BVMTDR 1 wk	0.067	0.236	0.778	0.001	0.240	0.995
BVMTDR 3–6 mo	− 0.082	0.202	0.687	− 0.099	0.208	0.635
JLO 1 wk	0.915	0.401	0.024	0.954	0.408	0.021
JLO 3–6 mo	1.139	0.436	0.011	1.242	0.446	0.007
Trails B 1 wk	− 5.623	2.366	0.019	− 4.724	2.396	0.051
Trails B 3–6 mo	1.442	2.221	0.518	1.158	2.285	0.614

The left panel of the table illustrates the results of the Pearson correlation analysis between CSF Aβ42/tau ratio and cognitive function in humans. The right panel of the table shows the results of the linear regression analysis after adjustment with age and sex.

TABLE 4. Correlation Between Cognitive Function and the CSF Aβ40/Tau Ratio

	Unadjusted			Adjusted by Age and Sex		
	Estimate (*Z* Score)	**Standard Error (*Z* Score)**	***P***	**Estimate (*Z* Score)**	**Standard Error (*Z* Score)**	***P***
HVLTRet 1 wk	1.900	2.797	0.498	2.367	2.791	0.398
HVLTRet 3–6 mo	− 0.950	2.918	0.745	− 0.742	2.893	0.798
HVLTTR 1 wk	0.259	0.400	0.519	0.267	0.404	0.509
HVLTTR 3–6 mo	0.494	0.422	0.244	0.428	0.424	0.316
BVMTTR 1 wk	− 0.585	0.573	0.309	− 0.399	0.566	0.482
BVMTTR 3–6 mo	0.958	0.515	0.066	1.045	0.512	0.044
BVMTDR 1 wk	− 0.227	0.239	0.345	− 0.230	0.241	0.343
BVMTDR 3–6 mo	0.413	0.204	0.045	0.418	0.207	0.046
JLO 1 wk	− 0.067	0.409	0.869	− 0.146	0.411	0.723
JLO 3–6 mo	− 0.289	0.465	0.536	− 0.317	0.472	0.504
Trails B 1 wk	1.855	2.409	0.443	1.882	2.391	0.433
Trails B 3–6 mo	− 1.712	2.291	0.457	− 1.688	2.324	0.469

The left panel of the table illustrates the results of the Pearson correlation analysis between CSF Aβ40/tau ratio and cognitive function in humans. The right panel of the table shows the results of the linear regression analysis after adjustment with age and sex.

are not usually included in the battery of cognitive tests commonly used for diagnosing AD.[17,18]

Interestingly, the CSF Aβ40/tau and Aβ42/tau ratios were associated with a different domain of POCC in our current studies. Aβ40 has an identical amino acid sequence with Aβ42 except for the lack of amino acids isoleucine and alanine at the C terminus. However, Aβ40 and Aβ42 have distinct clinical, biological, and biophysical characteristics.[22] Specifically, 90% Aβ is Aβ40 but Aβ42 is the major form of Aβ in senile plaques.[23–25] Aβ42 has a quicker rate of aggregation than Aβ40,[26,27] and it does so through different underlying mechanisms.[22,28] Finally, Aβ42 is more toxic to neurons than Aβ40.[29,30] Collectively, it is conceivable that Aβ40 and Aβ42 may have different effects on brain function, which suggest that it is also conceivable that the CSF Aβ40/tau and Aβ42/tau ratios may predispose patients to different domains of POCC. There are conflicting findings about the association of CSF biomarkers (eg, Aβ) with cognitive dysfunction.[31–34] The findings from the current studies that the CSF Aβ/tau ratio was associated only with specific components of cognitive change could explain the conflicting findings, which may result from the varying cognitive tests used in previous studies.

Both the Hopkins Verbal Learning Test and the Brief Visuospatial Memory Test measure anterograde memory function and thereby the functional integrity of the medial temporal lobe system.[19] Many studies have suggested that the low CSF Aβ level represents high brain Aβ levels, owing to the sequestration of Aβ into brain amyloid plaques[35,36] (reviewed in Holtzman[13] and Blennow and Zetterberg[37]), but CSF tau levels represent brain tau levels[35,36] (reviewed in Blennow and Zetterberg[37]). Taken together, the findings that the CSF Aβ/tau ratio is associated with Hopkins Verbal Learning Test and the Brief Visuospatial Memory Test suggest that CSF and/or brain Aβ and tau levels may be associated with the integrity of the medial temporal lobe system. Further studies are needed to test this hypothesis by determining whether the amount of amyloid in the medial temporal lobe system is specifically associated with verbal learning and visual memory impairment (eg, by using positron emission tomographic imaging with Amyvid).

The JLO can be used to assess spatial perception and orientation, and it has been shown to be sensitive to the right hemisphere dysfunction.[38,39] We have found that the CSF Aβ42/tau ratio is associated with the postoperative cognitive function of the JLO. These findings suggest that CSF Aβ42/tau ratio, the AD biomarker, is associated with increased vulnerability of certain parts of the brain and specific domains of cognitive function to the stress of surgery. It is notable that spatial perception and orientation are localized to areas of the brain that are different from those of visual memory and are reflected by differing biomarkers.

The values of human CSF Aβ and tau in our current studies were higher than those determined in the Alzheimer's Disease Neuroimaging Initiative studies[12] and in a recent study to assess the effects of anesthesia and surgery on human AD and inflammation biomarkers.[40] The reason for such a difference is not clear at the present time. However, there have been reports showing variable human CSF Aβ and tau values in different studies (reviewed in Holtzman[13]). Specifically, the values of Aβ and tau in our current studies were comparable with those measured in the studies by Fagan et al.[41] Moreover, all CSF samples in the current study were analyzed using the same methods. Therefore, although the absolute values of CSF Aβ and tau may differ from those reported in other studies, the relative differences in the values between the subjects are consistent and therefore our results should be valid.

Prior studies by Tang et al[40] and Palotas et al[42] have shown that anesthesia and surgery seem to modulate CSF levels of Aβ, tau, cytokines, and S100b; however, these studies did not attempt to determine the associations between the preoperative CSF biomarkers and postoperative cognitive function. Our current studies are different from these studies because we have focused on determining the potential association between preoperative CSF Aβ/tau ratio and POCC rather than the change in human CSF biomarkers after anesthesia and surgery. Further studies are warranted in the future to determine the effects of surgery on both pre- and postoperative CSF biomarkers in the same participant.

We found that there was a significant relationship existed between POCC and Aβ/tau ratios in some cognitive domains. Interestingly, because POCC was generally in the positive direction, these data suggest that even within a group of cognitively normal elderly patients, Aβ/tau ratios may allow stratification of learning ability.

This study has several limitations. First, the CSF Aβ42/tau ratio is not associated with all of the verbal functions tested. The ratio is associated only with HVLTRet and HVLTTR but not with BVMTDR (data not shown). The CSF Aβ40/tau ratio is also not associated with all of the visual functions tested. The ratio is associated only with BVMTTR and BVMTDR but not with Brief Visuospatial Memory Test Total Learning or Brief Visuospatial Memory Test Retention (data not shown). It is possible that certain aspects of memory functioning, for example, the ability to retrieve information that has effectively been stored in memory, may be more susceptible to postoperative decline in individuals with a relatively lower CSF Aβ/tau ratio in the current studies. Future studies should include memory measures in which semantic cues are provided to aid in the retrieval process, which may help further clarify the role of Aβ and tau in different aspects of cognitive dysfunction. Second, it is unknown whether the observed association between CSF Aβ40/tau or Aβ42/tau ratio and verbal function, visual function, spatial perception, and orientation is exclusively for postoperative cognitive function or for general cognitive function. Third, we could not draw the conclusion that the preoperative CSF Aβ/tau ratio is associated with POCD or postoperative cognitive improvement because the studies did not include a nonsurgical control group to quantify the learning effect. However, we were able to demonstrate that a correlation existed between preoperative CSF Aβ/tau ratio and change in performance in some cognitive domains. Interestingly, our data suggest that those with higher ratios had improved learning than those with lower ratios. Whether this observation translates to an ability of CSF Aβ/tau ratios to predict risk of postoperative cognitive decline, as suggested in a recent study of patients with normal pressure hydrocephalus,[43] is not yet clear. Fourth, we did not correct the *P* values for the multiple comparisons in Tables 3 and 4 because we expected that the cognitive domains tested were highly cross-correlated; therefore, the need to treat each comparison as "independent" is reduced. However, the possibility that there is no correlation among POCC domains cannot be excluded from the current studies. Finally, the average education in the participants was 17 years, which is skewed to the higher level. It is unknown whether such correlation between CSF Aβ/tau ratio and POCC would still exist in participants with lower education levels.

We did not use the global *Z* score in this study. Combining neuropsychology tests into a single test is controversial in the field of neuropsychology, and most of the POCD literature has not used this approach.[44] Creating meaningful global scores requires a sophisticated modern measurement approach that is beyond the scope of this analysis. Moreover, these data suggest that heterogeneity exists, meaning that CSF or brain levels of Aβ40, Aβ42, and tau may contribute only to certain, but not universal, components of POCD. Pending further studies, these results suggest that the CSF Aβ42/tau and CSF Aβ42/tau ratios could specifically be predictive of the verbal and visual learning domains of POCC.

[AQ8]

CONCLUSIONS

We have found associations between preoperative CSF Aβ42/tau or Aβ40/tau ratio and postoperative changes in specific cognitive domains. If confirmed and extended into future studies, these associations may shed light on the currently undefined neuropathogenesis of POCC, which will, hopefully, promote more animal and human research to further determine the neuropathogenesis and intervention of POCC, ultimately leading to safer surgery care and better postoperative outcomes for senior adults.

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Queries to Author

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