

# Cerebrospinal Fluid Biomarker for Alzheimer Disease Predicts Postoperative Cognitive Dysfunction

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## ABSTRACT

**Background:** Postoperative cognitive dysfunction (POCD) affects 16 to 21% of the elderly 3 months after anesthesia and surgery and is associated with adverse outcomes. The exact cause of POCD remains unknown. The authors hypothesized that elderly individuals with Alzheimer disease (AD) neuropathology, identified by cerebrospinal fluid (CSF) analysis, would have increased the risk for POCD.

**Methods:** CSF samples were collected from 59 patients 60 yr or older who received combined spinal and general anesthesia for elective total hip replacement. Patients underwent neuropsychological testing preoperatively and at 7 days, 3 months, and 12 months postoperatively. POCD at 3 months and cognitive decline at 12 months were calculated by using the reliable change index. CSF amyloid  $\beta_{1-42}$  ( $A\beta_{1-42}$ ), total-tau, phosphorylated-tau, and neurofilament light were assayed with enzyme-linked immunosorbent assay methods.

**Results:** POCD was identified in 5 of 57 patients (8.8%) at 3 months. For  $A\beta_{1-42}$ , 11 patients were below the cut-point for AD neuropathology of whom 3 were classified with POCD (27.3%; 95% CI, 6.0 to 61%), whereas of the 46 patients above the cut-point, 2 were classified with POCD (4.3%; 95% CI, 0.5 to 14.8%) ( $P = 0.01$ ). There was no significant difference in the incidence of POCD in relation to the cut-points for any of the other analytes.

**Conclusions:** Low CSF  $A\beta_{1-42}$  may be a significant predictor of POCD at 3 months. This indicates that patients with AD neuropathology even in the absence of clinically detectable AD symptoms may be susceptible to POCD. (**ANESTHESIOLOGY 2016; 124:353-61**)

**P**OSTOPERATIVE cognitive dysfunction (POCD) describes an objectively measured decline in cognitive function determined by administering a battery of neuropsychological tests before and after anesthesia and surgery. POCD may occur after cardiac surgery,<sup>1,2</sup> noncardiac surgery,<sup>3,4</sup> and even noninvasive procedures under sedation,<sup>5</sup> affects 16 to 21% of elderly patients,<sup>5</sup> and has been associated with an increased hospital stay,<sup>2</sup> an increased mortality,<sup>4</sup> and a decrease in long-term quality of life.<sup>6</sup> Determining the causative factors of POCD is important in order to identify the strategies for its prevention. Although the cause of POCD has not been established, it may be related to surgery, anesthesia, patient-related factors, or most likely a combination of these.<sup>7</sup>

An issue that has complicated the research into the cause of POCD is the long-term follow-up. It is possible that cognitive decline detected at 12 months or more after anesthesia and surgery may reflect some other central nervous system

### What We Already Know about This Topic

- Central nervous system dysfunction attendant with Alzheimer disease (AD) may increase the risk for the development of postoperative cognitive dysfunction (POCD). Cerebrospinal fluid (CSF) levels of amyloid  $\beta$  ( $A\beta$ ) can be used as biomarkers to identify those with AD neuropathology.
- To determine whether  $A\beta$  levels consistent with AD can identify patients at risk for the development of POCD, CSF levels of  $A\beta_{1-42}$  in patients undergoing hip surgery under general anesthesia were measured and their association with short- and long-term cognitive function was evaluated.

### What This Article Tells Us That Is New

- There was an association between low preoperative levels of amyloid  $\beta$  ( $A\beta$ ) in the cerebrospinal fluid (CSF) and postoperative cognitive dysfunction (POCD) at 3 months; POCD was not observed at 12 months.
- Patients with Alzheimer disease neuropathology, identified by low CSF levels of  $A\beta$ , may be at an increased risk of POCD even in the absence of clinically detectable symptoms.

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disruption and not be a direct consequence of the anesthesia or surgery. For this reason, we have used the term cognitive decline at 12 months rather than POCD.<sup>8</sup>

Descriptive studies have identified older age and lower number of years of education (or intelligence quotient) as increasing risk for POCD.<sup>3,4</sup> However, these factors also predict cognitive decline in population studies not involving surgery,<sup>9</sup> suggesting that there may be similarities between POCD and the cognitive decline that characterizes central nervous system disease common in older adults in the community, the most common of which is Alzheimer disease (AD).

In 2011, the National Institute of Aging and the Alzheimer's Association amended the criteria for AD to acknowledge that although AD dementia remained the final clinical stage of the disease, AD pathological processes could be detected with the use of validated biomarkers<sup>10</sup> many years before signs or symptoms became clinically evident.

The key biomarker characteristics of AD in cerebrospinal fluid (CSF) analyses<sup>11,12</sup> are a decrease in amyloid  $\beta_{1-42}$  ( $A\beta_{1-42}$ ) together with increased levels of total-tau (T-tau) and phosphorylated-tau (P-tau).<sup>13</sup> These analytes have been shown to reliably identify dementia,<sup>14,15</sup> Mild Cognitive Impairment (MCI),<sup>14,16</sup> and those in the preclinical phase at risk of future cognitive decline.<sup>17,18</sup>

We hypothesized that elderly patients with AD neuropathology, as determined by CSF analysis, who underwent surgery under general anesthesia would have an increased risk for POCD. The primary aim was to determine the predictive value of CSF  $A\beta_{1-42}$ , T-tau, and P-tau for POCD at 3 months after elective total hip joint replacement. The association of these biomarkers with preexisting cognitive impairment (PreCI),<sup>19</sup> POCD at 7 days, cognitive decline at 12 months, and dementia at 12 months was also investigated. A further aim was to examine the feasibility of taking CSF samples in the context of routine spinal anesthesia. This is of particular interest because it is unknown whether the strict preanalytical guidelines that ensure accurate CSF analysis<sup>20</sup> can be achieved in the routine surgical environment.

## Materials and Methods

### Participants and Study Design

Cerebrospinal fluid samples were collected in the final 59 consecutive patients enrolled in the prospective observational clinical trial, the Anaesthesia, Cognition, Evaluation (ACE) study (Australian Clinical Trials Registry: ACTRN12607000049471; registered at: January 16, 2007; principal investigator: B.S.). The primary aim of the ACE study was to identify the prevalence of preoperative cognitive impairment in 300 individuals undergoing elective total hip replacement and relate this to POCD at 7 days and 3 months and cognitive decline at 12 months. The full details of the study are published elsewhere<sup>8</sup> with an interim subset published as part of a comparative study in 2011.<sup>5</sup> The protocol was amended in 2011 to include CSF sampling in

response to the revised criteria for the diagnosis of AD, which recognized CSF biomarkers as diagnostic for the purpose of research.<sup>21</sup> We were able to recruit 59 of the remaining patients constituting a convenience sample. In addition, we use the term cognitive decline for what has previously been termed POCD at 12 months because the relation between the operation and subsequent cognitive decline at this time period is questionable.<sup>20</sup>

All participants gave written informed consent, and the study was approved by the institutional ethics review board (St. Vincent's Hospital Human Research Ethics Committee, Melbourne, Victoria, Australia). Inclusion criteria were age 60 yr or older, suitable for cognitive testing at home (including adequate English language skills), and no neurological deficit. Exclusion criteria were preexisting neurological or clinically evident neurovascular disease (*e.g.*, stroke), minimal state examination score of less than 26 or Clinical Dementia Scale (CDR) score of greater than 1 (*i.e.*, patients with mild/moderate dementia were excluded), associated medical problems that may have led to significant complications and subsequent loss to follow-up (American Society of Anesthesiologists physical status greater than 3), blindness, deafness, English not being the prime language, and geographical remoteness that may make it difficult to test patients at home. A nonoperative age- and sex-matched control group of individuals with osteoarthritis not scheduled for surgery was tested in identical manner at the same time points in order to calculate POCD.

All patients were administered spinal anesthesia (0.5% bupivacaine, either heavy or plain) at which time 5 ml of CSF was aspirated before the spinal anesthetic solution was injected. Sedation consisting of IV midazolam and fentanyl was given as indicated during the insertion of the spinal anesthetic. General anesthesia was administered in addition to the spinal anesthetic with anesthesiologists being asked to ensure that the bispectral index remained below 60 (to confirm general anesthesia), which was achieved with either volatile agents (sevoflurane) or IV agents (propofol) by clinical preference of the treating anesthesiologist. All other aspects of surgery and anesthesia were then undertaken according to routine clinical practice. Hypotension was treated as clinically appropriate with IV metaraminol or ephedrine. All details of clinical care were documented in a case report form.

The preanalytical handling of CSF is important to ensure that no proteins are degraded, aggregating, or adhering to the test tube wall before analysis.<sup>20</sup> CSF was aspirated gently by using polypropylene syringes, transferred to polypropylene tubes on ice, centrifuged, and then stored at  $-80^{\circ}\text{C}$ . At the end of the study, the samples were transferred on dry ice by courier to the Clinical Neurochemistry Laboratory at Sahlgrenska University Hospital, Mölndal, Sweden, for analyses.

### Neuropsychological Testing

Neuropsychological testing consisted of a battery of eight neuropsychological tests administered at baseline (during

the week before surgery) and at 7 days, 3 months, and 12 months after surgery. The test battery consisted of the Consortium to Establish a Registry in Alzheimer's Disease (CERAD) Auditory Verbal Learning Test, Trail Making Test parts A and B, Digit Symbol Substitution Test, Controlled Oral Word Association Test (verbal fluency), CERAD Semantic Fluency test (animals), and the Grooved Pegboard test (dominant and nondominant hands).<sup>2</sup> For timed tasks, an increase in time for each test was taken to imply a cognitive decline. Parallel forms were administered for the CERAD Auditory Verbal Learning Test, and all the tests were administered in the same order at all time points. The National Adult Reading Test was used to estimate the pre-morbid intelligence quotient<sup>22</sup> and was administered at the baseline assessment.

All these tests were used to assess POCD at 7 days and 3 months and cognitive decline at 12 months by using the reliable change index (RCI) calculated for each test at each time point by score – (baseline score) – (practice effect estimated from controls)/(SD of difference scores estimated from control group).<sup>23</sup> Age- and sex-matched controls with medically treated osteoarthritis were used to calculate the RCI.<sup>8</sup> POCD was defined in an individual when their RCI was 1.96 or less on two or more tests and/or their sum of *z* scores/SD of sum of *z* scores in controls was –1.96 or less.<sup>23</sup> PreCI<sup>19</sup> was used to assess baseline cognitive function using the same calculation as for POCD except cutoff was 2 SD on normative values, and the Digit Symbol Substitution Test was not used because we did not have access to population norms.<sup>24</sup>

### Assessment of Dementia

Each patient was classified using the CDR<sup>25</sup> sum of boxes (SB) score (total possible score: 18) and the CDR global score (0, 0.5, 1, 2, or 3). The CDR-SB score has been validated as the preferred endpoint for clinical research trials<sup>26</sup> because it has the ability to identify those at risk but who do not yet meet the criteria for a global CDR score of 0.5 or greater (*i.e.*, MCI) and was, therefore, used as the outcome measure for this investigation. Informant questionnaire for cognitive decline in the elderly (Informant Questionnaire on Cognitive Decline in the Elderly [IQCODE])<sup>27</sup> and instrumental activities of daily living questionnaire<sup>28</sup> were assessed at baseline and at 3 and 12 months postoperatively and used as adjuncts with the CDR.

A classification of dementia at 12 months was determined by an experienced academic old age psychiatrist (D.A.) with over 2 decades experience in the regular use of the CDR. Additional information for this classification included the delayed recall component of the CERAD Auditory Verbal Learning Test (part of the POCD neuropsychological battery, but not used for classification of POCD) and the mini-mental state examination. Patients who were unable to provide an informant were not included in the classification of dementia. The Geriatric Depression Score<sup>29</sup> was completed as part of the evaluation process for classification

of dementia to rule out depression as a cause of impaired cognitive function.

### Measurement of CSF A $\beta_{1-42}$ , T-tau, P-tau, and Neurofilament Light

Cerebrospinal fluid A $\beta_{1-42}$  levels were determined by using a sandwich enzyme-linked immunosorbent assay (ELISA; INNOTEST<sup>®</sup>  $\beta$ -AMYLOID (1–42); Fujirebio, Belgium), specifically constructed to measure A $\beta$  containing both the 1st and 42nd amino acid, as previously described.<sup>30</sup> CSF T-tau concentrations were determined by using a sandwich ELISA (Innotest hTAU-Ag; Fujirebio) specifically constructed to measure all tau isoforms irrespective of phosphorylation status, as previously described.<sup>31</sup> CSF tau phosphorylated at threonine 181 (P-tau181) was measured by using a sandwich ELISA method (INNOTEST<sup>®</sup> PHOSPHO-TAU (181P); Innogenetics, Belgium), as described previously in detail.<sup>32</sup> CSF levels of neurofilament light (NFL) protein, a biomarker for large-caliber white matter axons, was measured with a sensitive sandwich ELISA method (NF-light ELISA kit; UmanDiagnostics AB, Sweden), as described previously.<sup>33,34</sup> The CSF NFL level was used as an aid to identify the vascular causes of dementia.<sup>35</sup>

All biochemical analyzes were performed by board-certified staff blinded to patient identity and diagnosis. All intra-assay coefficients of variation were less than 10%. The cut-points for the assays in this laboratory have been determined by analyzing a large series of CSF samples from cognitively normal elderly and were found to be less than 550 pg/ml for A $\beta_{1-42}$ , greater than 400 pg/ml for T-tau, greater than 70 pg/ml for P-tau, and less than 1,850 ng/l for NFL.

### Statistical Analysis

Group comparisons were made using the independent *t* tests for continuous variables, Mann–Whitney U test for ranked data, chi-square or Fisher exact test for dichotomous data, and Pearson correlation coefficient for correlations. A *P* value of less than 0.05 was taken to indicate significance. Associations were determined by using univariable logistic regression. Odds ratios (ORs) and 95% CIs were determined for individual tests and combined outcomes. Cohen's *d* was used to estimate effects sizes. Tests were performed by using STATA (Version 12.0; Stata Corporation, USA).

### Results

The final 59 consecutive patients enrolled in the ACE study all underwent collection of CSF.

Fifty-one age- and sex-matched cognitively normal community controls were enrolled in order to calculate POCD at 7 days and 3 months and cognitive decline at 12 months. Baseline characteristics, including medical history, are shown in table 1 for the non-CSF cohort (*n* = 241) in the ACE study, the subgroup in the ACE study undergoing CSF collection (*n* = 59), and controls (*n* = 51).

Preexisting cognitive impairment was identified in 15 of 59 (25.4%; 95% CI, 15 to 38%) of the CSF substudy

**Table 1.** Patient and Control Demographics and Medical History

	Non-CSF Cohort, n		CSF Subgroup, n		Controls n	
Age, y	241	70.0 (6.4)	59	70.4 (7.0)	51	72.0 (7.2)
Sex, male (%)	241	84 (34.9)	59	19 (32.2)	51	13 (25.5)
Height, cm	241	166.8 (9.7)	58	164.5 (8.0)	49	166.0 (8.6)
Weight, kg	241	78.3 (14.0)	59	79.5 (15.9)	50	75.3 (17.3)
Body mass index, kg/m <sup>2</sup>	241	28.1 (4.8)	58	29.2 (5.2)	49	27.2 (5.0)
Diabetes mellitus	238	18 (7.6)	58	8 (13.8)	50	6 (12)
Hypertension	240	120 (50.0)	59	40 (67.8)	51	34 (66.7)
Peripheral vascular disease	230	2 (1.0)	57	1 (1.8)	51	3 (5.9)
History of myocardial infarct	236	9 (3.8)	59	3 (5.1)	50	7 (14.0)
History of smoking	241	114 (47.3)	59	30 (50.8)	51	20 (39.2)
Hypercholesterolemia	239	89 (37.2)	58	26 (44.8)	51	26 (51.0)
Estimated IQ	270	111.0 (10.3)	53	106.2 (10.6)	48	115.4 (9.0)
Prior general anesthesia	238	224 (94.1)	57	51 (89.5)	48	45 (93.8)

Continuous variables are presented as mean (SD) and categorical variables are presented as frequency (%). CSF = cerebrospinal fluid; IQ = intelligence quotient.

patients, which was not statistically different to PreCI for the non-CSF cohort 80 of 241 (33.2%; 95% CI, 27 to 40%)  $P = 0.24$ . General anesthesia was maintained with sevoflurane in oxygen in six patients, and the remaining 53 patients were anesthetized with IV propofol.

Fifty-seven of the 59 patients with CSF samples were assessed for POCD at 7 days and 3 months (two patients withdrew) and 53 for cognitive decline at 12 months (two further patient withdrawals and two refusals). POCD was identified in 11 of 57 (19.3%; 95% CI, 10 to 32%) patients at 7 days, and in 5 of 57 (8.8%; 95% CI, 3 to 20%) patients at 3 months postoperatively, whereas cognitive decline was present in 0 of 53 (0%; 95% CI, 0 to 7%) at 12 months postoperatively, which was not statistically different to the non-CSF cohort (38 of 229 [16.6%], 95% CI, 12 to 22%; 22 of 227 [9.7%], 95% CI, 6 to 14%; and 7 of 218 [3.2%], 95% CI, 1 to 7%, for 7 days, 3 months, and 12 months, respectively).

Dementia was assessed in 37 patients at 12 months (in addition to the 6 patients lost for POCD assessment, a further 6 patients did not have informants and, therefore, were not assessed for dementia). Incident dementia was diagnosed in one patient at 12 months. This patient was not categorized as having cognitive decline at 12 months and did not have AD biomarkers indicating AD or increased NFL.

For the CSF biomarkers, we obtained results for  $A\beta_{1-42}$  and NFL in all 59 patients and in 57 for T-tau and 56 for P-tau. Results were missing for T-tau in two patients and P-tau in three patients. Median (interquartile range) levels of CSF biomarkers were 759 pg/ml (612.0 to 926.0) for  $A\beta_{1-42}$ , 327 pg/ml (210.8 to 453.5) for T-tau, 44.5 pg/ml (30.9 to 60.0) for P-tau, and 772 ng/l (614.0 to 1,045.0) for NFL. Median levels of  $A\beta_{1-42}$  were significantly lower in those patients with POCD at 3 months compared with those without POCD at 3 months ( $P = 0.04$ ); however, there was no significant difference in the median levels of each

biomarker for those with and without PreCI, POCD, and cognitive decline at any other time (table 2).

Twelve of 59 patients fell below the cut-point for  $A\beta_{1-42}$ , 20 of 57 patients were above the cut-point for T-tau, and 8 of 56 were above the cut-point for P-tau. Of the 56 patients who were assayed for all three AD biomarkers, 4 patients had abnormal levels for all three, 4 patients were abnormal for two, and 19 patients were abnormal for one biomarker. No patients recorded increased NFL levels.

The incidence of POCD at 3 months according to cut-point for each analyte is shown in table 3. Eleven patients were below the cut-point for  $A\beta_{1-42}$  of whom 3 were classified with POCD (27.3%; 95% CI, 6.0 to 61%), whereas of the 46 patients above the cut-point, 2 were classified with POCD (4.3%; 95% CI, 0.5 to 14.8%) ( $\chi^2 = 5.83$ ;  $P = 0.01$ ). Univariable analysis identified POCD at 3 months as significantly associated with low  $A\beta_{1-42}$  at baseline (OR, 8.25; 95% CI, 1.18 to 57.49;  $P = 0.03$ ). There was no significant difference in the incidence of POCD in relation to the cut-points for any of the other analytes.

The difference between performances on the individual neuropsychological tests for patients on either side of the cut-point for each of the biomarkers is shown as Cohen's  $d$  effect size in figure 1. At 3 months postoperatively, low CSF  $A\beta_{1-42}$  demonstrated medium to large effects for the CERAD Auditory Verbal Learning Test (the domain of memory), CERAD Semantic fluency (attention), and Grooved Pegboard Test dominant (primarily the psychomotor domain). High baseline CSF P-tau was associated with medium to large effect sizes on Trail Making Test part A (executive function), CERAD Auditory Verbal Learning Test (memory), and Controlled Oral Word Association Test (primarily the domain of attention) at 3 months postoperatively. At 12 months postoperatively, low baseline CSF  $A\beta_{1-42}$  was associated with large effect sizes for Trail Making Test parts B (executive function) and Controlled Oral

**Table 2.** Concentrations of Biomarkers by Cognitive Impairment Classification

		Aβ <sub>1-42</sub> (59)	T-Tau (57)	P-Tau (56)	NFL (59)
Baseline	PreCI	763 (618–924)	275 (210–651)	38 (30–63)	887 (471–1,114)
	No PreCI	755 (608–928)	328 (215–445)	45 (31–58)	762 (647–1,010)
P value		0.52	0.94	0.93	0.54
Day 7	POCD	727 (612–766)	348 (210–404)	46 (30–55)	890 (614–1,489)
	No POCD	793 (618–931)	327 (217–477)	44 (32–59)	762 (637–1,019)
P value		0.36	0.55	0.91	0.46
3 months	POCD	485 (465–651)	327 (254–402)	42 (34–49)	890 (720–1,001)
	No POCD	762 (641–930)	316 (210–441)	44 (31–55)	762 (582–1,012)
P value		0.04	0.45	0.64	0.71

Biomarker levels given are in pg/ml and are median (interquartile range).

Aβ<sub>1-42</sub> = amyloid β; NFL = neurofilament light; POCD = postoperative cognitive dysfunction; PreCI = preexisting cognitive impairment; P-tau = phosphorylated-tau; T-tau = total-tau.

**Table 3.** Number of Patients with POCD at 3 Months According to Cut-point for Each Analyte

Analytes (n)	POCD with Normal Cut-point	POCD with Cut-point Associated with Alzheimer Disease	OR (95% CI)	P Value
3 Months				
Aβ <sub>1-42</sub> (59)	2/46 (4%)	3/11 (27%)	8.25 (1.18–57.49)	0.03
95% CI	(1–15%)	(6–61%)		
T-Tau (57)	3/37 (8%)	2/18 (11%)	1.42 (0.22–9.33)	0.71
95% CI	(2–22%)	(1–35%)		
P-Tau (56)	4/48 (8%)	1/6 (17%)	2.20 (0.20–23.74)	0.51
95% CI	(2–20%)	(0–64%)		
NFL (59)	5/54 (9%)	0/3 (0%)	N/A	
95% CI	(3–20%)	(0–71%)		

Normal levels defined as > 550 pg/ml for Aβ<sub>1-42</sub>, < 400 pg/ml for T-tau, < 70 pg/ml for P-tau, < 1,850 pg/ml; levels associated with Alzheimer disease defined as ≤ 550 pg/ml for Aβ<sub>1-42</sub>, ≥ 400 pg/ml for T-tau, and ≥ 70 pg/ml for P-tau. OR for NFL vs. POCD at 3 months is N/A because it cannot be calculated as one cell = 0.

Aβ<sub>1-42</sub> = amyloid β; N/A = not applicable; NFL = neurofilament light; OR = odds ratio; POCD = postoperative cognitive dysfunction; P-tau = phosphorylated-tau; T-tau = total-tau.

Word Association Test (attention). High baseline CSF P-tau was associated with medium to large effect sizes for CERAD Auditory Verbal Learning Test (memory) Controlled Oral Word Association Test (attention) and CERAD Semantic Fluency Test (attention). CSF T-Tau was not associated with medium or large effect sizes at either 3 or 12 months.

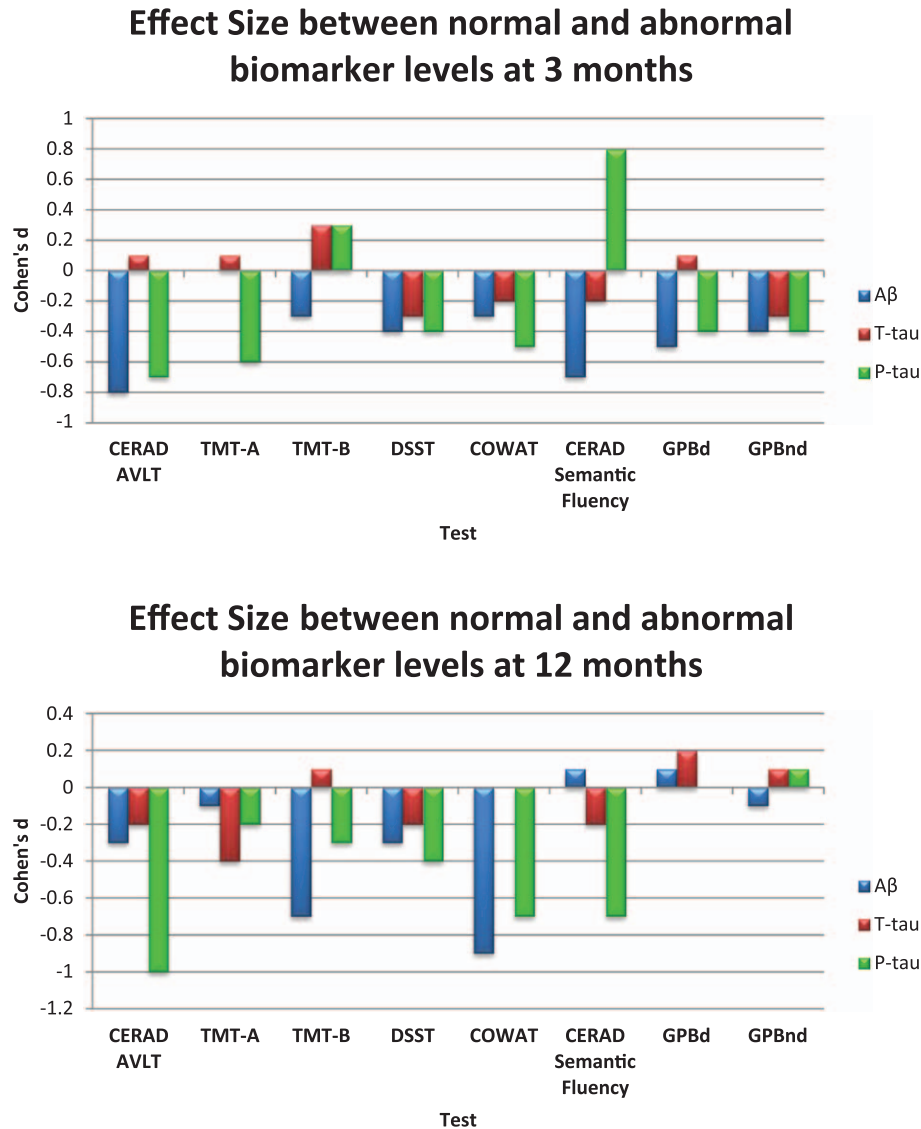
**Discussion**

We identified POCD in 8.8% of patients at 3 months after elective total hip replacement and cognitive decline in 0% at 12 months, whereas dementia was identified in one patient (2.7%) at 12 months. Low CSF Aβ<sub>1-42</sub> was a significant predictor of POCD at 3 months and the cut-point for Aβ<sub>1-42</sub> was a good indicator of POCD (OR, 8.25; 95% CI, 1.18 to 57.49). Thus, when analyzed by either continuous or binary methods, low CSF Aβ<sub>1-42</sub> levels were associated with subsequent POCD. In contrast, neither CSF T-tau nor P-tau predicted subsequent POCD. No patient classified with POCD at 3 months or incident dementia at 12 months had elevated CSF NFL, tending to mitigate against cerebrovascular damage as a cause of POCD.

Cognitive decline identified as POCD has been the subject of concern after both cardiac and noncardiac anesthesia

and surgery. Testing for POCD at 3 months postoperatively provides a reliable index of cognitive decline because early testing at 7 days may be compounded by hospitalization and the remnants of anesthetic and analgesic drugs,<sup>36</sup> whereas the incidence of POCD at 12 months may be indistinguishable from nonoperative controls.<sup>8,37</sup>

Cerebrospinal fluid biomarkers have been shown to predict progression of AD ranging from the very earliest preclinical stages with normal cognition to full-blown dementia.<sup>35</sup> Central to the amyloid cascade hypothesis<sup>38</sup> is that the change in Aβ<sub>1-42</sub> occurs before changes in tau proteins, and indeed, it has been suggested that in the early preclinical stages, low CSF Aβ<sub>1-42</sub> alone is associated with an increased risk of AD.<sup>39</sup> Several studies suggest that with cognitive decline due to AD, lowering of CSF Aβ<sub>1-42</sub> occurs in the very early stages, before levels of T-tau and P-tau start to increase as the disease progresses.<sup>18,40–42</sup> The current study demonstrates a significant association between low baseline CSF Aβ<sub>1-42</sub> and cognitive decline in the postoperative period, despite the lack of findings for T-tau and P-tau. Several studies have consistently shown that low CSF Aβ<sub>1-42</sub> corresponds to cortical Aβ deposition (for review, see the study by Blennow *et al.*<sup>43</sup>). Thus, our findings suggest that



**Fig. 1.** Effect size for neuropsychological tests. A $\beta$  = amyloid  $\beta_{1-42}$ ; AVLT = Auditory Verbal Learning Test; CERAD = Consortium to Establish a Registry for Alzheimer's Disease; COWAT = Controlled Oral Word Association Test; DSST = Digit Symbol Substitution Test; GPBd = Grooved Peg Board Test dominant; GPBnd = Grooved Peg Board Test nondominant; P-tau = phosphorylated-tau; TMTA = Trail Making Test Part A; TMTB = Trail Making Test Part B; T-tau = total-tau.

elderly individuals with A $\beta$  deposition due to preclinical AD are at risk for POCD.

Of particular interest is that baseline cognitive function, as measured by PreCI was not associated with low CSF A $\beta_{1-42}$ . We have previously shown that there is limited overlap between MCI and PreCI.<sup>24</sup> These two constructs use different information; for example, MCI includes subjective or informant memory complaints. This may account for why PreCI was not associated with low A $\beta_{1-42}$ . Our findings support the hypothesis that anesthesia and surgery act in some way to exacerbate or initiate cognitive decline in patients predisposed by the presence of preclinical AD identified by low levels of A $\beta_{1-42}$ .

It should be noted that the one patient who was classified with dementia at 12 months was not classified as having cognitive decline at this time point. Closer inspection of this

particular patient shows that this patient fell just short of  $-1.96$  SD RCI on the CERAD Auditory Verbal Learning Test and was  $-1.7$  SD RCI on the Digit Symbol substitution Test, and thus failed to qualify on the basis of 1.96 or less SD RCI on two tests, although this would have qualified for objective criteria for mild neurocognitive impairment on the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition.<sup>44</sup> However, the CDR global score for this patient was 1 and SB was 1.5 and the IQCODE partner score was 3.7 (indicating functional decline), which no doubt were important features leading to a classification of dementia.

Studies of CSF biomarkers in relation to anesthesia and surgery in humans have been limited. One study examined 11 patients with indwelling CSF catheters and found dynamic changes in the ensuing 48 h, which were notable

for increases in CSF T-tau and P-Tau as well as inflammatory markers, but they did not address baseline levels of the CSF biomarkers.<sup>45</sup> The influence of indwelling catheters that may disturb CSF dynamics may be a confounding factor.<sup>46</sup> In a pilot study of 14 patients after cardiac surgery, decreases in CSF  $A\beta_{1-42}$  and increases in T-tau at 6 months were related to cognitive decline, but this study also did not address the baseline levels of CSF biomarkers.

Other studies suggest that preoperative CSF biomarkers may correlate with postoperative cognitive outcome. Xie *et al.*<sup>47</sup> examined cognition in 136 elderly patients undergoing elective joint arthroplasty under spinal anesthesia with sedation (without general anesthesia). CSF was analyzed for  $A\beta_{1-40}$ ,  $A\beta_{1-42}$ , and T-Tau, and neuropsychological tests were administered at baseline and at 1 week and 3 to 6 months after surgery. Unfortunately, because no control group was studied, it was not possible to evaluate POCD. Lower CSF  $A\beta_{1-42}$ /T-tau ratio preoperatively was associated with poorer performance on tests for verbal memory and visuospatial judgment.

A Japanese study assayed CSF in 79 patients undergoing elective hip replacement surgery. General anesthesia was not administered and POCD was identified merely by a decrease of 10% in any one of several cognitive tests at 7 days.<sup>48</sup> This study found low  $A\beta_{1-42}$  and high T-tau in patients was associated with POCD (by their definition) at 7 days.

Although the ratio of  $A\beta_{1-42}$ /Tau was originally advocated as a good marker of AD and labeled as the “AD signature,”<sup>17</sup> more recent models of AD pathology hold that the  $A\beta$  pathology occurs before biomarker-detectable Tau pathology and thus the decrease in  $A\beta_{1-42}$  should come before an increase in Tau proteins.<sup>49</sup> This is supported by biomarker studies in sporadic AD that showed that the lowering  $A\beta_{1-42}$  of CSF is a very early change before changes in Tau occur.<sup>40</sup>

The use of a control group in the current study enabled us to formally address POCD, which is a comprehensive measure of cognitive decline after anesthesia and surgery as well as cognitive decline and dementia at 12 months.<sup>23</sup> The results suggest that baseline CSF  $A\beta_{1-42}$ , as an indicator of early AD neuropathology, may play a role in POCD.

With regard to the specific cognitive tests at 3 months, effect sizes between those above (normal) and below (abnormal) the cut-point for CSF  $A\beta_{1-42}$  showed differences in neuropsychological tests of memory, executive function, and psychomotor performance, with memory function showing the greatest change in cases with low CSF  $A\beta_{1-42}$ . This finding is consistent with the concept of memory function being most vulnerable to decline in AD, in agreement with previous work.<sup>47</sup>

A major limitation to this study is the small sample size, which was dependent on the timing of the introduction of the substudy and was not subjected to *a priori* power calculation. Despite this, the patients all underwent comprehensive neuropsychological assessment in comparison to previous studies, ensuring accurate reporting of the event rate. Nevertheless, the sample size necessitates cautious interpretation of

the results, which should be considered hypothesis generating rather than model fitting.

Many mechanisms for POCD have been suggested; however, the exact etiology remains unknown. The current findings suggest that individuals with preclinical AD defined by low CSF  $A\beta_{1-42}$  may be susceptible to POCD when exposed to anesthesia and surgery. However, the current study does not resolve the question of which aspects of anesthesia and surgery provoke the cognitive decline.

This study also shows that CSF collection during spinal anesthesia is feasible and practical and that the adherence to guidelines for preanalytical factors<sup>20</sup> to ensure accurate results is achievable in the perioperative setting. Thus, routine collection of CSF during (unrelated) hospital interventions may be an option for screening CSF in the elderly where elective lumbar puncture is less desirable for patients.

In conclusion, we have identified, in a small cohort of patients, an association between low preoperative CSF levels of  $A\beta_{1-42}$  (consistent with preclinical AD) and POCD at 3 months. We have also demonstrated the feasibility of routine perioperative CSF sampling of diagnostic quality. The opportunities for larger-scale investigations are thus justified.

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## Competing Interests

The authors declare no competing interests.

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